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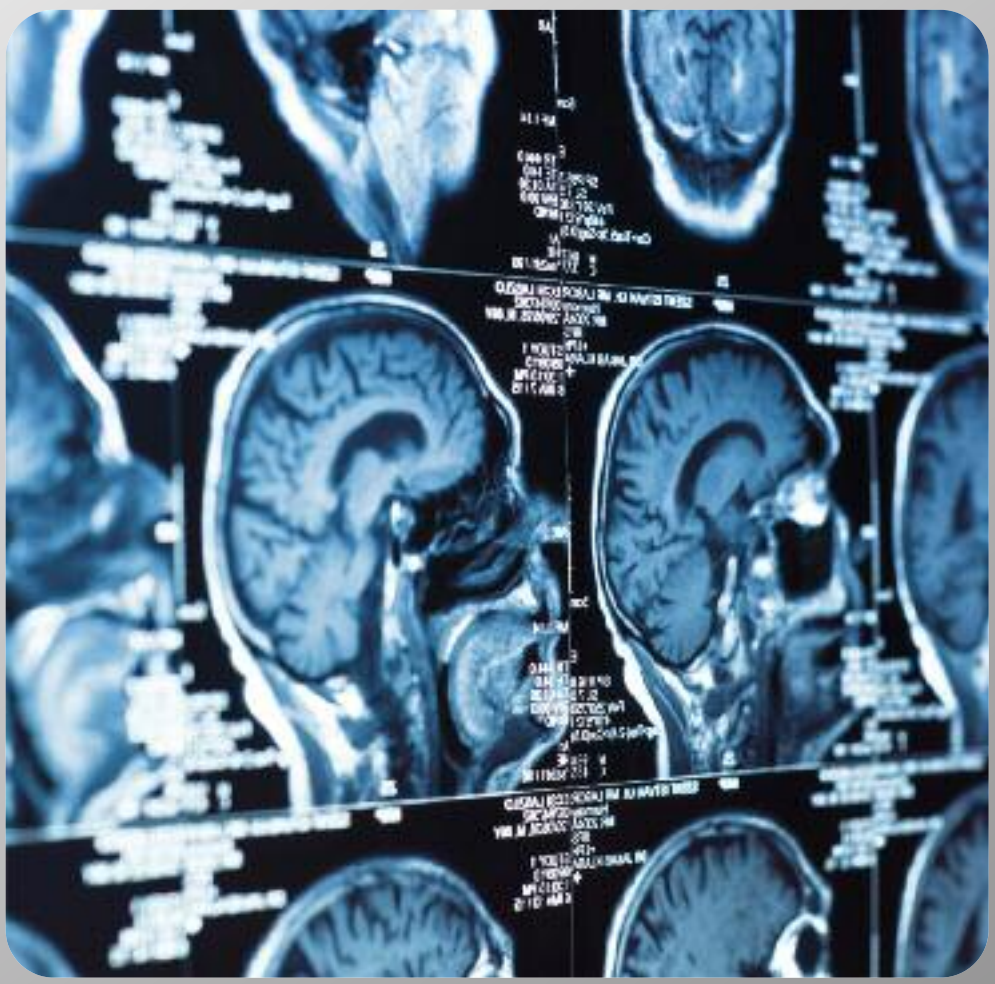

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Yondelis
trabectedin

ΘΕΡΑΠΕΥΤΙΚΗ ΠΡΟΤΑΣΗ
ΓΙΑ ΤΟΝ ΚΑΡΚΙΝΟ
ΤΩΝ ΩΟΘΗΚΩΝ[1]

ΕΛΕΓΧΕΙ ΤΗ ΝΟΣΟ
ΚΑΙ ΚΑΘΥΣΤΕΡΕΙ ΤΗΝ ΕΞΕΛΙΞΗ
ΣΤΟ ΠΡΟΧΩΡΗΜΕΝΟ
ΣΑΡΚΩΜΑ ΜΑΛΑΚΩΝ ΜΟΡΙΩΝ[4]

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ΜΗΧΑΝΙΣΜΟΣ ΔΡΑΣΗΣ[2,3]

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Contents

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Contents (suite)

ΠΕΡΙΛΗΨΗ ΤΩΝ ΧΑΡΑΚΤΗΡΙΣΤΙΚΩΝ ΤΟΥ ΠΡΟΪΟΝΤΟΣ: 1. ΟΝΟΜΑΣΙΑ ΤΟΥ ΦΑΡΜΑΚΕΥΤΙΚΟΥ ΠΡΟΪΟΝΤΟΣ: Yondelis 0,25 mg & 1mg κόνις για πυκνό διάλυμα για παρασκευή διαλύματος προς έγχυση. **2. ΠΟΙΟΤΙΚΗ ΚΑΙ ΠΟΣΟΤΙΚΗ ΣΥΝΘΕΣΗ:** • Yondelis 0,25 mg Κάθε φιαλίδιο περιέχει 0,25 mg τραβεκτεδίνης. 1 ml ανασυσταμένου διαλύματος περιέχει 0,05 mg τραβεκτεδίνης. Έκδοχα με γνωστές επιδράσεις: Κάθε φιαλίδιο περιέχει 2 mg καλίου και 0,1 g σακχαρόζης. • Yondelis 1 mg Κάθε φιαλίδιο περιέχει 1 mg τραβεκτεδίνης. 1 ml ανασυσταμένου διαλύματος περιέχει 0,05 mg τραβεκτεδίνης. Έκδοχα με γνωστές επιδράσεις: Κάθε φιαλίδιο περιέχει 8 mg καλίου και 0,4 g σακχαρόζης. **3. ΦΑΡΜΑΚΟΤΕΧΝΙΚΗ ΜΟΡΦΗ:** Κόνις για πυκνό διάλυμα για παρασκευή διαλύματος προς έγχυση. Λευκή έως υπόλευκη κόνις. **4. ΚΛΙΝΙΚΕΣ ΠΛΗΡΟΦΟΡΙΕΣ: 4.1 Θεραπευτικές ενδείξεις:** Το Yondelis ενδείκνυται για την αντιμετώπιση ασθενών με προχωρημένο σάρκωμα των μαλακών μορίων, μετά από αποτυχία ανθρακυκλινών και ιφοσφαμίδης, ή οι οποίοι είναι ακατάλληλοι να λάβουν αυτούς τους παράγοντες. Τα στοιχεία αποτελεσματικότητας βασίζονται κυρίως σε ασθενείς με λιποσάρκωμα και λειομυοσάρκωμα. Το Yondelis σε συνδυασμό με πεγκυλιωμένη λιποσωμιακή δοξορουβικίνη (PLD) ενδείκνυται για τη θεραπεία ασθενών με υποτροπιάζοντα, ευαίσθητο στην πλατίνα, καρκίνο των ωοθηκών. **4.2 Δοσολογία και τρόπος χορήγησης:** Το Yondelis πρέπει να χορηγείται υπό την επίβλεψη ιατρού έμπειρου στη χρήση χημειοθεραπείας. Θα πρέπει να χρησιμοποιείται μόνο από εξειδικευμένους ογκολόγους ή άλλους επαγγελματίες του τομέα υγειονομικής περίθαλψης ειδικευμένους στη χορήγηση κυτταροτοξικών παραγόντων. Δοσολογία: Για τη θεραπεία του σαρκώματος των μαλακών μορίων, η συνιστώμενη δόση είναι 1,5 mg/m^2 επιφάνειας σώματος, η οποία χορηγείται ως ενδοφλέβια έγχυση για 24 ώρες με διάστημα τριών εβδομάδων μεταξύ των κύκλων. Για τη θεραπεία του καρκίνου των ωοθηκών το Yondelis χορηγείται κάθε τρεις εβδομάδες ως 3ωρη έγχυση σε δόση 1,1 mg/m^2, αμέσως μετά από PLD 30 mg/m^2. Για να ελαχιστοποιήσει τον κίνδυνο αντιδράσεων από την έγχυση PLD, η αρχική δόση χορηγείται με ρυθμό όχι μεγαλύτερο από 1 mg/λεπτό. Εάν δεν παρατηρείται αντίδραση κατά την έγχυση, οι επόμενες εγχύσεις PLD μπορούν να χορηγούνται σε χρονική διάρκεια 1 ώρας. (Βλέπε επίσης Περίληψη Χαρακτηριστικών Προϊόντος PLD για ειδικές οδηγίες χορήγησης). Όλοι οι ασθενείς πρέπει να λάβουν κορτικοστεροειδή, π.χ., 20 mg δεξαμεθαζόνης ενδοφλεβίως 30 λεπτά πριν από την PLD (σε θεραπεία συνδυασμού) ή Yondelis (σε μονοθεραπεία) όχι μόνο ως αντιεμετική προφύλαξη, αλλά επίσης επειδή φαίνεται ότι παρέχει ηπατοπροστατευτικά αποτελέσματα. Μπορεί να χορηγηθούν πρόσθετα αντιεμετικά, όπως απαιτείται. Απαιτούνται τα ακόλουθα κριτήρια ώστε να επιτραπεί η θεραπεία με Yondelis: – Απόλυτος αριθμός ουδετερόφιλων (ANC) ≥1.500/mm^3 – Αριθμός αιμοπεταλίων ≥100.000/mm^3 – Χολερυθρίνη ≤ ανώτερο φυσιολογικό όριο (ULN) – Αλκαλική φωσφατάση ≤2,5 x ULN (εξετάστε ηπατικά ισοένζυμα 5-νουκλεοτιδάση ή GGT, εάν η αύξηση θα μπορούσε να είναι οστικής προέλευσης). – Λευκωματίνη ≥25 g/l. – Αμινοτρανσφεράση της αλανίνης (ALT) και Ασπαρτική αμινοτρανσφεράση (AST) ≤2,5 x ULN – Κάθαρση κρεατινίνης ≥30 ml/λεπτό (μονοθεραπεία), κρεατινίνη ορού ≤1,5 mg/dl (≤132,6 μmol/l) ή κάθαρση κρεατινίνης ≥60 ml/λεπτό (θεραπεία συνδυασμού) – Κρεατινοφωσφοκινάση (CPK) ≤2,5 x ULN – Αιμοσφαιρίνη ≥9 g/dl. Πρέπει να πληρούνται τα ίδια κριτήρια, όπως παραπάνω, για επανάληψη της θεραπείας. Ειδάλλως, η θεραπεία πρέπει να καθυστερεί έως 3 εβδομάδες έως ότου να πληρούνται τα κριτήρια. Θα πρέπει να διεξάγεται πρόσθετη παρακολούθηση των αιματολογικών παραμέτρων, χολερυθρίνη, αλκαλική φωσφατάση, αμινοτρανσφεράσες και CPK εβδομαδιαίως κατά τη διάρκεια των πρώτων δύο κύκλων θεραπείας, και τουλάχιστον μία φορά μεταξύ των θεραπειών σε επόμενους κύκλους. Θα πρέπει να χορηγείται η ίδια δόση για όλους τους κύκλους υπό την προϋπόθεση ότι δεν παρατηρούνται τοξικότητες βαθμού 3-4 και ότι ο ασθενής πληροί τα κριτήρια επανάληψης της θεραπείας. Ρυθμίσεις της δόσης κατά τη διάρκεια της θεραπείας Πριν την επανάληψη της θεραπείας, οι ασθενείς πρέπει να πληρούν τα κριτήρια αναφοράς που καθορίζονται παραπάνω. Εάν λαμβάνει χώρα οιοδήποτε από τα ακόλουθα συμβάματα οιαδήποτε στιγμή μεταξύ των κύκλων, η δόση πρέπει να μειώνεται ένα επίπεδο, σύμφωνα με τον πίνακα 1 παρακάτω,για τους επόμενους κύκλους: – Ουδετεροπενία <500/mm^3 που διαρκεί για περισσότερες από 5 ημέρες ή συνοδεύεται με πυρετό ή λοίμωξη – Θρομβοπενία <25.000/mm^3 – Αύξηση της χολερυθρίνης >ULN ή/και αλκαλική φωσφατάση >2,5 x ULN – Αύξηση στις αμινοτρανσφεράσες (AST ή ALT) >2,5 x ULN (μονοθεραπεία) ή >5 x ULN (θεραπεία συνδυασμού), η οποία δεν αποκαθίσταται έως την ημέρα 21 – Οιεσδήποτε άλλες ανεπιθύμητες αντιδράσεις βαθμού 3 ή 4 (όπως ναυτία, έμετος, κόπωση) Αφού μειωθεί η δόση εξαιτίας τοξικότητας, δεν προτείνεται αύξηση της δόσης στους επόμενους κύκλους. Εάν επανεμφανιστεί οιαδήποτε από αυτές τις τοξικότητες σε επόμενους κύκλους σε ασθενή ο οποίος παρουσιάζει κλινικό όφελος, η δόση μπορεί να μειωθεί περαιτέρω (βλέπε παρακάτω). Παράγοντες διέγερσης αποικιών μπορούν να χορηγούνται για αιματολογική τοξικότητα σύμφωνα με την τοπική συνήθη πρακτική. Πίνακας 1 Πίνακας τροποποίησης δόσεων για το Yondelis (ως μονός παράγοντας για STS ή σε συνδυασμό για καρκίνο των ωοθηκών) και PLD

	Σάρκωμα Μαλακών Μορίων	Καρκίνος Ωοθηκών	
	Yondellis	Yondelis	PLD
Εναρκτήρια δόση	1,5 mg/m^2	1,1 mg/m^2	30 mg/m^2
Πρώτη μείωση	1,2 mg/m^2	0,9 mg/m^2	25 mg/m^2
Δεύτερη μείωση	1 mg/m^2	0,75 mg/m^2	20 mg/m^2

Βλέπε την SPC της PLD για λεπτομερέστερες πληροφορίες για τις ρυθμίσεις δόσεων PLD. Στην περίπτωση όπου είναι απαραίτητες περαιτέρω μειώσεις της δόσης, θα πρέπει να εξετάζεται η διακοπή της θεραπείας. Διάρκεια της θεραπείας: Σε κλινικές δοκιμές, δεν υπήρχαν προκαθορισμένα όρια στον αριθμό των κύκλων που χορηγούνταν. Η θεραπεία συνεχίζονταν όσο διαρκούσε το κλινικό όφελος. Το Yondelis χορηγήθηκε για 6 ή περισσότερους κύκλους σε 29,5% και 52% των ασθενών που αντιμετωπίστηκαν θεραπευτικά με μονοθεραπεία και δόση συνδυασμού και το πρόγραμμα, αντίστοιχα. Τα σχήματα μονοθεραπείας και συνδυασμού χρησιμοποιήθηκαν για έως 38 και 21 κύκλους, αντίστοιχα. Δεν παρατηρήθηκαν σωρευτικές τοξικότητες σε ασθενείς που αντιμετωπίστηκαν με πολλαπλούς κύκλους. *Παιδιατρικός πληθυσμός:* Δεν έχει ακόμα τεκμηριωθεί η ασφάλεια και η αποτελεσματικότητα της τραβεκτεδίνης στον παιδιατρικό πληθυσμό. Δεν υπάρχουν διαθέσιμα στοιχεία. *Ηλικιωμένοι ασθενείς:* Δεν έχουν διεξαχθεί ειδικές μελέτες σε ηλικιωμένους ασθενείς. Συνολικά το 20% από τους 1164 ασθενείς στις ολοκληρωμένες αναλύσεις ασφαλείας κλινικών μελετών μονοθεραπείας ήταν άνω των 65 ετών. Από τους 333 ασθενείς με καρκίνο των ωοθηκών που έλαβαν τραβεκτεδίνη σε συνδυασμό με PLD, 24% ήταν ηλικίας 65 ετών ή μεγαλύτεροι και 6% ήταν άνω των 75 ετών. Δεν παρατηρήθηκαν σχετικές διαφορές στο προφίλ ασφαλείας σε αυτόν τον πληθυσμό ασθενών. Φαίνεται ότι η κάθαρση πλάσματος και ο όγκος κατανομής της τραβεκτεδίνης δεν επηρεάζεται από την ηλικία. Ως εκ τούτου, δεν συνιστώνται ρυθμίσεις των δόσεων με βάση αποκλειστικά τα ηλικιακά κριτήρια. *Ασθενείς με ηπατική δυσλειτουργία:* Δεν έχουν διεξαχθεί μελέτες με το προτεινόμενο σχήμα σε ασθενείς με ηπατική δυσλειτουργία. Έτσι, δεν διατίθενται δεδομένα ώστε να προταθεί μικρότερη εναρκτήρια δόση σε ασθενείς με ηπατική δυσλειτουργία. Ωστόσο, συνιστάται ιδιαίτερη προσοχή και μπορεί να απαιτούνται ρυθμίσεις της δόσης σε αυτούς τους ασθενείς καθώς αυξάνεται πιθανά η συστηματική έκθεση και μπορεί να αυξάνεται ο κίνδυνος ηπατοτοξικότητας. Οι ασθενείς με αυξημένη χολερυθρίνη δεν πρέπει να αντιμετωπίζονται θεραπευτικά με Yondelis (βλ. παράγραφο 4.4). *Ασθενείς με νεφρική δυσλειτουργία:* Δεν έχουν διεξαχθεί μελέτες οι οποίες να περιλαμβάνουν ασθενείς με νεφρική ανεπάρκεια (κάθαρση κρεατινίνης <30 ml/λεπτό για τη μονοθεραπεία, και <60 ml/λεπτό για το σχήμα συνδυασμού) και ως εκ τούτου το Yondelis δεν πρέπει να χρησιμοποιείται σε αυτόν τον πληθυσμό ασθενών (βλ. παράγραφο 4.4). Δεδομένων των φαρμακοκινητικών χαρακτηριστικών της τραβεκτεδίνης, δεν υπάρχει εγγύηση για ρυθμίσεις δόσεων σε ασθενείς με ήπια ή μέτρια νεφρική δυσλειτουργία. Μέθοδος χορήγησης: Συνιστάται ένθερμα η χορήγηση μέσω κεντρικής φλεβικής γραμμής. Για οδηγίες αναφορικά με την ανασύσταση και την αραίωση του φαρμακευτικού προϊόντος πριν τη χορήγηση, βλ. παράγραφο 6.6. **4.3 Αντενδείξεις:** – Υπερευαισθησία στην τραβεκτεδίνη ή σε κάποιο από τα έκδοχα – Υφιστάμενη σοβαρή ή μη ελεγχόμενη λοίμωξη – Γαλουχία (βλ. παράγραφο 4.6) – Συνδυασμός με εμβόλιο κίτρινου πυρετού (βλ. παράγραφο 4.4) **4.4 Ειδικές προειδοποιήσεις και προφυλάξεις κατά τη χρήση:** Ηπατική δυσλειτουργία: Οι ασθενείς θα πρέπει να πληρούν ειδικά κριτήρια ως προς τις παραμέτρους της ηπατικής λειτουργίας για να αρχίσουν θεραπεία με Yondelis. Καθώς πιθανώς αυξάνεται η συστηματική έκθεση στην τραβεκτεδίνη λόγω ηπατικής δυσλειτουργίας και επομένως μπορεί να αυξηθεί ο κίνδυνος ηπατοτοξικότητας, οι ασθενείς με κλινικά σχετικές ηπατικές νόσους, όπως ενεργή χρόνια ηπατίτιδα, πρέπει να παρακολουθούνται στενά και να ρυθμίζεται η δόση, εφόσον απαιτείται. Οι ασθενείς με αυξημένη χολερυθρίνη δεν πρέπει να υποβάλλονται σε θεραπεία με τραβεκτεδίνη (βλ. παράγραφο 4.2). Νεφρική δυσλειτουργία: Η κάθαρση κρεατινίνης πρέπει να παρακολουθείται πριν και κατά τη διάρκεια της θεραπείας. Τα σχήματα μονοθεραπείας και συνδυασμού με Yondelis δεν πρέπει να χρησιμοποιούνται σε ασθενείς με κάθαρση κρεατινίνης <30 ml/λεπτό και <60 ml/λεπτό αντίστοιχα (βλ. παράγραφο 4.2). Ουδετεροπενία και θρομβοπενία: Έχουν αναφερθεί πολύ συχνά βαθμού 3 ή 4 ουδετεροπενία και θρομβοπενία που σχετίζονται με τη θεραπεία με Yondelis. Θα πρέπει να διεξάγεται πλήρες αιμοδιάγραμμα συμπεριλαμβανομένου διαφορικού και μέτρηση αριθμού αιμοπεταλίων πριν την έναρξη, εβδομαδιαίως για τους πρώτους δύο κύκλους και στη συνέχεια μία φορά μεταξύ των κύκλων (βλ. παράγραφο 4.2). Οι ασθενείς οι οποίοι εμφανίζουν πυρετό θα πρέπει να αναζητήσουν έγκαιρα ιατρική φροντίδα. Εάν παρατηρηθεί αυτό, θα πρέπει να ξεκινήσει άμεσα υποστηρικτική θεραπεία. Το Yondelis δεν πρέπει να χορηγείται σε ασθενείς με αριθμό ουδετεροφίλων αναφοράς μικρότερο από 1.500 κύτταρα/mm^3 και αριθμό αιμοπεταλίων μικρότερο από 100.000 κύτταρα/mm^3. Εάν παρατηρηθεί σοβαρή ουδετεροπενία (ANC <500 κύτταρα/mm^3) που διαρκεί περισσότερες από 5 ημέρες ή συνοδεύεται με την εμφάνιση πυρετού ή λοίμωξης, συστήνεται η μείωση των δόσεων (βλέπε ενότητα 4.2). Ναυτία και έμετος: Πρέπει να χορηγείται αντιεμετική προφύλαξη με κορτικοστεροειδή όπως δεξαμεθαζόνη σε όλους τους ασθενείς (βλ. παράγραφο 4.2). Ραβδομυόλυση και σοβαρές αυξήσεις της CPK (>5 x ULN): Δεν πρέπει να χρησιμοποιείται τραβεκτεδίνη σε ασθενείς με CPK >2,5 x ULN (βλ. παράγραφο 4.2). Έχει αναφερθεί όχι συχνά ραβδομυόλυση, συνήθως σε συνδυασμό με μυελοτοξικότητα, σοβαρές μη φυσιολογικές δοκιμασίες ηπατικής λειτουργίας ή/και νεφρική ή πολυοργανική ανεπάρκεια. Επομένως, θα πρέπει να παρακολουθείται στενά η CPK όποτε ένας ασθενής μπορεί να παρουσιάζει οιαδήποτε από αυτές τις τοξικότητες ή μυϊκή αδυναμία ή μυϊκό πόνο. Εάν λάβει χώρα ραβδομυόλυση, θα πρέπει να εφαρμοστούν έγκαιρα υποστηρικτικά μέτρα όπως παρεντερική ενυδάτωση, αλκαλοποίηση των ούρων και αιμοδιύλιση, όπως ενδείκνυται. Η θεραπεία με Yondelis θα πρέπει να διακοπεί μέχρι την πλήρη ανάρρωση του ασθενή. Θα πρέπει να ληφθούν προφυλάξεις εάν χορηγούνται ταυτόχρονα με τραβεκτεδίνη φαρμακευτικά προϊόντα που σχετίζονται με ραβδομυόλυση (π.χ., στατίνες), επειδή μπορεί να αυξηθεί ο κίνδυνος ραβδομυόλυσης. Μη φυσιολογικές Δοκιμασίες Ηπατικής Λειτουργίας (LFT): Έχουν αναφερθεί στους περισσότερους ασθενείς αναστρέψιμες οξείες αυξήσεις της ασπαρτικής αμινοτρανσφεράσης (AST) και της αμινοτρανσφεράσης της αλανίνης (ALT). Το Yondelis δεν πρέπει να χρησιμοποιείται σε ασθενείς με αυξημένη χολερυθρίνη. Οι ασθενείς με αυξήσεις της AST, ALT και αλκαλικής φωσφατάσης μεταξύ των κύκλων μπορεί να απαιτούν μείωση της δόσης (βλ. παράγραφο 4.2). Αντιδράσεις της θέσης ένεσης: Συνιστάται εντόνως η χρήση κεντρικής φλεβικής πρόσβασης (βλ. παράγραφο 4.2). Οι ασθενείς μπορεί να αναπτύξουν δυνητικώς σοβαρή αντίδραση της θέσης ένεσης όταν η τραβεκτεδίνη χορηγείται μέσω περιφερικής φλεβικής γραμμής. Η εξαγγείωση της τραβεκτεδίνης μπορεί να προκαλέσει νέκρωση των ιστών, η οποία απαιτεί χειρουργικό καθαρισμό. Δεν υπάρχει συγκεκριμένο αντίδοτο για την εξαγγείωση της τραβεκτεδίνης. Η εξαγγείωση πρέπει να αντιμετωπίζεται με την συνήθη τοπική πρακτική. Άλλες: Η συγχορήγηση Yondelis με ισχυρούς αναστολείς του ενζύμου CYP3A4 θα πρέπει να αποφεύγεται (βλ. παράγραφο 4.5). Εάν αυτό δεν είναι δυνατό, απαιτείται προσεκτική παρακολούθηση της τοξικότητας και θα πρέπει να εξετάζεται η μείωση της δόσης τραβεκτεδίνης. Θα πρέπει να λαμβάνονται προφυλάξεις εάν χορηγούνται φαρμακευτικά προϊόντα που σχετίζονται με ηπατοτοξικότητα μαζί με τραβεκτεδίνη, επειδή ο κίνδυνος ηπατοτοξικότητας μπορεί να αυξηθεί. Η ταυτόχρονη χρήση τραβεκτεδίνης με φαινυτοΐνη μπορεί να μειώσει την απορρόφηση της φαινυτοΐνης, οδηγώντας σε παρόξυνση των σπασμών. Δεν συνιστάται ο συνδυασμός τραβεκτεδίνης με φαινυτοΐνη ή εμβόλια εξασθενημένων ζώντων ιών και αντενδείκνυται ρητά με το εμβόλιο για τον κίτρινο πυρετό (βλ. παράγραφο 4.3). Η ταυτόχρονη χρήση τραβεκτεδίνης με αλκοόλ πρέπει να αποφεύγεται (βλ. παράγραφο 4.5). Οι άνδρες σε γόνιμη ηλικία και οι γυναίκες σε αναπαραγωγική ηλικία πρέπει να χρησιμοποιούν αποτελεσματική αντισύλληψη κατά τη διάρκεια της θεραπείας και 3 μήνες μετά για τις γυναίκες και να πληροφορήσουν άμεσα τον θεράποντα ιατρό εάν σημειωθεί εγκυμοσύνη, και 5 μήνες μετά τη θεραπεία για τους άνδρες (βλ. παράγραφο 4.6). Το φάρμακο αυτό περιέχει κάλιο, λιγότερο από 1 mmol (39 mg) ανά φιαλίδιο, δηλ., είναι ουσιαστικά " ελεύθερο καλίου". Βλέπε επίσης Περίληψη Χαρακτηριστικών του Προϊόντος της PLD για περισσότερες λεπτομερείς πληροφορίες για προειδοποιήσεις και προφυλάξεις. **4.5 Αλληλεπιδράσεις με άλλα φαρμακευτικά προϊόντα και άλλες μορφές αλληλεπίδρασης:** Επιδράσεις άλλων ουσιών στην τραβεκτεδίνη: Δεν έχουν διεξαχθεί *in vivo* μελέτες αλληλεπίδρασης. Επειδή η τραβεκτεδίνη μεταβολίζεται κυρίως από το CYP3A4, η συγχορήγηση ουσιών που αναστέλλουν αυτό το ισοένζυμο π.χ., κετοκοναζόλη, φλουκοναζόλη, ριτοναβίρη, κλαριθρομυκίνη ή απρεπιτάντη μπορούν να μειώσουν τον μεταβολισμό και να αυξήσουν τις συγκεντρώσεις τραβεκτεδίνης. Εάν απαιτούνται τέτοιοι συνδυασμοί, απαιτείται στενή παρακολούθηση των τοξικοτήτων (βλ. παράγραφο 4.4). Παρομοίως, η συγχορήγηση με ισχυρούς επαγωγείς του ενζύμου αυτού (π.χ., ριφαμπικίνη, φαινοβαρβιτάλη, Saint John's Wort) μπορεί να μειώσει τη συστηματική έκθεση στην τραβεκτεδίνη. Η κατανάλωση αλκοόλ πρέπει να αποφεύγεται κατά τη διάρκεια της θεραπείας με τραβεκτεδίνη λόγω ηπατοτοξικότητας του φαρμακευτικού προϊόντος (βλ. παράγραφο 4.4). Τα προκλινικά δεδομένα έδειξαν ότι η τραβεκτεδίνη είναι υπόστρωμα στο P-gp. Η ταυτόχρονη χορήγηση αναστολέων του P-gp, π.χ., κυκλοσπορίνη και βεραπαμίλη, μπορεί να μεταβάλει την κατανομή και/ή την απομάκρυνση της τραβεκτεδίνης. Η σημασία αυτής της αλληλεπίδρασης, για παράδειγμα η τοξικότητα του ΚΝΣ, δεν έχει τεκμηριωθεί. Θα πρέπει να δίνεται προσοχή σε τέτοιες περιπτώσεις. **4.6 Γονιμότητα, κύηση και γαλουχία:** Κύηση: Δεν διατίθενται επαρκή κλινικά δεδομένα σχετικά με έκθεση κατά την εγκυμοσύνη.Ωστόσο, με βάση τον γνωστό μηχανισμό δράσης της, η τραβεκτεδίνη μπορεί να προκαλέσει σοβαρές γεννητικές ανωμαλίες όταν χορηγείται κατά τη διάρκεια της εγκυμοσύνης. Η τραβεκτεδίνη δεν πρέπει να χρησιμοποιείται κατά τη διάρκεια της εγκυμοσύνης εκτός εάν είναι σαφώς απαραίτητο. Εάν χρησιμοποιηθεί κατά τη διάρκεια της εγκυμοσύνης, ο ασθενής θα πρέπει να ενημερωθεί για τον πιθανό κίνδυνο για το έμβρυο και να παρακολουθείται προσεκτικά. Εάν χρησιμοποιείται τραβεκτεδίνη στο τέλος της εγκυμοσύνης, οι πιθανές ανεπιθύμητες ενέργειες θα πρέπει να παρακολουθούνται στενά στα νεογέννητα. Θηλασμός: Δεν είναι γνωστό εάν η τραβεκτεδίνη απεκκρίνεται στο μητρικό γάλα. Η απέκκριση τραβεκτεδίνης στο γάλα δεν έχει μελετηθεί σε ζώα. Ο θηλασμός αντενδείκνυται κατά τη διάρκεια της θεραπείας και 3 μήνες μετά (βλ. παράγραφο 4.3). Γονιμότητα: Οι άνδρες σε γόνιμη ηλικία και οι γυναίκες σε αναπαραγωγική ηλικία πρέπει να χρησιμοποιούν αποτελεσματική αντισύλληψη κατά τη διάρκεια της θεραπείας και 3 μήνες μετά για τις γυναίκες και να πληροφορήσουν άμεσα τον θεράποντα ιατρό εάν σημειωθεί εγκυμοσύνη και 5 μήνες μετά τη θεραπεία για τους άνδρες (βλ. παράγραφο 4.4). Η τραβεκτεδίνη μπορεί να έχει γονοτοξικές επιδράσεις. Θα πρέπει να αναζητηθούν συμβουλές για τη διατήρηση του σπέρματος προ της θεραπείας, λόγω της πιθανότητας μη αναστρέψιμης στειρότητας εξαιτίας της θεραπείας με Yondelis. Εάν σημειωθεί εγκυμοσύνη κατά τη διάρκεια της θεραπείας, θα πρέπει να εξεταστεί η πιθανότητα γενετικής καθοδήγησης. Συνιστάται επίσης γενετική καθοδήγηση για ασθενείς που επιθυμούν να αποκτήσουν παιδιά μετά τη θεραπεία. **4.7 Επιδράσεις στην ικανότητα οδήγησης και χειρισμού μηχανών:** Δεν πραγματοποιήθηκαν μελέτες σχετικά με τις επιδράσεις στην ικανότητα οδήγησης και χειρισμού μηχανών. Ωστόσο, έχουν αναφερθεί κόπωση και/ή εξασθένιση σε ασθενείς που λάμβαναν τραβεκτεδίνη. Οι ασθενείς οι οποίοι παρουσιάζουν οιοδήποτε από αυτά τα συμβάματα κατά τη διάρκεια της θεραπείας δεν πρέπει να οδηγούν ή να χειρίζονται μηχανές. **4.8 Ανεπιθύμητες ενέργειες:** Εκτός εάν ορίζεται διαφορετικά, το ακόλουθο προφίλ ασφάλειας του Yondelis βασίζεται στην αξιολόγηση σε κλινικές δοκιμές σε ασθενείς οι οποίοι υποβλήθηκαν σε θεραπεία με τα συνιστώμενα θεραπευτικά σχήματα και για τις δύο ενδείξεις. Οι περισσότεροι ασθενείς στους οποίους χορηγήθηκε Yondelis αναμένεται να έχουν ανεπιθύμητες ενέργειες οιουδήποτε βαθμού (91% σε μονοθεραπεία και 99% σε θεραπεία συνδυασμού) και λιγότερο από ένα τρίτο σοβαρές ανεπιθύμητες ενέργειες βαρύτητας βαθμού 3 ή 4 (10% σε μονοθεραπεία και 25% σε θεραπεία συνδυασμού). Οι πιο συχνές ανεπιθύμητες αντιδράσεις οιουδήποτε βαθμού βαρύτητας ήταν ουδετεροπενία, ναυτία, έμετος, αυξήσεις σε AST/ALT, αναιμία κόπωση, θρομβοκυτταροπενία, ανορεξία και διάρροια. Θανατηφόρες ανεπιθύμητες ενέργειες παρατηρήθηκαν στο 1,9% και 0,9% των ασθενών στους οποίους χορηγήθηκαν σχήματα μονοθεραπείας και συνδυασμού, αντίστοιχα. Ήταν συχνά αποτέλεσμα ενός συνδυασμού συμβαμάτων όπως πανκυτταροπενία, εμπύρετη ουδετεροπενία, ορισμένα από αυτά με σηψαιμία, ηπατική προσβολή, νεφρική ή πολυοργανική ανεπάρκεια και ραβδομυόλυση. Ανεπιθύμητες αντιδράσεις Οι συχνότητες των ανεπιθύμητων αντιδράσεων που αναφέρονται παρακάτω ταξινομούνται ως πολύ συχνές (≥1/10), συχνές (≥1/100, έως <1/10) και όχι συχνές (≥1/1000, <1/100). Ο παρακάτω πίνακας παρουσιάζει τις ανεπιθύμητες αντιδράσεις που αναφέρθηκαν σε ≥ 1% των ασθενών οι οποίοι αντιμετωπίστηκαν θεραπευτικά με το συνιστώμενο σχήμα για σάρκωμα μαλακών μορίων (1,5 mg/m^2, 24ωρη έγχυση κάθε 3 εβδομάδες) σύμφωνα με την τυποποιημένη κατηγορία/οργανικό σύστημα του MedDRA. Έχουν χρησιμοποιηθεί τόσο ανεπιθύμητες ενέργειες όσο και εργαστηριακές τιμές για παροχή συχνοτήτων. Εντός κάθε κατηγορίας συχνότητας εμφάνισης, οι ανεπιθύμητες ενέργειες παρατίθενται κατά φθίνουσα σειρά σοβαρότητας.

Κατηγορία/οργανικό σύστημα	Ανεπιθύμητες ενέργειες που αναφέρθηκαν σε ≥1% ασθενών σε κλινικές δοκιμές στο συνιστώμενο θεραπευτικό σχήμα [1,5 mg/m^2, 24ωρη έγχυση κάθε 3 εβδομάδες]
Παρακλινικές εξετάσεις	**Πολύ συχνές:** Αυξημένη κρεατινοφωσφοκινάση αίματος* (Βαθμός 3-4=4%), αυξημένη κρεατινίνη αίματος*, μειωμένη λευκωματίνη αίματος* **Συχνές:** Μειωμένο σωματικό βάρος
Διαταραχές του αιμοποιητικού και του λεμφικού συστήματος	**Πολύ συχνές:** Ουδετεροπενία* (Βαθμός 3=26%, Βαθμός 4=24%), θρομβοπενία* (Βαθμός 3=11%, Βαθμός 4=2%), αναιμία* (Βαθμός 3=10%, Βαθμός 4=3%), λευκοπενία* **Συχνές:** Εμπύρετη ουδετεροπενία
Διαταραχές του νευρικού συστήματος	**Πολύ συχνές:** Κεφαλαλγία **Συχνές:** Περιφερική αισθητική νευροπάθεια, δυσγευσία, ζάλη, παραισθησία
Διαταραχές του αναπνευστικού συστήματος, του θώρακα και του μεσοθωράκιου	**Συχνές:** Δύσπνοια (Βαθμός 3-4=2%), βήχας
Διαταραχές του γαστρεντερικού	**Πολύ συχνές:** Έμετος (Βαθμός 3-4=6,5%), ναυτία (Βαθμός 3-4=6%), δυσκοιλιότητα (Βαθμός 3-4<1%) **Συχνές:** Διάρροια (Βαθμός 3-4<1%), στοματίτιτδα (Βαθμός 3-4<1%), κοιλιακό άλγος, δυσπεψία, άλγος άνω κοιλιακής χώρας
Διαταραχές του δέρματος και του υποδόριου ιστού	**Συχνές:** Αλωπεκία
Διαταραχές του μυοσκελετικού συστήματος και του συνδετικού ιστού	**Συχνές:** Μυαλγία, αρθραλγία, οσφυαλγία
Διαταραχές του μεταβολισμού και της θρέψης	**Πολύ συχνές:** Ανορεξία (Βαθμός 3-4 <1%) **Συχνές:** Αφυδάτωση, Μειωμένη όρεξη, Υποκαλιαιμία
Λοιμώξεις και παρασιτώσεις	**Συχνές:** Λοίμωξη
Αγγειακές διαταραχές	**Συχνές:** Υπόταση, Έξαψη
Γενικές διαταραχές και καταστάσεις της οδού χορήγησης	**Πολύ συχνές:** Κόπωση (Βαθμός 3-4=9%), Εξασθένιση (Βαθμός 3-4=1%) **Συχνές:** Πυρεξία, Οίδημα, Περιφερικό οίδημα, Αντίδραση της θέσης ένεσης
Διαταραχές του ήπατος και των χοληφόρων	**Πολύ συχνές:** Υπερχολερυθριναιμία* (Βαθμός 3=1%), Αυξημένη αμινοτρανσφεράση της αλανίνης* (Βαθμός 3=38%, Βαθμός 4=3%), αυξημένη ασπαρτική αμινοτρανσφεράση* (Βαθμός 3=44%, Βαθμός 4=7%), αυξημένη αλκαλική φωσφατάση αίματος*, αυξημένη γ-γλουταμυλτρανσφεράση*
Ψυχιατρικές διαταραχές	**Συχνές:** Αϋπνία

*Εξάγεται από εργαστηριακά δεδομένα

Ο πίνακας παρακάτω παρέχει τη συχνότητα και τη βαρύτητα των ανεπιθύμητων αποτελεσμάτων που θεωρούνται δυνητικά σχετιζόμενα με το φάρμακο της μελέτης και αναφέρονται σε ≥5% των ασθενών με καρκίνο των ωοθηκών που τυχαιοποιούνται ώστε να λάβουν Yondelis 1,1 mg/ m^2/PLD 30 mg/m^2 ή PLD 50 mg/m^2 στη μελέτη ET743-OVA-301. Χρησιμοποιήθηκαν τόσο ανεπιθύμητες ενέργειες όσο και εργαστηριακές τιμές. Εντός κάθε ομαδοποίησης συχνότητας, τα ανεπιθύμητα αποτελέσματα παρουσιάζονται κατά σειρά μειωμένης βαρύτητας.

Ανεπιθύμητες ενέργειες που αναφέρθηκαν σε ≥5% των ασθενών στην κλινική μελέτη ET743-OVA-301

Κατηγορία /Οργανικό σύστημα	Συχνότητα	Σύμβαμα	Yondelis+PLD n=333 Όλοι οι Βαθμοί (%)	Yondelis+PLD n=333 Βαθμός 3 (%)	Yondelis+PLD n=333 Βαθμός 4 (%)	PLD n=330 Όλοι οι Βαθμοί (%)	PLD n=330 Βαθμός 3 (%)	PLD n=330 Βαθμός 4 (%)
Παρακλινικές εξετάσεις	Συχνά	Αυξημένη κρεατινική φωσφοκινάση αίματος*	22.0	0.9	0.9	13.7		
Διαταραχές του αιμοποιητικού και του λεμφικού συστήματος	Πολύ συχνά	Ουδετερπενία*	91.6	29.7	42.3	73.5	19.7	9.8
		Λευκοπενία*	94.9	44.7	17.7	81.8	16.0	4.0
		Αναιμία*	94.9	12.9	5.7	82.1	6.2	2.2
		Θρομβοκυτταροπενία*	63.7	12.3	10.8	27.4	2.5	1.8
	Συχνά	Εμπύρετη Ουδετεροπενία*	6.9	4.5	2.4	2.1	1.8	0.3
Διαταραχές του νευρικού συστήματος	Συχνά	Κεφαλαλγία	6.6	0.3		2.4		
		Δυσγευσία	5.4	0.3		2.7		
Διαταραχές του αναπνευστικού συστήματος, του θώρακος και του μεσοθωράκιου	Συχνά	Δύσπνοια	6.6	0.3		3.3	0.3	0.3
Διαταραχές του γαστρεντερικού	Πολύ συχνά	Ναυτία	70.9	8.7		37.6	2.4	
		Έμετος	51.7	9.9	0.3	23.9	2.1	
		Δυσκοιλιότητα	20.4	0.9		15.5	0.3	
		Στοματίτιτδα	19.2	0.9		31.2	4.8	0.3
		Διάρροια	17.1	2.1		10	1.2	
	Συχνά	Κοιλιακό άλγος	9.3	0.6		7	0.9	
		Δυσπεψία	7.5	0.3		6.1	0.6	
Διαταραχές του δέρματος και του υποδόριου ιστού	Πολύ συχνά	Σύνδρομο παλαμοπελματιαίας ερυθροδυσαισθησίας	24	3.9		53.6	18.5	1.2
		Αλωπεκία	12			13.3	0.3	
	Συχνά	Εξάνθημα	8.1			16.1	0.9	
		Υπέρχρωση δέρματος	5.4			7		
Διαταραχέ του μεταβολισμού και της θρέψης	Πολύ συχνά	Ανορεξία	28.8	2.1		20	1.5	
	Συχνά	Υποκαλιαιμία	6.3	2.1		2.1		
Γενικές διαταραχές και καταστάσεις της οδού χορήγησης	Πολύ συχνά	Κόπωση	42.3	5.7	0.3	29.7	2.4	0.3
		Εξασθένιση	15.3	1.2		9.1	0.3	
		Φλεγμονή βλεννογόνου	11.4	2.1		18.8	5.8	
		Πυρεξία	10.2	0.9		4.5	0.3	
Διαταραχές του ήπατος και των χοληφόρων	Πολύ συχνά	Υπερχολερυθριναιμία*	(25.2)	(0.3)		(12.9)	(0.3)	
		Αυξημένη αλανινική αμινοτρανσφεράση*	96.1	45.6	4.5	36.0	2.2	
		Αυξημένη ασπαρτική αμινοτρανσφεράση*	89.5	12.0	1.8	42.6	1.2	0.3
		Αυξημένη αλκαλική φωσφατάση αίματος*	61.3	1.5		41.8	1.2	

*Εξάγεται από εργαστηριακά δεδομένα

Οι ακόλουθες αντιδράσεις αναφέρθηκαν με συχνότητα κάτω από 5% στην ομάδα συνδυασμού, αλλά περιλαμβάνονται εδώ για την κλινική σχέση τους: ουδετεροπενική λοίμωξη (<1%), ουδετεροπενική σηψαιμία (<1%), πανκυτταροπενία(1,8%), ανεπάρκεια μυελού των οστών (1,5%), κοκκιοκυτταροπενία (1,5%), αφυδάτωση, αϋπνία, περιφερική αισθητική νευροπάθεια, συγκοπή, αριστερή κοιλιακή δυσλειτουργία (<1%), πνευμονική εμβολή (1,2%), πνευμονικό οίδημα (<1%), βήχας, ηπατοτοξικότητα (<1%), αυξημένη γάμμα γλουταμυλική τρανσφεράση, αυξημένη συζευγμένη χολερυθρίνη, μυοσκελετικό άλγος, μυαλγία, αυξημένη κρεατινίνη αίματος, οίδημα/περιφερικό οίδημα, αντιδράσεις στο σημείο καθετηριασμού. Στην ομάδα του Yondelis + PLD, οι μη λευκοί (κυρίως ασιάτες) ασθενείς είχαν υψηλότερη συχνότητα εμφάνισης σε σχέση με τους λευκούς ασθενείς σε ανεπιθύμητες ενέργειες βαθμού 3 ή 4 (96% *έναντι* 87%), και σοβαρές ανεπιθύμητες αντιδράσεις (44% *έναντι* 23% όλων των βαθμών). Οι διαφορές που παρατηρήθηκαν κυρίως σε σχέση με την ουδετεροπενία (93% *έναντι* 66%), αναιμία (37% *έναντι* 14%) και θρομβοκυτταροπενία (41% *έναντι* 19%). Ωστόσο, οι συχνότητες εμφάνισης κλινικών επιπλοκών που σχετίζονται με αιματολογική τοξικότητα όπως σοβαρές λοιμώξεις ή αιμορραγία, ή εκείνες που οδηγούν στον θάνατο ή στον τερματισμό της θεραπείας, ήταν παρόμοιες και στους δύο υποπληθυσμούς. Συχνότερες ανεπιθύμητες αντιδράσεις: *Διαταραχές του αιμοποιητικού και του λεμφικού συστήματος: Ουδετεροπενία:* Η ουδετεροπενία είναι η πιο συχνή αιματολογική τοξικότητα. Ακολούθησε προβλέψιμη μορφή ταχείας εμφάνισης και αναστρεψιμότητας, και σπάνια συνδυάστηκε με πυρετό ή λοίμωξη. Οι κατώτερες τιμές ουδετεροφίλων παρουσιάστηκαν σε διάμεσο 15 ημερών καιαποκαταστάθηκαν εντός μίας εβδομάδας. Η ανάλυση ανά κύκλο που διεξήχθηκε σε ασθενείς στους οποίους χορηγήθηκε σχήμα μονοθεραπείας κατέδειξε ουδετεροπενία βαθμού 3 και 4 περίπου σε 19% και 8% των κύκλων αντίστοιχα. Σε αυτόν τον πληθυσμό εμπύρετη ουδετεροπενία παρουσιάστηκε στο 2% των ασθενών και σε <1% των κύκλων. *Θρομβοκυτταροπενία:* Συμβάματα αιμορραγίας που σχετίζονταν με θρομβοκυτταροπενία εμφανίστηκαν σε <1% των ασθενών στους οποίους χορηγήθηκε σχήμα μονοθεραπείας. Η ανάλυση ανά κύκλο που διεξήχθηκε σε αυτούς τους ασθενείς κατέδειξε ότι παρουσιάστηκε θρομβοπενία βαθμού 3 και 4 περίπου σε 3% και <1% των κύκλων αντίστοιχα. *Αναιμία:* Αναιμία παρουσιάστηκε σε 93% και 94% των ασθενών στους οποίους χορηγήθηκε σχήμα μονοθεραπείας και συνδυασμού, αντίστοιχα.Τα ποσοστά των ασθενών με αναιμία κατά την αναφορά ήταν 46% και 35%, αντίστοιχα. Η ανάλυση ανά κύκλο που διεξήχθηκε στους ασθενείς στους οποίους χορηγήθηκε σχήμα μονοθεραπείας κατέδειξε ότι παρουσιάστηκε αναιμία βαθμού 3 και 4 περίπου σε 3% και 1% των κύκλων αντίστοιχα. *Διαταραχές του ήπατος και των χοληφόρων: Αυξήσεις των AST/ALT:* Παρατηρήθηκαν παροδικές αυξήσεις της ασπαρτικής αμινοτρανσφεράσης (AST) και της αμινοτρανσφεράσης της αλανίνης (ALT) βαθμού 3 σε 38% και 44% των ασθενών και αυξήσεις βαθμού 4 σε 3% και 7% των ασθενών αντίστοιχα. Ο διάμεσος χρόνος για την επίτευξη των μέγιστων τιμών ήταν 5 ημέρες τόσο για την AST όσο και για την ALT. Οι περισσότερες τιμές μειώθηκαν σε βαθμό1 ή υποχώρησαν έως την ημέρα 14-15 (βλ. παράγραφο 4.4). Η ανάλυση ανά κύκλο που διεξήχθηκε σε ασθενείς στους οποίους χορηγήθηκε σχήμα μονοθεραπείας κατέδειξε αυξήσεις βαθμού 3 των AST και ALT σε 12% και 20% των κύκλων αντίστοιχα. Παρατηρήθηκαν αυξήσεις βαθμού 4 των AST και ALT σε 1% και 2% των κύκλων αντίστοιχα. Οι περισσότερες αυξήσεις τρανσαμινασών βελτιώθηκαν σε βαθμό 1 ή στα επίπεδα προ της επανάληψης της θεραπείας εντός 15 ημερών, και λιγότερο από 2% των κύκλων είχαν χρόνους επανόρθωσης μεγαλύτερους των 25 ημερών. Οι αυξήσεις των ALT και AST δεν ακολούθησαν αθροιστική μορφή αλλά επέδειξαν τάση λιγότερο σοβαρών αυξήσεων κατά τη διάρκεια του χρόνου. *Υπερχολερυθριναιμία:* Η χολερυθρίνη έφτασε στη μέγιστη τιμή μία εβδομάδα μετά την εκδήλωση και υποχώρησε περίπου δύο εβδομάδες μετά την εκδήλωση. Οι εξετάσεις ηπατικής λειτουργίας διέγνωσαν σοβαρή τοξικότητα (ικανοποιεί τον νόμο του Hy) και οι κλινικές εκδηλώσεις σοβαρής ηπατικής βλάβης ήταν όχι συχνές με μικρότερη από1% συχνότητα εμφάνισης μεμονωμένων ενδείξεων και συμπτωμάτων περιλαμβανομένων ίκτερου, ηπατομεγαλίας ή ηπατικού άλγους. Παρουσιάστηκε θνησιμότητα σε παρουσία ηπατικής βλάβης σε λιγότερο από 1% των ασθενών και στα δύο σχήματα. Άλλες ανεπιθύμητες αντιδράσεις: *Αυξήσεις CPK και ραβδομυόλυση:* Αυξήσεις CPK οιουδήποτε βαθμού παρατηρήθηκαν σε 23-26% των ασθενών και στα δύο σχήματα. Αυξήσεις της CPK σε συνδυασμό με ραβδομυόλυση αναφέρθηκαν σε λιγότερο από 1% των ασθενών. *Αλωπεκία:* Αναφέρθηκε αλωπεκία σε περίπου 3% των ασθενών στους οποίους χορηγήθηκε σχήμα μονοθεραπείας, από τους οποίους η πλειοψηφία είχε αλωπεκία βαθμού 1. Εμπειρία μετά την κυκλοφορία του προϊόντος Κατά την επιτήρηση μετά την κυκλοφορία του προϊόντος έχουν αναφερθεί λίγες περιπτώσεις εξαγγείωσης της τραβεκτεδίνης με επακόλουθη *νέκρωση ιστών*, η οποία απαιτεί χειρουργικό καθαρισμό (βλ. ενότητα 4.4). **4.9 Υπερδοσολογία:** Υπάρχουν περιορισμένα δεδομένα για τις επιδράσεις της υπερδοσολογίας με τραβεκτεδίνη. Οι κύριες αναμενόμενες τοξικότητες είναι γαστρεντερικές, καταστολή του μυελού των οστών και ηπατική τοξικότητα. Δεν υπάρχει συγκεκριμένο αντίδοτο διαθέσιμο για την τραβεκτεδίνη. Σε περίπτωση υπερδοσολογίας, οι ασθενείς θα πρέπει να παρακολουθούνται στενά και θα πρέπει να ξεκινούν συμπτωματικά μέτρα υποστηρικτικής φροντίδας, όπως απαιτείται. **7. ΚΑΤΟΧΟΣ ΤΗΣ ΑΔΕΙΑΣ ΚΥΚΛΟΦΟΡΙΑΣ:** Pharma Mar, S.A. Avda. de los Reyes 1, Poligono Industrial La Mina 28770 Colmenar Viejo (Madrid) Ισπανία **8. ΑΡΙΘΜΟΣ(ΟΙ) ΑΔΕΙΑΣ ΚΥΚΛΟΦΟΡΙΑΣ:** EU/1/07/417/001, EU/1/07/417/002. **9. ΗΜΕΡΟΜΗΝΙΑ ΠΡΩΤΗΣ ΕΓΚΡΙΣΗΣ/ ΑΝΑΝΕΩΣΗΣ ΤΗΣ ΑΔΕΙΑΣ:** Ημερομηνία πρώτης έγκρισης: 17 Σεπτεμβρίου 2007. Ημερομηνία τελευταίας ανανέωσης της άδειας: **10. ΗΜΕΡΟΜΗΝΙΑ ΑΝΑΘΕΩΡΗΣΗΣ ΤΟΥ ΚΕΙΜΕΝΟΥ:** 01/2012. Λεπτομερή πληροφοριακά στοιχεία για το παρόν φαρμακευτικό προϊόν είναι διαθέσιμα στον δικτυακό τόπο του Ευρωπαϊκού Οργανισμού Φαρμάκων: http://www.ema.europa.eu.

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Different facets of the same problem

Editorial

Vassilios Barbounis

In recent years, we experience various contradictions within the oncological community. On one extreme there is a plethora of new drugs for a number of malignancies, combined with a profusion of new information which gives hope for favourable outcomes in the fight against cancer.

On the other extreme, however, on both sides of the Atlantic, many cancer patients are deprived of basic oncological drugs while novel molecules are out of reach.

There is a paradox here: many inexpensive but essential drugs are not produced because they are not profitable enough; equally essential but highly priced drugs are not reimbursed due to financial constraints of the health systems, or because the drug cost exceeds the approved cost of a life-year-gained.

The result is the same in both cases, unmet basic medical needs. The same economic model produces different health policies, and different end results; moreover, although opposite pathways are used similar outcomes are evolved: an unacceptable shortage in drugs of huge significance.

Likewise, the development of increasingly expensive pharmaceutical agents leads in a vicious circle that exhausts health systems endurances and results in shortage of essential therapeutic agents. S. Retsas, an experienced medical oncologist, in his article (Retsas S. Cancer care in the face of predatory capitalism. FCO 2012; 1:9-10) depicts some of the most repulsive aspects of liberal economy in a clear and eloquent manner.

Under the current perspective, systems based on the ideas of a modern mercantilism may nowadays seem absolutely necessary.

Cancer care in the face of predatory capitalism

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Key words: cancer; oncology; drug shortages; health care.

We live in an extraordinary era of antinomies and confused societal values. In our time, biologists and geneticists unravel within a decade the mysteries of diseases that have eluded human understanding for millennia. Therapeutic innovation now emerges with lightning speed, unimaginable in our student years -yet such innovations prove unaffordable even to wealthy members of the richest societies from which they emanate. What is the purpose of medical progress if these advances become increasingly inaccessible to the many?

In an article recently published in the *New England Journal of Medicine* entitled "The shortage of essential chemotherapy drugs in the United States", Gatesman and Smith discuss a problem which is now causing serious concerns about safety, cost, and availability of life-saving anti-cancer treatments [1]. Drugs, mainly generic, that have been successfully used for decades in the treatment of paediatric and adult malignancies such as vincristine, methotrexate, doxorubicin, paclitaxel and others, are now in short supply.

In a surprisingly frank analysis of this problem, Gatesman and Smith argue that the main cause of these drug shortages is economic. According to these authors, if drug manufacturers do not make enough profit they will not make drugs [1]. Generic drugs for which manufacturers no longer hold a patent are considerably less expensive than brands for which a pharmaceutical company retains the exclusive right of production. For example, the initial cost of a vial of carboplatin at $125 has now been reduced to $3.5. Another example highlighted by these authors is the generic, solvent-bound paclitaxel at a cost of $312 and the newly branded, protein-bound version of paclitaxel, Abraxane at a cost of $5,824. In the formulation used for Abraxane, the paclitaxel molecule is linked to albumin thus reducing the risk of anaphylaxis associated with the cremophor solvent used in the original drug. This advantage and ease of administration would be welcomed by oncologists and their patients, essentially however, the anti-tumour activity and toxicity profiles of the two versions are largely equivalent [2, 3].

The problem is compounded because oncologists in the USA may have less incentive to administer generic rather than brand-name drugs. The reason -always according to Gatesman and Smith- is that chemotherapeutic drugs are bought and sold in the doctor's office, a practice that has been established in the USA over the past forty years [1]. The Medicare and Medicaid health insurances in the USA reimburse the average sales price of a drug plus 6% to cover practice costs. So, continue Gatesman and Smith, why use paclitaxel (and receive 6% of $312) when you can use Abraxane (for 6% of $5,824)? [1].

The shortage of generic drugs has reached crisis levels recently and required the intervention of the President of the USA. On October 31, President Barack Obama issued an executive order instructing the FDA to broaden reporting of potential drug shortages, expedite reviews of applications to begin or modify production of these drugs, and provide more information to the Justice Department about possible cases of collusion or price gouging. The President also announced his support for House and Senate legislation that would require drug companies to notify the FDA 6 months ahead of a potential shortage [4].

Barack Obama's executive order was greeted by Michael Link, President of the American Society of Clinical Oncology (ASCO), as *"a good first step to addressing the problem"* [4].

Will the shortage of generic chemotherapy drugs in the USA [1, 4, 5] influence oncological practice in Europe?

Reflecting on past experience the short answer is "yes" for a number of reasons.

Oncologists may recall the difficulties some

years ago with the lack of supplies of Dacarbazine for the treatment of melanoma. The reason for this was never officially disclosed. It may be a coincidence, or maybe not, that this was happening at a time when temozolomide, the oral equivalent of Dacarbazine, was making its debut in the field.

The majority of innovations in cancer therapy originate on the other side of the Atlantic. Even if a drug is first developed and approved in Europe, its commercial viability is dependent also upon approval by the FDA. The oxaliplatin saga, first approved in France in 1996 for the treatment of metastatic colorectal cancer, is a good example.

The common practice of comparing a new drug for licensing purposes to a "standard" treatment with drug(s) also approved by the FDA essentially determines oncology practices worldwide [6]. The latest example of Ipilimumab compared with dacarbazine for the treatment of melanoma exemplifies the issue [7]. Interestingly, the National Institute for Clinical Excellence (NICE) in the UK criticised this comparison on the basis that this does not necessarily reflect standard UK practice.

The lessons learned from the drug shortages in the USA cannot be ignored by oncologists and their patients in Europe where a financial crisis has already established roots in Greece and Italy and is knocking the door of the more robust economies in the Union.

In sickness or in health the "unacceptable face of capitalism" [8] should be resisted. But when the lives of patients struck by cancer are besieged by profit, predatory capitalism must be repelled.

Europe has the know-how to produce generic drugs at affordable prices. In the circumstances and in the interest of patients everywhere, Greece should seize the initiative and lead the way.

Conflicts of interest

The author declares no conflict of interest.

REFERENCES

1. Gatesman ML, Smith TJ. The shortage of essential chemotherapy drugs in the United States. N Engl J Med 365; 18:1653-55. Epub 2011 Nov 3.
2. Henderson IC, Bhatia V. Nab-paclitaxel for breast cancer: a new formulation with an improved safety profile and greater efficacy. Expert Rev Anticancer Ther 2007 Jul; 7(7):919-43.
3. Yamamoto Y, Kawano I, Iwase H. Nab-paclitaxel for the treatment of breast cancer: efficacy, safety, and approval. Onco Targets Ther 2011; 4:123-36. Epub 2011 Jul 18.
4. The ASCO Post. SIDEBAR: White House Issues Executive Order on Drug Shortage. November 15, 2011, Volume 2, Issue 17.
5. The ASCO Post. Hagop M. Kantarjian. Chemotherapy Drug Shortages: A Preventable Human Disaster. November 15, 2011, Volume 2, Issue 17.
6. Retsas S. Systemic treatment of melanoma: quo vadis oncologist? J BUON 2007; 12(1):29.
7. Retsas S. Latest developments in the treatment of melanoma: 'a penicillin moment for cancer'? JRSM 2011; 104(6):269-272.
8. Sir Edward Heath. British Statesman and Conservative Prime Minister. House of Commons statement, May 1973.

Clinical practice guidelines in oncology: pros and cons – Second Part

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ABSTRACT

Evidence-based clinical practice guidelines are widely used to promote effective and efficient health care. Clinical oncology practice guidelines are developed for a variety of purposes: to improve quality of care, outcomes of patients, reliability of medical decisions and cost-effectiveness; to increase patients' information and autonomy of choice; to disseminate best practice by use of standardized criteria; to facilitate training, research and education; to inform third parties; and to decrease practice variation, harm to patients, and professional misconduct. The ethical implications for guideline use are complex and far-reaching. However, practice guidelines can never substitute the clinical judgment of qualified health care professionals, and it is crucial not to be allowed to hinder the development of more effective treatment strategies in the management of cancer patients.

This work reviews the pros and cons of using guidelines in Oncology for patients, healthcare professionals, policy-makers, payers and managers. Moreover, it presents potential barriers to physician adherence to guidelines and their dependence on physician knowledge, attitudes and behavior. Finally it examines the minimum requirements for a local group or national body to develop / adopt / review / appraise and evaluate guidelines for a specific clinical area and the ways to disseminate and implement them.

Key words: clinical practice guidelines; cancer treatment outcomes; evidence-based medicine; quality of life.

PHYSICIAN / ONCOLOGIST BEHAVIOR TOWARDS CPGS

Why physicians / oncologists follow / don't follow CPGs?

Regularly monitoring physicians' attitudes toward CPGs and the way they are implemented can be helpful in evaluating potential barriers to their adoption [1, 2, 3, 4, 5, 6, 7]. According to recent surveys focused on various medical or surgical topics and originating in Europe, the United States, Canada and Australia [8, 9, 10, 11, 12] the majority of physicians:

- refer to CPGs and follow their recommendations most of the time;
- believe that guidelines are credible, easy to follow, lead to better patient outcomes, and serve an important role in ensuring high quality care.

These conclusions are not universally accepted: according to some researchers, CPGs, despite wide promulgation, have had limited effect on changing physician behavior [13, 14, 15, 16, 17, 18]. Especially in Oncology, a rapidly changing field, providers report real barriers to actually following the recommended guidelines [19, 20, 21] and evidence suggests that adherence to CPGs is uneven [22, 23, 24].

These disparate sentiments and the growing awareness of their limitations and harms have done little to curtail the rapid dissemination of guidelines around the world. The enthusiasm for guidelines, and the unrealistic expectations about what they will accomplish, frequently reveals lack of experience and unfamiliarity with their limitations and potential hazards:

- The majority of guideline users uncritically accept official recommendations as valuable tools, especially when they stem from prominent professional groups or government bodies.
- More conscious users of CPGs investigate carefully the methods used in their development [25].

CPG pathway to affect patient outcomes and barriers to physician adherence

In spite of positive attitudes about CPGs overall, physicians cite many barriers to using guidelines consistently, effectively, and efficiently in the healthcare setting. Before a practice guideline can affect patient outcomes, it first affects physician knowledge, then attitudes, and finally behavior.

Factors limiting adherence include a) a cognitive component (barriers affecting knowledge), b) an affective component (barriers affecting attitude), c) a restriction of physician ability (barriers affecting behavior) [6, 10, 14, 26, 27]. Barriers to Physician Adherence to CPGs have been reviewed by several authors. Among them, Cabana *et al.* [14] have reviewed 76 articles including 120 different surveys investigating 293 potential barriers to physician guideline adherence (see Table 3).

If Table 3 indicates a defensive reaction, these attitudes re-

Table 3.
Barriers to Physician Adherence

Knowledge	
Lack of Familiarity and/or Awareness	
■ Volume of information ■ Time needed to stay informed ■ Guideline accessibility ■ (eventually) Skill deficit	Lack of knowledge (regarding indications and/or contradictions, current recommendations, results of recent drug trials and results of clinical research) does not guarantee familiarity with guideline recommendations and the ability to apply them correctly. Lack of familiarity among physicians is more common than lack of awareness [14, 27]. The expanding body of research makes it difficult for any physician to be aware of every applicable guideline and critically apply it to practice.
Attitudes	
Lack of Agreement with Guidelines in General	
■ Too Cookbook" – oversimplified guidelines ■ Too rigid to apply, decrease flexibility ■ Biased synthesis ■ Reduce autonomy ■ Not practical ■ Not applicable to a practice population ■ Decrease physicians' self-respect ■ Lacked credible authors ■ Would make the patient-physician relationship impersonal	■ Physicians may not agree with a specific guideline or the concept of guidelines in general. Although physicians commonly indicate a lack of agreement when asked about guidelines in theory (from Cabana *et al.* [14] analysis and others), when asked about specific guidelines, physician lack of agreement is less common. ■ Practice guidelines were generally perceived to be less useful than other sources of medical information (e.g. personal experience, conferences, colleagues, articles, the Internet, and textbooks [pharmaceutical representatives were the exception]). ■ Most physicians thought that guidelines are developed for cost-containment reasons [1, 28, 29, 30]. ■ Physicians perceived practice guidelines as externally imposed rather than as decision-supporting tools. Guidelines might be perceived as rigid protocols and a "challenge to physicians' autonomy" rather than as "systematically developed statements to assist practitioner and patient decisions for specific clinical circumstances" [31]. ■ Guidelines seemed to end up being considered as administrative rather than educational and informative. ■ Physicians seem to resist the idea that guideline development should be multidisciplinary (health administrators, nurses, communication experts, even non-specialist physicians, patient groups and insurance companies) [1, 32]. Only medico-legal experts and methodologists' participation was considered important. ■ Concerns about their limited applicability to individual patients and local settings.
Lack of Agreement with Specific Guidelines	
■ Differences in evidence interpretation ■ Not cost-beneficial (benefits were not worth patient risk, discomfort, or cost) ■ Lack of credibility by guideline authors (lack of confidence in guideline developer)	Guidelines are developed by humans and the process is, therefore, prone to errors and subjective interpretations on the one hand and personal values and cultural backgrounds on the other. Even when clear evidence is available, it is often interpreted differently by different guideline developers in different settings from different cultural or professional backgrounds [33]. For example, USA guidelines for the management of patients with high risk of breast cancer recommend regular self-examination and prophylactic mastectomy (requiring patient consent only). In contrast, the French guidelines do not recommend self-examination (because this may induce fear) and are very strict with regard to prophylactic mastectomy [34].

Lack of Outcome Expectancy

- Performance of guideline recommendation will not lead to desired outcome (physicians)
- Lack of optimism in the success of counseling, which suggests poor outcome expectancy (patients)

If a physician believes that a recommendation will not lead to an improved outcome, the physician will be less likely to adhere. For example, physicians provide smoking cessation counseling. Although most physicians are aware of and agree with the recommendation, many smokers are not counseled to quit during a physician visit. Although counseling may increase a population's quit rate from 3% to only 5% [35], given the prevalence of smoking, even this small change is enormously beneficial.

Lack of Self-Efficacy

- Inability to perform guideline recommendation

Low self-efficacy due to a lack of confidence, inability or a lack of preparation may lead to poor adherence.

Lack of Motivation / Inertia of Previous Practice / Psychosocial Barriers

- Habit
- Routines
- Feelings
- Attitudes
- Beliefs, values and previous experience that affect clinical practice
- Physicians / providers interpersonal relationships

Physicians may not be able to overcome the inertia of previous practice, or they may not have the motivation to change [8, 30, 36, 37]. The *readiness for change* model, developed by Prochaska and DiClemente [38] describes behavior change as a continuum of steps that include pre-contemplation, contemplation, preparation, action, and maintenance and was applied to physician attitudes toward cancer screening guidelines. The results suggest that close to half of physicians surveyed were in a pre-contemplation stage and not ready to change behavior (i.e. adopt guideline recommendations). The change process model described by Geertsma *et al.* [16] and the theory of learning and change model described by Fox *et al.* [39] also suggest similar constructs, i.e. a priming phase and the need for an initial force for change, professional, personal, and/or social.

Behavior (External Barriers)*

Patient Factors

- Inability to reconcile patient preferences with guideline recommendations
- Patient psychological barriers

The inability to reconcile patient preferences with guideline recommendations is a barrier to adherence [40, 41, 42, 43, 44, 45]. Patients may perceive a recommendation as offensive or embarrassing. Patient Psychological Barriers could be patient- or family attitudes, feelings, beliefs, values and experiences that interfere with successful treatment. Suggested steps for shared decision-making are found in the literature [46, 47].

Guideline Factors

- Guideline characteristics (guidelines are not easy to use, not convenient, cumbersome)
- Presence of contradictory guidelines (confusing)

- Guidelines recommending [16, 39] elimination of an established behavior may be more difficult to follow than guidelines that recommend adding a new behavior [14].
- Physicians tend to disagree over the frequency with which physicians implement CPGs and whether physicians document the reason why they choose not to follow CPGs.
- Trialability of a guideline and its complexity are also described as significant predictors of adoption [48].

Environmental Factors

- Lack of time
- Lack of resources
- Lack of reimbursement
- Organizational constraints
- Increase in malpractice liability

Adherence to CPGs may require changes not under physician control, such as acquisition of new resources (e.g. tools, equipment) or facilities, lack of a reminder system, lack of counseling materials, insufficient staff or consultant support, poor reimbursement, accountability gaps, increased practice costs, and increased liability. Lack of time is also commonly described as a barrier to adherence.

present important barriers to guideline implementation. Exploring and understanding them might increase the acceptance and use of practice guidelines and the likelihood of producing the expected changes. Researchers [1, 49] point out the difference in attitude among non-practicing clinicians and those directly involved at the patient bedside: hospital clinicians, as they have to apply their decisions to individual patients, seem to have more reservations about guidelines, their usefulness, and the participation of non-physicians in their development and use.

DEVELOP / SEARCH AND IMPLEMENT CPGS

Studies that report *large improvements* in clinical care suggest the potential of guidelines when detection or development, evaluation, dissemination, and implementation are all appropriate [50, 51]. Studies that report *small improvements* or none may reflect failure at any stage during the introduction or evaluation of the guidelines [52]. Table 4 briefly presents the different stages / steps for the development and dissemination of CPGs. It is underlined that only if appropriate strategies are selected at each stage will CPGs achieve full potential.

In order to find or develop guidelines, there are requirements which must be met at a satisfactory level:

Resources and skills at the organizational level [22, 27, 54, 55, 56]:

- Good interpersonal skills.
- Specific skills for monitoring the use of guidelines and knowledge of methods of guideline development and appraisal.
- Identification of the appropriately skilled and experienced people (and a leader) to coordinate and develop the necessary interventions.
- Cost estimation of guideline production.
- Coordination of data sources involved in determining practice patterns and needs, professional associations interested in CPG development, hospitals, CME providers [55] and patient or healthcare provider groups.
- Knowledge of the effectiveness of different dissemination and implementation strategies.

Levels of evidence

Results of CPG assessments provided an ambiguous picture of the quality of sources which do not match the definition of systematic review; or the searching methods were unclear (at least a considerable number of them) used to build guidelines. The main conclusions that can be drawn from these results are:

- The quality of a guideline is determined by the quality of the base of evidence, and not only by the rigor of its development.
- When using recommendations, oncologists should be aware that these could be based on poor underlying documents, i.e. their credibility could be undermined by lack of methodological rigor.

The *highest level of evidence* (see Table 5) is derived from large, high-quality RCTs (the "best" clinical trials) or meta-analyses [57]. There are two important remarks / questions on this point:

a) The former relates to how groups of methodological experts would define "the best clinical trials" as even RCTs that are large and well-designed, have limitations. These include: a) the selection of a limited sample of patients, who may not be typical of others with the same disease, b) the application of treatments under ideal conditions, which may not be applicable to a wider population. Large, well conducted outcome studies that take into account underlying differences in populations can provide a relatively high level of evidence regarding different strategies of management, and are complementary to RCTs.

Table 4.
Steps in the development and dissemination of CPGs [from 48, 53]

1.	A local group or a national body **decides to develop CPGs** in a clinical area in which there is a need for such guidelines (select clinical problem: rank in order of priority, define and refine the problem, frame the clinical problem).
2.	**Data is synthesized** from research information and relevant practice patterns by searching the literature (including existing guidelines) and then weighing the strength of the evidence from the resulting trials or studies.
3.	**Data is reviewed,** appraised, distilled and collated as guidelines; that is, as recommendations about strategies for investigation and management.
4.	The sponsoring organization and other interested organizations then **endorse the guidelines.**
5.	**CPGs are disseminated,** usually by traditional means such as mailing them to members or publishing them in recognized professional clinical journals.
6.	Various groups or individual practitioners may attempt to **implement the guidelines** more actively, through various and often multiple strategies to assist, convince or otherwise influence physicians, patients and their caregivers.
7.	CPGs are subjected to **re-appraisal, evaluation** and **reiteration** of the process.

Table 5.
Levels of evidence at descending order, used in establishing guidelines [25, 58, 59]

1.	High-quality randomized controlled trials or meta-analyses
2.	Small randomized controlled trials
3.	Non-randomized trials with concurrent controls
4.	Non-randomized trials with historical controls
5.	Quasi-experimental studies
6.	Non-experimental descriptive studies (e.g. comparative, and case-control studies)
7.	Expert committee reports or opinions or clinical experience of respected authorities, or both

b) The latter relates to whether this best evidence, once identified, can indeed inform a clinician on how to treat a patient. It is important to remember that a clinical trial can only answer the question that it has been designed to address: *"is drug A better than, equal to, or worse that drug B in treating patients with newly-diagnosed leukemia?"* The real question that such a trial is designed to answer is: *"is drug A, when used as it was in this trial, better than, equal to, or worse than drug B when used as it was in this trial, in the population included in the trial, for the endpoints addressed in this trial?"* [60].

The *lowest level of evidence* derives from the opinion of an expert panel. As stated by Feinstein: "The opinion of experts has been a traditional source of all the errors throughout medical history" [61].

Developing, appraising and adapting guidelines

Development of CPGs: The development of guidelines raises several process issues with ethical and practical dimensions. These include choice of topics, group composition, definition of benefits and harms to include as outcomes, evaluating evidence, and forming recommendations. Maximizing the validity [62] of guidelines and ensuring their use in clinical practice also requires evidence-based implementation strategies to local factors [63, 64]. A number of National Organizations have at one point created their own guidelines based on the local needs. The process by which they can set their clinical priorities, and produce and disseminate the corresponding CPGs comprise a number of components/steps which should be followed and completed [22, 53, 56, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, see also Table 4].

Nevertheless, most healthcare organizations do not have the resources and skills to develop valid guidelines from scratch [25, 75]. They should try to identify previously developed rigorous guidelines and adapt them for local use. Identifying published CPGs is problematic. Many guidelines are not indexed in the commonly available bibliographic databases. Some CPGs are catalogued on the internet and such sites may become the best source for identifying guidelines [58].

The first step in gathering the evidence [25] is to see whether a suitable, recent systematic review has already been published. If not, a computer search of Medline and Embase is the usual starting point. For example, randomized controlled trials provide the best evidence to answer questions about the effectiveness of treatments, whereas prospective cohort studies generally provide the best evidence for questions about risk. The Cochrane controlled trials register [77] contains references to over 200,000 clinical trials that have been identified though database and hand searching. Checking references in articles will show additional relevant articles not identified by the computer search, and having experts in the field examine the list of articles helps ensure that there are no obvious omissions.

Evaluation and Appraisal: Evaluating CPGs guidelines to assess their quality, potential inherent risks [50, 78, 79] and impact on practice, ensures that the process of care reflects guideline recommendations [80]. When an organization has identified relevant guidelines of acceptable quality, it should appraise their validity before deciding whether to adopt their recommendations. Adopting recommendations from guidelines of questionable validity may lead to harming patients or wasting resources on ineffective interventions [54]. If appraised guidelines are not available from these sources, organizations should undertake their own appraisal [criteria available, e.g. 21, 81, 82, 83].

Find appraisal instruments

In the literature, one can find appraisal instruments to evaluate the CPGs [3, 31, 66, 81, 84, 85, 86]. E.g. the Appraisal of Guidelines, Research, and Evaluation - (AGREE) Collaboration, endorsed by the WHO as accepted standard in guidelines development [21, 58, 80, 87, 88, 89, 90, 91, 92, www.agreecollaboration.org] provides a framework for international CPG development. AGREE is easy to use and could be applied consistently on a broad range of guidelines. It has been noted that scores for cancer guidelines were high with the instrument. The final AGREE instrument consists of 23 key items categorized into six domains. Each domain is intended to measure a separate dimension of guideline quality [87].

Table 6.
The AGREE Instrument

Domains	Comments
1. Scope and Purpose	
■ The overall objectives of the guideline are specifically described. ■ The clinical questions covered by the guideline are specifically described. ■ The patients to whom the guideline is meant to apply are specifically described.	Address the overall aim of the guideline, the specific clinical questions and the target patient population.
2. Stakeholder Involvement	
■ The guideline development group includes individuals from all pertinent professional groups. ■ Patients' views and preferences have been sought. ■ Guideline target users are clearly defined. ■ The guideline has been piloted among target users.	Focus on the extent to which the guideline represents the views of its intended users. Guideline development needs to be carried out by a local multidisciplinary cancer specialists' group to ensure local acceptance and use [21, 69, 75, 93]. This also includes patient groups.
3. Rigor of Development	
■ Systematic methods were used to search for evidence. ■ The criteria for selecting the evidence are clearly described. ■ The methods for formulating the recommendations are clearly described. ■ The health benefits, side-effects and risks have been considered in formulating the recommendations. ■ There is an explicit link between the recommendations and the supporting evidence. ■ The guideline has been externally reviewed by experts prior to its publication. ■ A procedure for updating the guideline is provided.	Evaluate the process used to locate and synthesize the evidence and to formulate and update the recommendations.
4. Clarity and Presentation	
■ The recommendations are specific and unambiguous. ■ The different options for condition management are clearly presented. ■ Key recommendations are easily identifiable. ■ The guideline is supported with tools for application.	Address language and format. Busy clinicians need patient-specific, user-friendly guidelines that can be easily consulted in the daily medical practice by referring to flowcharts or written statements [94]. Good guidelines present clear information with a precise and simple terminology about the management options available and the likely consequences of each [95, 96].
5. Applicability	
■ The potential organizational barriers in applying the recommendations have been discussed. ■ The potential cost implications of applying the recommendations have been considered. ■ The guidelines present key review criteria for monitoring and/or audit purposes.	Guidelines should be useable in the current organization of care and must fit into routine practice and the time constraints present. In addition, review criteria should be developed, linking the guideline use to audits and other quality improvement initiatives.

6. Editorial Independence	
■ The guideline is editorially independent from the funding body. ■ Conflicts of interest of guideline development members have been recorded.	An increasing number of guidelines are externally funded, either directly or indirectly. There should be an explicit statement that the views and/or interests of the funding body have not influenced the final recommendations.

It is worthwhile to notice that a high number of cancer guidelines are included in the AGREE project [88].

Dissemination and implementation

It has been shown that applying CPGs in Oncology has lead to changes in practice when a) they are part of a structured program and are issued by a recognized professional organization [27, 88, 97]; b) dissemination and implementation are an integral part of the guideline development process [85, 91, 98, 99]; and c) the strategy of their dissemination is active and aggressive [4, 5, 22, 51, 54, 100, 101].

Evidence-based guidelines have to be complemented by evidence-based implementation ["Conformance quality", 102]. In this context, researchers [8, 14, 22, 53, 54, 86, 102, 103, 104, 105, 106, 107, 108, 109, 110] were able to identify that CPG dissemination or implementation processes have mixed results:

- the *most common way* to access CPGs is online, either through medical journals or guideline statements. Additionally, health information technology - HIT tools (customized electronic medical records, clinical decision support modules, information networks) would make it easier to provide evidence-based care;
- a number of strategies had *some effect* (educational outreach visits, academic detailing, reminders, interactive educational meetings, conferences, *ad hoc* workshops and information meetings for small groups);
- some strategies were *moderately effective* (audit with feedback, local opinion leaders, local consensus procedures, patient mediated interventions);
- some relatively passive methods are *weak* (mailing to targeted healthcare professionals, educational materials, didactic educational meetings and traditional continuing medical education) and have little or no effect.

However, no strategy is invariably effective. The adoption of any innovation or the dissemination of new medical knowledge should be considered in a holistic, contextual manner [53]. Organizations should use multifaceted interventions to disseminate and implement guidelines [5, 15, 54, 62, 72, 73, 111, 112, 113, 114].

Keep guidelines up-to-date: A final, but important consideration is the need to keep guidelines up-to-date. The use of recent systematic reviews can considerably limit the workload of literature searching [115, 116, 117, 118]. The guideline can be updated as soon as each piece of relevant new evidence is published, but it is better to specify a date for updating the systematic review underpinning the guideline [25]. It has been suggested that, in principle, the update procedure should be performed every three years [82, 119, 120].

Quality of Oncology CPGs

Using various appraisal instruments, results show that the quality scores for the oncology guidelines are higher than those obtained for guidelines in other disease areas (e.g. see Bergers *et al.* [121], 100 guidelines, including 32 oncology guidelines, 13 countries) for almost all aspects:

Multidisciplinary development, selecting evidence and formulating recommendations: The higher scores might reflect a specificity of oncology, which has the tradition of a multidisciplinary approach and is heavily reliant on clinical trials as part of routine practice. Cancer patients often require a transparent, multidisciplinary treatment approach because the treatment modalities (such as surgery, radiotherapy, and chemotherapy) cannot be provided by the same specialist. There is some evidence to suggest that the absence of multidisciplinary care may affect survival [121, 122].

Health benefits, side-effects, and harms (various options clearly presented): Cancer treatments tend to have more side-effects, some of which are short term and other long term. The uncertainty of the outcome for an individual patient, particularly in terms of length of survival, means that other outcomes such as quality of life need to be considered. This might explain the significant differences in favor of oncology guidelines [121].

Applicability: The lower scores in the domain of "Applicability" [88, 123] are explained by the fact that guidelines generally fail to address issues such as barriers to implementation and cost implications, and do not include criteria for monitoring. These low scores emphasize the need to take into consideration implementation during the development process to ensure that guidelines have an influence on clinical practice [13, 124].

Patient involvement: Even if patient preferences seem to be more routinely considered in oncology than in other fields [121, 125, 126, 127, 128], the scores are low. This could be explained by the difficulty of identifying the most appropriate methods and the lack of resources for involving patients in the process of guideline development; therefore, more research is needed in this area.

CONCLUSIONS

CPGs increasingly form part of current practice and will become more common over the next decade. They represent the current "state of the art" in medicine. The major aim of developing CPGs should be to improve the quality of care delivered by providers rather than to punish those who do not meet criteria. For this purpose guidelines should be valid, reliable, clinically applicable, clear and revised whenever new scientific evidence emerges or if consensus changes.

CPGs in Oncology:

- are useful tools for increasing patient access to optimal cancer strategies (diagnostic and therapeutic) resulting in improved health outcomes in terms of avoidance or reduction in morbidity and mortality and of improving cost-effective management of individuals with malignancies;
- decrease any inappropriate variation in performance and increase the likelihood of patients receiving a uniform and consistent standard of care, irrespective of where they live and by whom they are treated;
- patients are comforted by the fact that there is solid evidence backing why the practitioner has chosen a particular type of treatment;
- can be used as citable evidence for malpractice litigation.

However:

- Statistics and medical evidence do not necessarily apply to any single patient and there is substantial medical uncertainty regarding individual outcomes.
- CPGs might be too restrictive in their recommendations or controversial.
- CPGs will not address all the uncertainties of current clinical practice and should be seen as only one strategy that can help improve the quality of care that patients receive.
- CPGs can never substitute the clinical judgment of qualified health care professionals, and when the patient fails standard therapy, or does not fit the criteria, practitioners must use their best judgment, hopefully with documented input from peers.
- CPGs should not be allowed to hinder the development of more effective treatment strategies in cancer patient management. Recommendations that do not take into account the latest evidence can result in suboptimal, ineffective or even harmful practice [21].

Is cancer treatment being applied well?

The choice of therapy for a particular patient depends optimally on evidence that the selected treatment leads to a better outcome and/or lower risk of side-effects compared with alternative management strategies.

Even if management of patients complies with guidelines and with evidence-based medicine, the outcome remains depending on how well treatment is delivered. Quality of cancer care is difficult to define and evaluate. Determining the right treatment requires a hierarchy of evidence from clinical trials -and high quality clinical trials at that- to determine and supplement that evidence. Evidence-based guidelines are then useful in increasing compliance with evidence-based treatment.

Multiple studies (reviewed in Hillner *et al.* [129]) have shown that this depends on how frequently a practitioner or center treats a particular cancer site: generalists/oncologists should concentrate on what they do well and most often. This also has implications for health-care policy makers who need to consider restricting complex treatments to centers with a minimum volume level.

Another way to improve quality of care may be to recruit patients to clinical trials. Several studies have suggested that patients treated in clinical trials have a better outcome than patients who receive similar treatment but are not in a clinical trial [130, 131, 132].

Treatment of the patient as a whole requires that the oncologist not only attempts to treat the tumor and increase survival, but relieves the side-effects of both cancer and the treatment, and improves QOL [133]. In other words:

- Take into account patient's preferences regarding treatment (e.g. aggressive treatment for small gains in survival, or the reverse) [47, 134].
- Improving QOL and symptom control are important goals of cancer treatment, and important endpoints of clinical trials (e.g. management of pain and cancer-related fatigue) [135].
- Apply effective communication, e.g. patient satisfaction leaving consultation, high use of open-ended questions, great empathy, use of psychosocial probing [17, 136, 137, 138, 139].

In summary,

The past decade has seen a remarkable growth in the development of CPGs and an increased realization of their value. Initially driven by the principles of evidence-based medicine, the need for cost-efficient care and the desire to optimize health outcomes, the CPG movement is now firmly ensconced in the literature and in the minds of many practicing oncologists.

Aimed at using guidelines effectively, ESMO has initiated an important process to inform clinical decisions in medical oncology. ESMO has chosen a number of important disease entities and created a set of relevant Minimal Clinical Recommendations [48 85, 140, 141, 142, 143, 144, 145, 146]. Each of the MCRs provides vital, evidence-based information for physicians, including malignancy incidence, diagnostic criteria, staging of disease and risk assessment, treatment plans and follow-up. They aim to provide the user with a set of requirements for a basic standard of care that ESMO considers necessary in European countries without any intention to replace extensive clinical practice guidelines or review articles.

Finally, wavering among very opposite statements as e.g. *"Few buzzwords can irritate me more than 'quality of care', especially when someone else's standards are applied to my clinical work..."* and *"The key point is that implementing guidelines means modifying behavior"* is better to adopt behavior as follows: *"Guidelines must enhance -not limit- decision making within the physician-patient relationship"* [96, 147].

Open remark [148, 149, 150, 151]:

"What is required is PROTOCOLS, rather than guidelines. Guidelines connote an officially sanctioned truth from which one departs at her or his peril. Protocols are procedures for the management of specific conditions developed by expert groups. Unlike guidelines, protocols do not pretend to contain the ensemble of current wisdom, and different schools of thought may have different protocols for managing the same condition. It is essential that competing protocols are allowed to co-exist, so that experience may eventually show that some are superior to others".

As an example, the literature and guidelines primarily recommend radiotherapy for patients with one to three brain metastases and extracranial disseminated disease with poor systemic treatment options [152, 153, 154, 155]. However, some experts endorse that surgery is an option for symptom palliation in patients with significant neurological dysfunction [156]. Given that the care of each patient must be individualized, it may be useful to explore the 'whys' and 'why nots' of this particular situation and how they might apply to the broader context of oncological care near the end of life…

REFERENCES

1. Formoso G, Liberat A & Magrini N. Practice Guidelines: Useful and "Participative" Method? Arch Intern Med 2001; 161:2037-2042.
2. Grilli R, Apolone G, Marsoni S, Nicolucci A, Zola P, Liberati A. The impact of patient management guidelines on the care of breast, colorectal, and ovarian cancer patients in Italy. Med Care 1991; 2:50-63.
3. Grilli R, Magrini N, Penna A, et al. Practice guidelines developed by specialty societies: the need for a critical appraisal. Lancet 2000; 355:103-106.
4. Grol R. National standard setting for quality of care in general practice: attitudes of general practitioners and response to a set of standards. Br J Gen Pract 1990; 40:361-364.
5. Grol R. Beliefs & evidence in changing clinical practice. BMJ 1997; 315:418-427.
6. Mansfield C. Attitudes and behaviors towards clinical guidelines: the clinicians' perspective. Quality in Health Care 1995; 4:250-255.
7. Thorsen T & Makela M. Changing Professional Practice: Theory and Practice of Clinical Guidelines Implementation. Copenhagen, Denmark: Danish Inst. for Health Services R&D. 1999.
8. ACCC. Use of clinical practice guidelines in community cancer centers. ACCC site. 2011; Available from: www.accc-cancer.org.
9. Browman GP, Newman TE, Mohide EA, et al. Progress of clinical oncology guidelines development using the Practice Guidelines Development Cycle: The role of practitioner feedback. J Clin Oncol 1998; 16:1226-1231.
10. Farquhar CM, Kafa EW & Slutsky JR. Clinicians' attitudes to clinical practice guidelines: a systematic review. Med J Aust 1999; 171:362-366.
11. Graham ID, Evans WK, Logan D, et al. Canadian oncologists and clinical practice guidelines: a national survey of attitudes and reported use. Oncology 2000; 59(4):283-290.
12. Pavlidis N, Hansen H & Stahel R. ESMO clinical recommendations: a practical guide for medical oncologists. Ann Oncol 2007; 18:1759-1763.
13. Bennett CL, Somerfield MR, Pfister DG, et al. Perspectives on the value of ASCO clinical guidelines as reported by Oncologists and Health Maintenance Organizations. J Clin Oncol 2003; 21; 937-941.
14. Cabana MD, Rand CS, Powe NR, et al. Why don't physicians follow clinical practice guidelines. JAMA 1999; 282(15):1458-1465.
15. Michie S & Johnston M. Changing clinical behavior by making guidelines specific. BMJ 2004; 328:343-345.
16. Geertsma RH, Parker RC & Whitbourne SK. How physicians view the process of change in their practice behavior. J Med Educ 1982; 57:752-761.
17. Jenkins V & Fallow eld L. Can communication skills training alter physicians' beliefs and behavior in clinics? J Clin Oncol 2002; 20:765-769.
18. Woolf SH. Barriers and strategies to influencing physician behavior. Am J Med Quality 2007; 22:5-7.
19. Markman M. Quality assurance in oncology: More substance, more questions. Current Onc Reports 2006; 8(3):155-156.
20. Markman M. Clinical practice guidelines in oncology: pros and cons. Cancer Res Clin Oncol 1996; 122:381-382.
21. Woolf SH, Grol R, Hutchinson A, Eccles M & Grimshaw J. Clinical guidelines: the potential benefits, limitations, and harms of clinical guidelines. BMJ 1999; 318:527-530.
22. Feder G, Eccles M, Grol R, Griffiths C & Grimshaw J. Using clinical guidelines. BMJ 1999; 318:728-730.
23. Smith TJ & Hillner BE. Ensuring quality cancer care by the use of clinical practice guidelines and critical pathways. J Clinical Oncology 2001; 19(11):2886-2897.
24. Greco P & Eisenberg J. Changing physician's practices. NEJM 1993; 329(17):1271-1275.
25. Shekelle PG, Woolf SH, Eccles M & Grimshaw J. Clinical Guidelines. Developing guidelines. BMJ 1999; 318:593-596.
26. Solberg LI, Brekke ML & Kottke TE. How important are clinician and nurse attitudes to the delivery of clinical preventive services. J Fam Pract 1997; 44:451-461.
27. Borbas C, Morris N, McLaughlin B, Asinger R & Gobel F. The role of clinical opinion leaders in guideline implementation and quality improvement. Chest 2000; 118:24S-32S.
28. Inouye J, Kristopatis R, Stone E, et al. Physicians' changing attitudes toward guidelines. J Gen Intern Med 1998; 13:324-326.
29. Gupta L, Ward JE & Hayward RS. Clinical practice guidelines in general practice: a national survey of recall, attitudes and impact. Med J Aust 1997; 166:69-72.
30. Hayward RSA, Guyatt GH, Moore K-A, et al. Canadian physicians' attitudes about and preferences regarding clinical practice guidelines. Can Med Assoc 1997; 156(12):1715-1723.
31. Field MJ & Lohr MJ. Clinical practice guidelines: directions for a new program. Field MJ & Lohr MJ, eds. Nat Acad Press 1990.
32. Grilli R, Penna A, Zola P & Liberati A. Physicians' view of practice guidelines: a survey of Italian physicians. Soc Sci Med 1996; 43:1283-1287.
33. Fahey TP & Peters TJ. What constitutes controlled hypertension? Patient-based comparison of hypertension guidelines. BMJ 1996; 313:93-96.
34. Eisinger F, Geller G, Burke W & Holtzman NA. Cultural basis for differences between US and French clinical recommendations for women at increased risk of breast and ovarian cancer. Lancet 1999; 353:191-200.
35. Wilson DM, Taylor DW, Gilbert JR, et al. A randomized trial of family physician intervention for smoking cessation. JAMA 1988; 260:1570-1574.
36. Weinstein A. All is not perfect with clinical practice guidelines in oncology. Cancer Care 2010 Dec 9. Available at: http://acccbuzz.wordpress.com.
37. Robertson N, Baker R & Hearnshaw H. Changing the clinical behavior of doctors: a psychological framework. Quality in Health Care 1996; 5:51-54.
38. Prochaska JO & DiClemente CC. Stages and processes of self-change of

smoking: toward an integrative model of change. J Consult Clin Psychol 1983; 51:390-395.
39. Fox RD, Mazmanian PE & Putnam RW. A theory of learning and change. In: Fox RD, et al. eds. New York, NY: Praeger 1989; Changing & Learning in the Lives of Physicians.
40. Hlatky MA. Patient preferences and clinical guidelines. JAMA 1995; 273:1219-1220.
41. Woo B, Woo B, Cook EF, Weisberg M & Goldman L. Screening procedures in the asymptomatic adult: comparison of physicians' recommendations, patients' desires, published guidelines, and actual practice. JAMA 1985; 254:1480-1484.
42. Chong C, Chen I, Naglie G & Krahn MD. How well do guidelines incorporate evidence on patient preferences? J Gen Intern Med 2009; 24(8):977-982.
43. Say R & Thomson R. The importance of patient preferences in treatment decisions - challenges for doctors. BMJ 2003; 327:542-545.
44. Ramfelt E & Lützén K. Patients with cancer: their approaches to participation in treatment plan decisions. Nursing Ethics 2005; 12(2):143-156.
45. Pieterse AH, Baas-Thijssen MCM, et al. Clinician and cancer patient views on patient participation in treatment decision-making: a quantitative and qualitative exploration. Br J Cancer 2008; 99:875-882.
46. Towle A. Physician and patient communication skills: competencies for informed shared decision-making. Univ Br Columbia 1997; Vancouver, Canada.
47. Elwyn G, Edwards A, Gwyn R & Grol R. Towards a feasible model for shared decision making: focus group study with general practice registrars. BMJ 1999; 319:753-756.
48. Grilli R & Lomas J. Evaluating the message: the relationship between compliance rate and the subject of a practice guideline. Med Care 1994; 32:202-213.
49. Coulter I, Adams A, Shekelle P. Impact of varying panel membership on ratings of appropriateness in consensus panels: a comparison of multi and single disciplinary panel. Health Serv Res 1995; 30:577-591.
50. Grimshaw JM & Russell IT. Effect of clinical guidelines on medical practice: A systematic review of rigorous evaluations. Lancet 1993; 342(8883):1317-1322.
51. Grol R, Dalhuijsen J, Thomas S, Veld C, Rutten G & Mokkink H. Attributes of clinical guidelines that influence use of guidelines in general practice: observational study. BMJ 1998; 317:858-861.
52. Russell IT & Grimshaw JM. The effectiveness of referral guidelines: a review of the methods and findings of published evaluations. In Roland M & Coulter A, eds. Hospital referrals 1992; Oxford: Oxford University Press.
53. Davis DA, Taylor-Vaisey A. Translating guidelines into practice. Can Med Assoc J 1997; 157:408-416.
54. Bero L, Grilli R, Grimshaw JM & Oxman AD. The Cochrane Effective Practice and Organisation of Care Review Group. In: Bero et al. eds. Issue 3. 1998; Oxford: Update Software.
55. Dodek P & Ottoson J. Implementation link between clinical practice guidelines and continuing medical education. J Cont Educ In Health Prof 1996; 16:82-93.
56. Eccles M & Mason J. How to develop cost-conscious guidelines. Health Technol Assess 2001; 5:1-69.
57. Saarni SI & Gyllin HA. Evidence based medicine guidelines: a solution to rationing or politics disguised as science? J Med Ethics 2004; 30:171-175.
58. Oosterhuis W, Bruns D, Watine J, et al. Evidence-based guidelines in laboratory medicine: principles and methods. Clinical Chemistry 2004; 50(5):806-818.
59. Vardy J & Tannock IF. Quality of cancer care. Annals of Oncology 2004; 15:1001-1006.
60. French J. Can evidence-based guidelines & clinical trials tell us how to treat patients? Epilepsia 2007; 48(7):1264-1267.
61. Feinstein AR. Fraud, distortion, delusion, and consensus: the problems of human and natural deception in epidemiologic science. Am J Med 1988; 84:475-478.
62. Grimshaw J, Freemantle N, Wallace S, et al. Developing and implementing clinical practice guidelines. Qual Health Care 1995; 4:55-56.
63. BASO; Breast Group Quality Assurance Guidelines for Surgeons in Breast Cancer Screening. NHS-BSP 1996; publ. No 20.
64. NHSBSP & BASO. "An Audit of Screen Detected Breast Cancer for the Year of Screening, April 1998-March 1999". NHS Cancer, Screening Programmes, 2000.
65. Inouye J, Kristopatis R, Stone E, et al. Physicians' changing attitudes toward guidelines. J Gen Intern Med 1998; 13:324-326.
66. Hellbruck RP. Medical guidelines: a valid and reliable management tool? Int J Health Plann Manage 1997; 12:51-62.
67. Browman GP, Levine MN, Mohide EA, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995; 13:502-512.
68. Fervers B, Fervers J, Haugh M, et al. Adaptation of clinical guidelines: literature review and proposition for a framework and procedure. Int J Qual Health Care 2006; 18(3):167-176.
69. Miller J & Petrie J. Development of practice guidelines. Lancet 2000; 355(9198):82-83.
70. Haines A & Feder G. Guidance on guidelines. BMJ 1992; 305:785-786.
71. Brennan PJ & Abrutyn E. Developing policies and guidelines. Infect Control Hosp Epidemiol 1995; 16:512-517.
72. Hayward RSA & Laupacis A. Initiating, conducting and maintaining guidelines development programs. Can Med Assoc J 1993; 148:507-512.
73. Kelly JT & Toepp MC. Practice parameters: development, evaluation, dissemination, and implementation. Qual Rev Bull 1992; 18:405-409.
74. McMaster P, Rogers D, Kerr M & Spencer A. Getting guidelines to work in practice. Arch Dis Child 2007; 92:104-106.
75. Risdale L, Griffiths C & Feder G. "Using clinical guidelines in a general practitioner consultation" in "Evidence-based practice in primary health care". Risdale L, ed. 1998; London, Churchill Livingstone.
76. Rush J. Clinical practice guidelines. Good news, bad news, or no news? Arch Gen Psychiatry 1993; 50:483-490.
77. Cochrane Library. Evidence to inform healthcare decision-making. Available from: www.cochrane.org; J. Wiley & Sons, Ltd.
78. Grimshaw JM & Russell IT. Achieving health gain through clinical guidelines II: ensuring guidelines change medical practice. Qual Health Care 1994; 3:24-52.
79. LeLorier J, Gregoire G, Benhaddad A, et al. Discrepancies between meta-analyses and subsequent large randomized, controlled trials. New Engl J Med 1997; 337:536-542.
80. MacDermid JC, Brooks D, Solway S, et al. Reliability and validity of the AGREE instrument used by physical therapists in assessment of clinical practice guidelines. BMC Health Serv Res 2005; 5:18-32.
81. Cluzeau F, Littlejohns P & Grimshaw J. Appraising clinical guidelines - towards a 'Which' guide for purchasers. Quality in Health Care 1994; 3:121-122.
82. Petrie JC, Grimshaw JM & Bryson A. The Scottish Intercollegiate Guidelines Network initiative: getting validated guidelines into local practice. Health Bull 1995; 53:345-348.
83. Hayward RSA, Wilson MC, Tunis SR, et al. Users' guides to the medical literature. VII. How to use CPGs. A: are the recommendations valid? JAMA 1995; 274(7):570-574.
84. Meade MO & Richardson SW. Selecting and appraising studies for a systematic review. Ann Intern Med 1997; 127:531-537.
85. Fervers B, Philip T, Browman G. Clinical appraisal of the Minimal Critical Recommendations (MCR) of ESMO: challenges for a European framework for the development of clinical practice guidelines. Ann Oncol 2002; 13:1507-1510.
86. Haynes RB, Davis DA, McKibbon A & Tugwell P. A critical appraisal of the efficacy of continuing medical education. JAMA 1984; 251:61-64.
87. Grol R, Cluzeau FA & Burgers JS. Clinical practice guidelines: Towards better quality guidelines and increased international collaboration. Br J Cancer 2003; 89(suppl 1):S4-S8.
88. Fervers B, Fervers J, Haugh M, et al. Predictors of high quality clinical practice guidelines: examples in oncology. Int J Qual Health Care 2005; 17(2):123-132.
89. Cluzeau FA, Burgers JS, Brouwers M, et al. (The AGREE Group). Development and validation of an international appraisal instrument for assessing the quality of clinical practice guidelines: the AGREE project. Qual Saf Health Care 2003; 12:18-23.
90. Brouwers MC, Kho ME, Browman GP, et al. AGREE II: advancing guideline development, reporting and evaluation in health care. J Clin Epidemiol 2010; 63(12):1308-1311.

91. Burgers JS, Grol R, Klazinga NS, Makela M & Zaat J. The AGREE Collaboration towards evidence-based clinical practice: an International Survey of 18 clinical guideline programmes. Int J Qual Health Care 2003; 15:31-45.

92. Burgers JS, Cluzeau FA, Hanna SE, Hunt C & Grol R. The AGREE Collaboration Characteristics of high quality guidelines: evaluation of 86 clinical guidelines developed in ten European countries and Canada. Int J Technol Assess Health Care 2003; 19:148-157.

93. Vigna-Taglianti F, Vineis P, Liberati A & Faggiano F. Quality of systematic reviews used in guidelines for oncology practice. Ann Oncol 2006; 17:691-701.

94. Michie S & Johnston M. Changing clinical behavior by making guidelines specific. BMJ 2004; 328:343-345.

95. Grilli R & Lomas J. Evaluating the message: the relationship between compliance rate and the subject of a practice guideline. Med Care 1994; 32:202-213.

96. Grol R. Beliefs & evidence in changing clinical practice. BMJ 1997; 315:418-427.

97. Natsch S & van der Meery JWM. The role of clinical guidelines, policies and stewardship. J Hosp Infection 2003; 53:172-176.

98. Ray-Coquard I, Philip T, Lehmann M, Fervers B, et al. Impact of a clinical guidelines program for breast and colon cancer in a French cancer center. JAMA 1997; 278:1591-1595.

99. Fervers B, Hardy J & Philip T. Standards, options and recommendations – SOR. Clinical practice guidelines for cancer care from the French National Federation of Cancer Centres (FNCLCC). Br J Cancer 2001; 84(suppl 2):1-92.

100. Grol R & Grimshaw J. Evidence-based implementation of evidence based medicine. Jt Comm J Qual Improv 1999; 25:503-513.

101. Grol R, Eccles M, Maisonneuve H, Woolf S. Developing clinical practice guidelines: the European experience. Dis Man Health Outcomes 1998; 4:255-266.

102. Kedikoglou S, Syrigos K, Skalkidis Y, et al. Implementing clinical protocols in oncology: quality gaps and the learning curve phenomenon. Eur J Public Health 2005; 15(4):368-371.

103. Baker R. Is it time to review the idea of compliance with guidelines? Br J Gen Practice 2001 Jan; 51(462:7.

104. Brook RH. Practice guidelines and practicing medicine. Are they compatible? JAMA 1989; 262(21):3027-3030.

105. Davis DA, Thomson MA, Oxman AD & Haynes RB. Evidence for the effectiveness of CME. A review of 50 randomized controlled trials. JAMA 1992; 268:1111-1117.

106. Davis DA, Thomson MA, Oxman AD & Haynes RB. Changing physician performance: a systematic review of the effect of continuing medical education strategies. JAMA 1995; 274:700-705.

107. Freemantle N, Harvey E, Grimshaw JM, et al. The effectiveness of printed educational materials in changing the behavior of health care professionals. In: Cochrane Collab Cochrane Library. Issue 3. Oxford: Update Software 1996.

108. Oxman AD, Thomson MA, Davis DA & Haynes RB. No magic bullets: a systematic review of 102 trials of interventions to improve professional practice. Can Med Assoc J 1995; 153:1423-1431.

109. Pauly M. Practice guidelines: can they save money? Should they? J Law Med Ethics 1995; 23(1):65-74.

110. Robinson MB. Evaluation of medical audit. J Epidemiol Community Health 1994; 48:435-440.

111. Fox RD, Mazmanian PE & Putnam RW. A theory of learning and change. In: Fox RD, et al. eds. New York, NY: Praeger 1989; Changing & Learning in the Lives of Physicians.

112. AHCPR. Using clinical practice guidelines to evaluate quality of care. Rockville, MD: US Dept. Health and Human Services 1995; pub. no 95 0045, V.1.

113. Moulding NT, Silagy CA & Weller DP. A framework for effective management of change in clinical practice: dissemination and implementation of clinical practice guidelines. Quality in Health Care 1999; 8:177-183.

114. Royal College of Radiologists Working Party. Influence of the Royal College of Radiologists' guidelines on hospital practice: a multicenter study. BMJ 1992; 304:740-743.

115. Shekelle P, Eccles MP, Grimshaw JM & Woolf SH. When should clinical guidelines be updated? BMJ 2001; 323:155-157.

116. Cook DJ, Mulrow CD & Haynes RB. Systematic reviews: synthesis of best evidence for clinical practice. Ann Int Med 1997; 126:376-380.

117. Cook DJ, Greengold NL, Ellrodt AG & Weingarten SR. The relation between systematic reviews and practice guidelines. Ann Intern Med 1997; 127:210-216.

118. Silagy CA, Stead LF & Lancaster T. Use of systematic reviews in clinical practice guidelines: case study of smoking cessation. BMJ 2001; 323:833-836.

119. Shekelle PG, Ortiz E, Rhodes S, Morton SC, Eccles MP, Grimshaw JM & Woolf SH. Validity of the agency for healthcare research and quality practice guidelines: how quickly do guidelines become outdated? JAMA 2001; 286:1461-1467.

120. Baker R & Feder G. Clinical guidelines: where next? Int J Qual Health Care 1997; 9:399-404.

121. Burgers JS, Fervers B, Haugh M, et al. International Assessment of the Quality of Clinical Practice Guidelines in Oncology Using the Appraisal of Guidelines and Research and Evaluation Instrument. J Clin Oncol 2004; 22:2000-2007.

122. Junor EJ, Hole DJ & Gillis CR. Management of ovarian cancer: Referral to a multidisciplinary team matters. Br J Cancer 1994; 70:363-370.

123. Ray-Coquard I, Philip T, de Laroche G, et al. A controlled 'before-after' study: impact of a clinical guidelines programme and regional cancer network organization on medical practice. Br J Cancer 2002; 86:313-321.

124. Browman GP. Improving clinical practice guidelines for the 21st century: Attitudinal barriers and not technology are the main challenges. Int J Technol Assess Health Care 2000; 16:959-968.

125. Abbatucci JS. Long-term experience with multidisciplinary approach in oncology. Rays 1983; 8:165-172.

126. Chang JH, Vines E, Bertsch H, et al. The impact of a multidisciplinary breast cancer center on recommendations for patient management: The University of Pennsylvania experience. Cancer 2001; 91:1231-1237.

127. Ray MD. Shared borders: Achieving the goals of interdisciplinary patient care. Am J Health Syst Pharm 1998; 55:1369-1374.

128. Tripathy D. Multidisciplinary care for breast cancer: Barriers and solutions. Breast J 2003; 9:60-63.

129. Hillner BE, Smith TJ & Desch CE. Hospital and physician volume or specialization and outcomes in cancer treatment: importance in quality of cancer care. J Clin Oncol 2000; 18:2327-2340.

130. Davis S, Wright PW, Schulman SF, et al. Participants in prospective, randomized clinical trials for resected non-small cell lung cancer have improved survival compared with non-participants in such trials. Cancer 1985; 56:1710-1718.

131. Karjalainen S &, Palva I. Do treatment protocols improve end results? A study of survival of patients with multiple myeloma in Finland. BMJ 1989; 299:1069-1072.

132. Mayers C, Panzarella T & Tannock IF. Analysis of the prognostic effects of inclusion in a clinical trial and of myelosuppression on survival after adjuvant chemotherapy for breast carcinoma. Cancer 2001; 91:2246-2257.

133. Tannock IF. Treating the patient, not just the cancer. N Engl J Med 1987; 317:1534-1535.

134. Bottomley A, Jones D & Claassens L. Patient-reported outcomes: Assessment and current perspectives of the guidelines of the Food and Drug Administration and the reflection paper of the European Medicines Agency. Eur J Cancer 2009; 45:347-353.

135. Stone P, Richardson A, Ream E, et al. Cancer-related fatigue: inevitable, unimportant and untreatable? Results of a multi-centre patient survey. Cancer Fatigue Forum Ann Oncol 2000; 11:971-975.

136. Fallow eld L & Jenkins V. Effective communication skills are the key to good cancer care. Eur J Cancer 1999; 35:1592-1597.

137. Ellis PM & Tattersall MH. How should doctors communicate the diagnosis of cancer to patients? Ann Med 1999; 31:336-341.

138. Baile WF, Lenzi R, Kudelka AP, et al. Improving physician-patient communication in cancer care: outcome of a workshop for oncologists. J Cancer Educ 1997; 12:166-173.

139. Fallowfield L, Jenkins V, Farewell V, et al. Efficacy of a Cancer Research UK communication skills training model for oncologists: a randomised controlled trial. Lancet 2002; 359:650-656.

140. Pavlidis N. Evidence-based medicine: Development and implementation of guidelines in oncology. Eur J Cancer 2009; 45:468-470.

141. Pavlidis N, Hansen H & Stahel R. ESMO Clinical Recommendations: a practical guide for medical oncologists. Ann Oncol 2007; 18:1759-1763.

142. Pavlidis N, Hansen H & Stahel R. ESMO Clinical Recommendations: using the easier and faster approach to oncology guidelines. The original idea. Ann Oncol 2009; 20(suppl 4):iv7-iv9.

143. Pavlidis N, Hansen H & Stahel R. ESMO Clinical Practice Guidelines: development, implementation and dissemination. Annals of Oncology 2010; 21(suppl 5):v7-v8.

144. Pentheroudakis G, Stahel R, Hansen H & Pavlidis N. Heterogeneity in cancer guidelines: should we eradicate or tolerate? Ann Oncol 2008; 19:2067-2078.

145. Stahel R. Letter to the Editor. Ann Onc 2002; 13:1507-1510.

146. Stahel R. ESMO Minimum Clinical Recommendations: assuring common standards of care. Annals of Oncology 2005; 16(suppl 1):i5-i6.

147. Talcott JA. Quality of care in prostate cancer: important to start and too important to stop here. J Clin Oncol 2003; 21:1902-1903.

148. More J. Protocols rather than Guidelines. BMJ 1999; 318:661.

149. Bottomley A. Developing clinical trial protocols for quality of life assessment. Appl Clin Trials 2001; 10:40-44.

150. Katterhagen G. Physician compliance with outcome-based guidelines and clinical pathways in oncology. Oncology (Huntingt) suppl 1996; 10:113-121.

151. Sisk JE. Promises and hazards of strategies to implement change. J Qual Improv 1995; 21:357-360.

152. Langer CJ & Mehta MP. Current management of brain metastases, with a focus on systemic options. J Clin Oncol 2005; 23:6207-6219.

153. Brem SS, Bierman PJ, Black P, et al. Central nervous system cancers: Clinical practice guidelines in oncology. J Nat Compr Canc Netw 2005; 3:644-690. NCCN; Clinical practice guidelines in oncology. Available from: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp 2011.

154. Kalemkerian G. Guidelines are never enough: A commentary on when guidelines are not enough. J Clin Oncol 2007; 25(13):1810-1811.

155. Noordijk EM, Vecht CJ, Haaxma-Reiche H, et al. The choice of treatment of single brain metastasis should be based on extracranial tumor activity and age. Int J Radiat Oncol Biol Phys 1994; 29:711-717.

156. Bajaj GK, Kleinberg L & Terezakis S. Current concepts and controversies in the treatment of parenchymal brain metastases: Improved outcomes with aggressive management. Cancer Invest 2005; 23:363-376.

Expression of components of Notch signaling pathway in head and neck squamous cell carcinoma (HNSCC) using AQUA: Association with survival and p16 expression

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ABSTRACT

Background: Deregulation of Notch signaling is implicated in carcinogenesis. The role of Notch in solid malignancies is highly context-dependent as it functions as an oncogene in some cancers and as a tumor suppressor in others. We sought to determine the association between components of Notch signaling pathway and outcome in a retrospective cohort of HNSCC.

Patients & Methods: We analyzed protein expression levels of Notch1, Notch3, Notch4, Jagged1 using automated image acquisition and analysis (AQUA) on a tissue microarray, composed of 122 primary HNSCC cases. We examined the association of Notch protein expression with outcome (overall survival) and p16 expression status.

Results: Eighty-two of 122 (67%) cases had sufficient tissue for analysis concerning all the examined proteins. There was an association of high Notch4 with improved overall survival (Hazard Ratio: 2.2 for low versus high Notch4, p= 0.05). We found statistically significant positive correlations between all the examined proteins and p16 expression.

Conclusions: High protein levels of Notch4 are associated with improved overall survival in HNSCC. Notch4, similar to Notch1, may have a tumor suppressor role in head and neck carcinogenesis but this result needs to be validated in large cohorts.

Key words: Notch signaling pathway; AQUA; tissue microarray; HNSCC; p16.

INTRODUCTION

The Notch pathway is a highly conserved cell signaling mechanism present in most multicellular organisms. It controls cell fate decisions, including cell proliferation, differentiation and apoptosis [1]. Notch proteins constitute a family of four transmembrane receptors (Notch1 to Notch4) that contain an extracellular domain with EGF-like repeats and an intracellular domain. The extracellular domain acts as receptor [2, 3]. Ligand binding leads to a cleavage in the transmembrane region of the C-terminal protein fragment, resulting in the release of the intracellular domain (Notch-IC) followed by its nuclear translocation. The whole procedure results in Notch target genes transcription activation.

The Notch ligands (Jagged1, Jagged2, and Delta1 to Delta4) represent transmembrane proteins that, like Notch, contain multiple epidermal growth factor-like repeats in their extracellular domain. Because most ligands are also transmembrane proteins, the receptor is normally triggered only from direct cell-to-cell contact and groups of cells can organize themselves [3-6].

Notch signaling is involved in many non-malignant diseases including CADASIL (Cerebral Autosomal Dominant Arteriopathy with Sub-cortical Infarcts and Leukoencephalopathy) [7], MS (Multiple Sclerosis) [8], Tetralogy of Fallot [9], Alagille syndrome: (genetic disorder that affects the liver, heart, and other systems) [10].

Regarding malignant neoplasms, Notch1 is involved in the pathogenesis of T-lymphoblastic leukemia (T-ALL), where it was shown that aberrant Notch signaling promotes tumorigenesis [11, 12]. The role of Notch as oncogenic factor was further supported in several studies [13-15]. However, there are also studies which strongly indicate a tumor

suppressor function for Notch [6, 12, 16-18]. Two recent studies showed that Notch1 mutations is a frequent event in HNSCC [19, 20]. In the study by Agrawal *et al.*, 40% of the Notch1 mutations were predicted to result in truncated gene product implying a tumor suppressor function of Notch in this malignancy [19].

Notch1 gene is a p53 target in human keratinocytes [18]. Inactivation of p53 by E6 protein of high-risk human papillomaviruses (HPVs) results in reduced Notch1 expression [21]. In oropharyngeal cancer cell lines, Deltex-1, a significant activator of Notch pathway, and HES1, a transcription factor whose expression is initiated by Notch, were found to be upregulated after repression of E6/E7 viral oncogenes [22]. Therefore, restoration of p53 after E6 silencing results in activation of Notch pathway in HPV16+ head and neck squamous cell carcinomas cell lines [22]. Taken together, it appears that Notch1 also functions as a tumor suppressor in HPV-associated malignancies.

In head and neck carcinomas, p16 expression is a surrogate marker for oropharyngeal primary site and HPV-association [23]. p16 expression defines biologically and clinically distinct subgroups of oropharyngeal squamous cell cancers (OSCC) [24]. In the present study, we sought to examine the prognostic value of Notch signaling pathway proteins in a retrospective cohort of HNSCC. In addition, our plan was to determine the association between p16 protein status and Notch signaling network protein expression.

PATIENTS & METHODS

Inclusion criteria were histologically confirmed primary squamous cell carcinomas of the head and neck treated at Yale-New Haven Hospital and the Aristotle University Hospital between 1992 and 2005, with either external beam radiotherapy (EBRT) or gross total surgical resection and postoperative radiotherapy. Exclusion criteria included presentation with metastatic or recurrent disease or failure to receive a full course of radiation therapy. Patients with incomplete clinical-pathological data or those lost to follow-up were also excluded.

Tissue Microarray Construction

Following institutional review board approval, tissue microarray was constructed as previously described [25]. Tissue cores of 0.6 mm in size were obtained from paraffin-embedded formalin-fixed tissue blocks from the archives of the Yale University and Aristotle University of Thessaloniki Department of Pathology. Hematoxylin- and eosin-stained slides from all blocks were first reviewed by a pathologist to select representative areas of invasive tumor to be cored. The cores were placed on the recipient microarray block using a Tissue Microarrayer (Beecher Instrument, Silver Spring, MD). All tumors were represented with at least two-fold redundancy. Previous studies have demonstrated that the use of tissue microarrays containing one to two histospots provides a sufficiently representative sample for analysis by immunohistochemistry. Addition of a duplicate histospot, while not necessary, does provide marginally improved reliability [25]. Cores from HPV16-positive SiHa cell lines fixed in formalin and embedded in paraffin were selected for positive controls and included in the array.

Quantitative Immunohistochemistry

Tissue microarrays were deparaffinized and stained as previously described [26, 27]. We analyzed the expression of Notch signaling pathway proteins (Notch1, Notch3, Notch4, Jagged1) using automated image acquisition and analysis (AQUA) on tissue microarray. Moreover, we examined expression of the Notch proteins in relation to outcome (overall survival) and p16 protein expression status.

Slides were incubated with primary antibody at 4°C overnight (see Table 1). For the correlation with p16 we used the p16 AQUA scores from a previous study, where the same tissue microarray was used [28]. These antibodies have been extensively validated in previous studies using immunohistochemistry and Western blot analysis of neoplastic tissue and tumor cell lines. Subsequently, slides were incubated with goat anti-mouse secondary antibody conjugated to a horseradish peroxidase-decorated dextran polymer backbone (Envision, Dako Corporation, Carpinteria, CA) for 1hr at room temperature. Tumor cells were identified by use of anti-cytokeratin antibody (rabbit anti-pan-cytokeratin antibody, 1:100, Z0622, Dako Corporation, Carpinteria, CA) with subsequent goat anti-rabbit antibody conjugated to Alexa 546 fluorophore (1:100, A11035, Molecular Probes,

Table 1.
Antibodies used for immunohistochemistry

Antibody target	Species	Type	Dilution	Company	Identifier
Notch1	rabbit	Monoclonal	1:100	Cell Signaling	
Notch3	rabbit	Polyclonal	1:250	Santa Cruz	sc-5593
Notch4	rabbit	Polyclonal	1:250	Santa Cruz	sc-5594
Jagged1	rabbit	Polyclonal	1:250	Santa Cruz	sc-8303

Eugene, OR). We added 4´, 6-diamidino-2-phenylindole (DAPI) to visualize nuclei (Prolong Gold with DAPI, P36931, Molecular Probes, Eugene, OR). Fluorescent chromogen Cy-5 tyramide (1:50, Perkin Elmer Corp, Wellesley, MA) was used for target identification. Cy-5 (red) was used because it is well outside the green-orange spectrum of tissue auto-fluorescence.

Automated Image Acquisition and Analysis

Automated image acquisition and analysis using automated quantitative protein analysis (AQUA) has previously been described [29]. It is an automated scoring system for assessing biomarker expression and constitutes an ideal scoring system for tissue microarrays, as it eliminates the subjectivity of the traditional scoring system and provides more continuous and reproducible results. In brief, monochromatic, high-resolution (1,024 1,024 pixel; 0.5µm) images were obtained of each histospot. We distinguished areas of tumor from stromal elements by creating a mask from the cytokeratin signal. 4´, 6-diamidino-2-phenylindole signal was used to identify nuclei, and the cytokeratin signal was used to define cytoplasm. Overlapping pixels (to a 99% confidence interval) were excluded from both compartments. The signal (AQUA score) was scored on a normalized scale of 0 to 255 expressed as pixel intensity divided by the target area. AQUA scores for each subcellular compartment as well as the tumor mask were recorded. AQUA scores for duplicate tissue cores were averaged to obtain a mean score for each tumor.

Statistical Analysis

Histospots containing <5% tumor as assessed by mask area (automated) were excluded from further analysis. Progression-free survival and overall survival were assessed by Kaplan-Meier analysis with log-rank score for determining statistical significance. We used the X-tile program [30] to select the optimal single cutoff for each of the examined proteins to distinguish between a group with high expression and a group with low expression. Associations between markers were assessed using a nonparametric Spearman rank correlation coefficient, rho and unpaired t test.

RESULTS

Clinical and Pathological Variables

Our study included 122 patients with histologically confirmed primary HNSCC. Demographic and clinicopathological variables for the cohort are summarized in Table 2. Eighty-one out of 122 cases had sufficient tissue for Notch1 analysis. Sixty-six out of 122 cases had sufficient tissue for Notch3 analysis. Eighty-two out of 122 cases had sufficient tissue for Notch4 analysis. Eighty-two out of 122 cases had sufficient tissue for Jagged1 analysis. For each of the examined proteins we excluded from the analysis those cases (among 122) which did not have sufficient tissue for our estimations. These cases did not differ from the ones included in our analysis with respect to patient gender, tumor, site, TNM stage, histological grade, and OS, as assessed by Fisher's exact test, and log-rank test, respectively. Demographic, clinical and pathologic data are given in Table 2.

The median tumor mask AQUA scores were: For Notch1: 902 (range 198-11017), for Notch3: 3191 (range 422-8874), for Notch4: 3691 (range 1001-9497) (Figures 1, 2), for Jagged1: 7545 (2649-16096). No correlation between AQUA score and survival was observed for Notch1, Notch3, Jagged1 (Figure 3A, 3B, 3C). However, using the X-tile program, we found a cutoff AQUA score (4657) at which high values of Notch4 were associated with better 5-year survival. The 5-year survival rate was 57% for patients with low Notch4 expression, while it was 72% for patients with high Notch4 expression. The Hazard Ratio was 2.2 for low Notch4 versus high Notch4 (p=0.05) (Figure 3D).

There were positive correlations between Notch1 and p16 (r=0.3538, p=0.0014), Notch1 and Jagged (r=0.3860, p=0.0005), Notch4 and p16 (r=0.2284, p<0.05), Notch4 and Jagged (r=0.6207, p<0.0001), Notch3 and p16 (r=0.3040, p=0.0131), Notch3 and Jagged (r=0.6877, p<0.0001), Notch1 and Notch4 (r=0.5199, p<0.0001), Notch1 and Notch3 (r=0.6134, p<0.0001), Notch3 and Notch4 (r=0.6422, p<0.0001). Each of the aforementioned correlations was validated by means of unpaired t test (p<0.05 in all cases).

Table 2.
Demographic, clinical and pathologic data

	n
Gender	
Male	66
Female	16
TNM stage	
I	6
II	11
III	23
IV	39
Unknown	3
Tumor site	
Oral cavity	25
Larynx	28
Oropharynx	22
Hypopharynx	3
Unknown	4
Tumor grade	
Well differentiated	12
Moderately differentiated	38
Poorly differentiated	22
Unknown	10

Figure 1.
Two histospots with low Notch4 expression (tumor mask AQUA score 1498 and 1074, respectively)

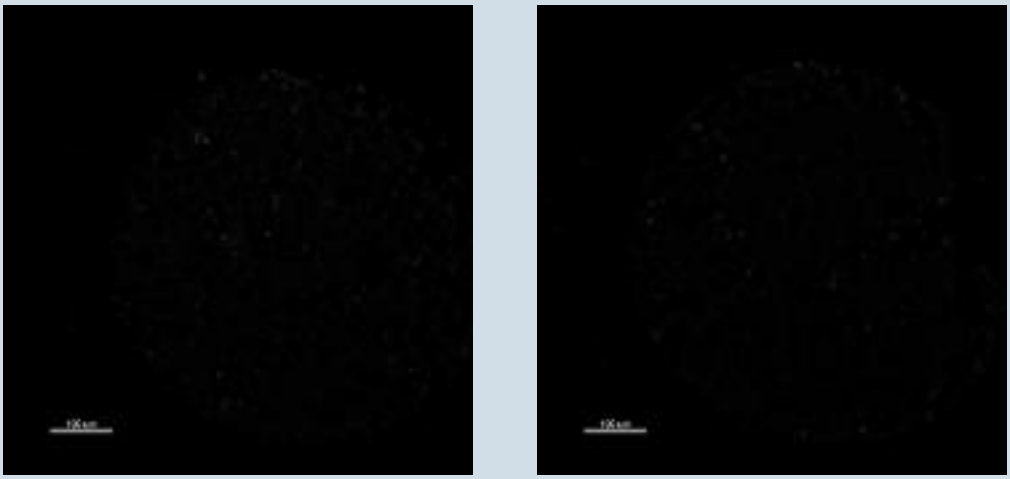
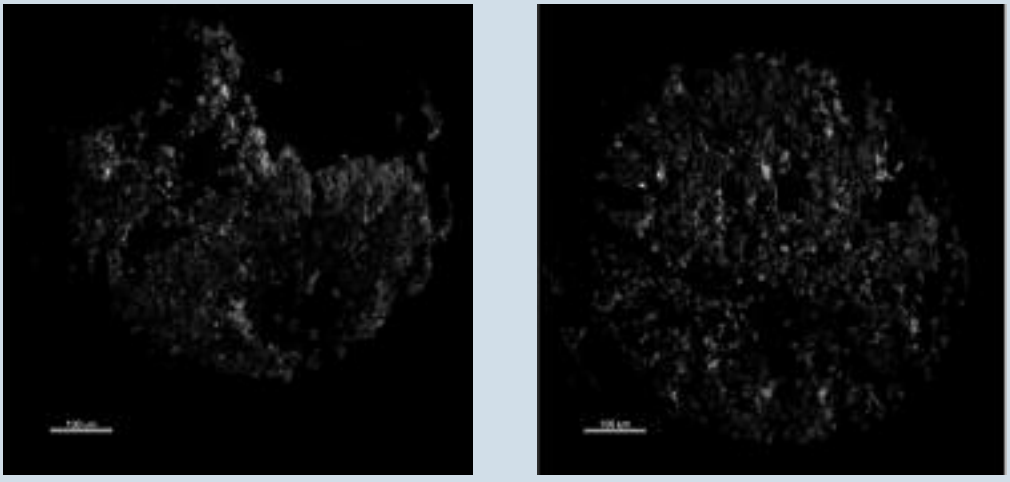


Figure 2.
Two histospots with high Notch4 expression (tumor mask AQUA score 6104 and 6265, respectively)



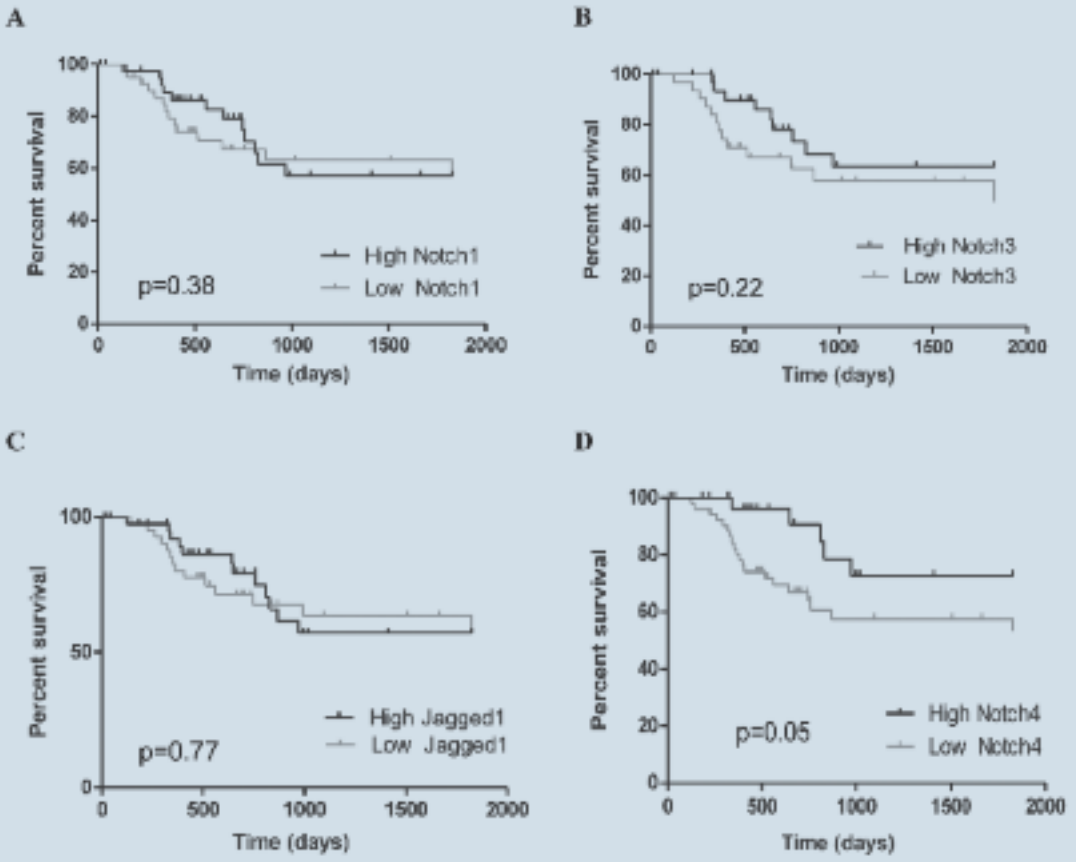
DISCUSSION

In the present study, we found that Notch4 protein expression might be a favorable prognostic marker in HNSCC. There was no association of Notch1, Notch3, Jagged1 with prognosis. Our study is limited by the retrospective nature of the cohort and the small number of cases. In addition, the statistical significance of the positive prognostic impact of Notch4 was marginal (p=0.05). Therefore, these results need validation in large cohorts before their clinical implementation.

Two recent studies reported on the mutational landscape of HNSCC [19, 20]. Agrawal *et al.* [19], by performing exome sequencing of HNSCC, identified inactivating mutations in Notch1 as a frequent event in this tumor type. Forty percent of the 28 mutations identified in Notch1 were predicted to result in truncated protein, suggesting that Notch1 functions as a tumor suppressor gene in HNSCC. In addition, Notch1 null mice develop epithelial tumors [16]. A tumor suppressor role for Notch1 has also been found in chronic myelomonocytic leukemia [31]. As discussed previously, Notch plays a dual role in carcinogenesis in a cell-type specific context: as an oncogene leading to stem cell maintenance in

Figure 3.

Kaplan-Meier survival curves comparing overall survival estimations between low and high Notch1 (A), Notch3 (B), Jagged1 (C) and Notch4 (D) groups. Patients with high Notch4 expression exhibit a higher probability of OS (OS at 5 years 72% vs. 57%)



some leukemias or as tumor suppressor leading to terminal differentiation in others such as HNSCC. Our findings are in line with these studies indicating a tumor suppressor role for Notch [6, 12, 16-19] in HNSCC. Contrary to our findings, a previous study had shown an association of Jagged1 and Notch1 expression with poor prognosis in head and neck cancer [32].

Positive correlations between each one of the three examined Notch proteins (Notch1, Notch3, Notch4) and Jagged are quite expected, because of the well-known role of Jagged as a Notch ligand. However, there seems to be an interesting co-expression of Notch1, Notch3, Notch4. There is also positive correlation between Notch1, Notch3, Notch4 with p16. As we have already mentioned, Deltex-1, a significant activator of Notch pathways, and HES1, a transcription factor whose expression is initiated by Notch, were found to be upregulated after repression of E6/E7 viral oncogenes [22]. In other words, HPV-induced oropharyngeal cancers are expected to demonstrate low expression of Notch pathway proteins. Regarding p16, HPV-induced oropharyngeal cancers demonstrate high expression of p16 [24]. Therefore, HPV-induced oropharyngeal cancers seem to be characterized by low Notch and high p16. It appears that inactivation of Notch is one of the mechanisms the virus utilizes to induce malignant phenotype in host cells.

In our study there is a positive correlation of Notch1, Notch3 and Notch4 with p16. What differentiates this study is that it includes cancers from all the head and neck sites, the vast majority of which are not HPV-induced. A previous study, which also included cancers from all the head and neck sites, validated p16 as a favorable prognostic marker in head and neck cancer [28], besides to its well-known role as favorable prognostic marker in oropharyngeal cancer. Therefore, the positive correlation of Notch proteins with p16 shown in our study is consistent with a possible role of Notch4 as positive prognostic factor. It is also consistent with the tumor suppressor function of Notch. The role of Notch signaling pathway proteins in head and neck cancer deserves further study.

REFERENCES

1. Artavanis-Tsakonas S, Rand MD, Lake RJ. Notch signaling: cell fate control and signal integration in development. Science 1999 Apr 30; 284(5415):770-6. Review.
2. Artavanis-Tsakonas S, Matsuno K, Fortini ME. Notch signaling. Science 1995 Apr 14; 268(5208):225-32. Review.
3. Gray GE, Mann RS, Mitsiadis E, Henrique D, Carcangiu ML, Banks A, et al. Human ligands of the Notch receptor. Am J Pathol 1999 Mar; 154(3):785-94.
4. Kunisch M, Haenlin M, Campos-Ortega JA. Lateral inhibition mediated by the Drosophila neurogenic gene delta is enhanced by proneural proteins. Proc Natl Acad Sci USA 1994 Oct 11; 91(21):10139-43.
5. Rooke JE, Xu T. Positive and negative signals between interacting cells for establishing neural fate. Bioessays 1998 Mar; 20(3):209-14. Review.
6. Dotto GP. Notch tumor suppressor function. Oncogene 2008 Sep 1; 27(38):5115-23. Review.
7. Louvi A, Arboleda-Velasquez JF, Artavanis-Tsakonas S. CADASIL: a critical look at a Notch disease. Dev Neurosci 2006; 28(1-2):5-12. Review.
8. Juryńczyk M, Selmaj K. Notch: a new player in MS mechanisms. J Neuroimmunol 2010 Jan 25; 218(1-2):3-11. Epub 2009 Sep 12. Review.
9. Eldadah ZA, Hamosh A, Biery NJ, Montgomery RA, Duke M, Elkins R, Dietz HC. Familial Tetralogy of Fallot caused by mutation in the Jagged1 gene. Hum Mol Genet 2001 Jan 15; 10(2):163-9.
10. Artavanis-Tsakonas S. Alagille syndrome - a notch up for the Notch receptor. Nat Genet 1997 Jul; 16(3):212-3.
11. Ellisen LW, Bird J, West DC, Soreng AL, Reynolds TC, Smith SD, Sklar J. TAN-1, the human homolog of the Drosophila notch gene, is broken by chromosomal translocations in T lymphoblastic neoplasms. Cell 1991 Aug 23; 66(4):649-61.
12. Radtke F, Raj K. The role of Notch in tumorigenesis: oncogene or tumour suppressor? Nat Rev Cancer 2003 Oct; 3(10):756-67. Review.
13. Zagouras P, Stifani S, Blaumueller CM, Carcangiu ML, Artavanis-Tsakonas S. Alterations in Notch signaling in neoplastic lesions of the human cervix. Proc Natl Acad Sci USA 1995 Jul 3; 92(14):6414-8.
14. Fre S, Pallavi SK, Huyghe M, Laé M, Janssen KP, Robine S, et al. Notch and Wnt signals cooperatively control cell proliferation and tumorigenesis in the intestine. Proc Natl Acad Sci USA 2009 Apr 14; 106(15):6309-14. Epub 2009 Feb 27.
15. Capobianco AJ, Zagouras P, Blaumueller CM, Artavanis-Tsakonas S, Bishop JM. Neoplastic transformation by truncated alleles of human NOTCH1/TAN1 and NOTCH2. Mol Cell Biol 1997 Nov; 17(11):6265-73.
16. Nicolas M, Wolfer A, Raj K, Kummer JA, Mill P, van Noort M, et al. Notch1 functions as a tumor suppressor in mouse skin. Nat Genet 2003 Mar; 33(3):416-21. Epub 2003 Feb 18.
17. Proweller A, Tu L, Lepore JJ, Cheng L, Lu MM, Seykora J, et al. Impaired notch signaling promotes de novo squamous cell carcinoma formation. Cancer Res 2006 Aug 1; 66(15):7438-44.
18. Lefort K, Mandinova A, Ostano P, Kolev V, Calpini V, Kolfschoten I, et al. Notch1 is a p53 target gene involved in human keratinocyte tumor suppression through negative regulation of ROCK1/2 and MRCKalpha kinases. Genes Dev 2007 Mar 1; 21(5):562-77.
19. Agrawal N, Frederick MJ, Pickering CR, Bettegowda C, Chang K, et al. Exome sequencing of head and neck squamous cell carcinoma reveals inactivating mutations in NOTCH1. Science 2011 Aug 26; 333(6046):1154-7. Epub 2011 Jul 28.
20. Stransky N, Egloff AM, Tward AD, Kostic AD, Cibulskis K, et al. The mutational landscape of head and neck squamous cell carcinoma. Science 2011 Aug 26; 333(6046):1157-60. Epub 2011 Jul 28.
21. Yugawa T, Handa K, Narisawa-Saito M, Ohno S, Fujita M, Kiyono T. Regulation of Notch1 gene expression by p53 in epithelial cells. Mol Cell Biol 2007 May; 27(10):3732-42. Epub 2007 Mar 12.
22. Rampias T, Sasaki C, Burtness BA, Psyrri A. Gene expression differences associated with silencing of E6 and E7 viral oncogenes in HPV16$^+$ oropharyngeal cancer cell lines. J Clin Oncol 2008 May 20; 26(suppl):abstr 6009.
23. Begum S, Gillison ML, Ansari-Lari MA, et al. Detection of human papillomavirus in cervical lymph nodes: a highly effective strategy for localizing site of tumor origin. Clin Cancer Res 2003; 9:6469-75.
24. Weinberger PM, Yu Z, Haffty BG, Kowalski D, Harigopal M, Brandsma J, et al. Molecular classification identifies a subset of human papillomavirus-associated oropharyngeal cancers with favorable prognosis. J Clin Oncol 2006 Feb 10; 24(5):736-47. Epub 2006 Jan 9.
25. Rimm DL, Camp RL, Charette LA, Costa J, Olsen DA, Reiss M. Tissue microarray: a new technology for amplification of tissue resources. Cancer J 2001; 7:24-31.
26. Psyrri A, Yu Z, Weinberger PM, et al. Quantitative determination of nuclear and cytoplasmic epidermal growth factor receptor expression in oropharyngeal squamous cell cancer by using automated quantitative analysis. Clin Cancer Res 2005; 11:5856-62.
27. Weinberger PM, Yu Z, Haffty BG, et al. Prognostic significance of p16 protein levels in oropharyngeal squamous cell cancer. Clin Cancer Res 2004; 10:5684-91.
28. Psyrri D, Pectasides E, Weinberger P, Sasaki C, Burtness B, Fountzilas G. Outcome and molecular features of head and neck squamous cell carcinomas (HNSCC) bearing a p16 high phenotype. J Clin Oncol 2009; 27:15s (suppl; abstr 6031).
29. Camp RL, Chung GG, Rimm DL. Automated subcellular localization and quantification of protein expression in tissue microarrays. Nat Med 2002 Nov; 8(11):1323-7. Epub 2002 Oct 21.
30. Camp RL, Dolled-Filhart M, Rimm DL. X-tile: a new bio-informatics tool for biomarker assessment and outcome-based cut-point optimization. Clin Cancer Res 2004; 10:7252-9.
31. Klinakis A, Lobry C, Abdel-Wahab O, Oh P, Haeno H, Buonamici S, van De Walle I, Cathelin S, Trimarchi T, Araldi E, Liu C, Ibrahim S, Beran M, Zavadil J, Efstratiadis A, Taghon T, Michor F, Levine RL, Aifantis I. A novel tumour-suppressor function for the Notch pathway in myeloid leukaemia. Nature 2011 May 12; 473(7346):230-3.
32. Lin JT, Chen MK, Yeh KT, Chang CS, Chang TH, Lin CY, Wu YC, Su BW, Lee KD, Chang PJ. Association of high levels of Jagged-1 and Notch-1 expression with poor prognosis in head and neck cancer. Ann Surg Oncol 2010 Nov; 17(11):2976-83. Epub 2010 Jun 2.

Linguistic validation of the Greek M.D. Anderson Symptom Inventory – Head and Neck Module

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ABSTRACT

Background: Our goal is to linguistically validate the Greek translation of the M.D. Anderson Symptom Inventory – Head and Neck Module.

Patients & Methods: Following forward and backward translation of the previously validated head and neck cancer specific items of the English MDASI-HN into Greek (G-MDASI-HN), it was administered along with a cognitive debriefing to head and neck cancer patients able to read and understand Greek. Individual and group responses are presented using descriptive statistics.

Results: From 02/2009 through 06/2009 30 subjects with head and neck cancer completed the G-MDASI-HN followed by completion of the accompanying cognitive debriefing. Ninety-eight percent of the individual G-MDASI-HN items were completed. "Voice" item was not completed by 5 patients. Average time to complete the G-MDASI-HN was 13.3 minutes. Average ease of completion was rated at 1.21 on a 0 to 10 scale with "0" being "very easy" and "10" being "very hard". Only 10% of patients reported trouble completing any item, namely "distress" and "numbness".

Conclusions: The Greek-MDASI-HN is linguistically valid and a patient-reported instrument that can be used both in outcomes research and as a clinical tool.

Key words: head and neck cancer; patient symptoms; patient-reported questionnaire; Greek MDASI-HN.

INTRODUCTION

Patients with cancer may be experiencing substantial tumor- or treatment-related symptoms, which can have great impact on their overall comfort and function. Optimal symptom control requires adequate and ongoing symptom assessment and should be guided by patient report, rather than by physician rating alone. Use of patient symptom reports for clinical decision making and effectiveness research may be preferred over quality of life measures, as patient symptoms are felt to more closely reflect the disease and treatment process [1]. The M.D. Anderson Symptom Inventory (MDASI) is a brief, reliable, and validated patient-reported questionnaire designed to capture and quantify general cancer- and treatment-related symptoms, which can help guide patient-specific and programmatic evaluations and interventions. The MDASI contains 13 core items representing important symptoms common across all cancer types and 6 items of how these symptoms interfere with major activities of daily life [2]. A Greek version of the MDASI has been previously validated in terms of content, construct, reliability, and known group validity [3].

The MDASI was designed so that modules for specific tumor and treatment sites could be developed. For a given anatomic location and depending on local tumor extent, patients with head and neck cancer can be subjected to a number of unique and serious symptoms. Furthermore, patients with head and neck cancer are commonly treated with a combined modality approach (combinations of chemotherapy, surgery, and/or radiation), known to be associated with significant acute and long-term toxicity. The MDASI-head and neck module (MDASI-HN) is a validated disease site-specific instrument, inclusive of the same 13 core and 6 interference items, plus an additional 9 tumor- and treatment-related symptoms important in head and neck cancer patients [4].

In order to ensure inclusion of Greek-speaking

head and neck cancer patients in future symptom prevention and intervention research studies that use the MDASI-HN as a primary endpoint measure and to allow integration of the MDASI-HN as a clinical assessment tool in primary Greek-speaking regions, our goal is to linguistically validate the Greek version of the MDASI-HN (G-MDASI-HN).

PATIENTS & METHODS

The MDASI had previously been translated into a Greek language version (G-MDASI) [3]. In order to develop the G-MDASI-HN, the 9 head and neck cancer specific items of the MDASI-HN were subsequently translated into Greek using standard forward and backward translation methods, procedures that we have been following as necessary first steps when psychometrically validating foreign language versions of the MDASI [5-9] and were recommended by an international task force [10].

Consecutive adult patients with malignancy of the head and neck region, able to read and understand Greek, were recruited at the Democritus University of Thrace Department of Radiation Oncology in Alexandroupolis, Greece. The G-MDASI-HN was self-administered by the participating patients and was completed using pencil and paper. All G-MDASI-HN symptom items are rated on 0 to 10 numeric scales from "not present" to "as bad as you can imagine", and the G-MDASI-HN interference items are rated on 0 to 10 numeric scales from "did not interfere" to "interfered completely". Time taken by each participant to complete the G-MDASI-HN was recorded by nursing staff. Since the purpose of this study was purely linguistic validation, patient demographic, tumor, and treatment details were not recorded.

To ensure ease of completion, relevance, and comprehensibleness of this translated version, and in keeping with recent recommendations, subjects also completed a cognitive debriefing of the G-MDASI-HN [10, 11]. The cognitive debriefing was completed with the assistance of nursing staff, who were both Greek- and English-speaking. Subjects were asked to rate overall ease of completion of the G-MDASI-HN. Subjects were queried if they were comfortable answering each specific item; if any item was unclear; and if they had any suggestion on how to make any item better. Subjects were also asked if any item was redundant; if any item should be deleted; or if any item should be added. Here we present the G-MDASI-HN item response rate and cognitive debriefing results using descriptive statistics.

RESULTS

From 02/2009 through 06/2009, 30 subjects participated and completed the G-MDASI-HN and the accompanying cognitive debriefing. Overall, 822 of the possible 840 (98%) individual G-MDASI-HN items were completed by the subjects. The most and second most likely items to be left blank by subjects were problems with "voice" and "constipation", which were not completed by 5/30 and 3/30 subjects, respectively.

Average time to complete the G-MDASI-HN was 13.3 minutes (range 5-30 minutes). Average G-MDASI-HN ease of completion was rated at 1.21 (range 0 to 7) on a 0 to 10 scale with "0" being "very easy" and "10" being "very hard". The majority of participants (19/30) thought that all G-MDASI-HN items, question, phrases, and words were easy to understand. Of the remaining 11, 6 subjects reported difficulty understanding "distress" or "numbness" items (3 for each item). Other individual items rated with some difficulty in understanding were "drowsy" (1 subject); "pain" (1 subject); "sad" (1 subject); "voice" (2 subjects); and "relate" (1 subject). All (30/30) subjects reported feeling "comfortable" answering each item. No subject thought any specific item should be deleted, and one subject suggested adding an alopecia-related item.

DISCUSSION

Here we report the linguistic validation results of the G-MDASI-HN. These cognitive debriefing results suggest overall ease of completion, relevance, and comprehensibleness of this translated patient-reported instrument in this Greek patient population. However, a few points require further discussion. Problems with "voice" was left blank by 5/30 subjects. While we don't have patient, tumor, or previous treatment details available, during cognitive debriefing two of these 5 queried whether this question pertained to "before or after laryngectomy". However, the MDASI-HN asks patients to rate the severity of their symptoms on a 0-10 scale over the past 24 hours. Therefore, we hypothesize that this question was left blank by these two subjects not because of trouble understanding the "voice" item, but rather failure to rate this item over the last 24 hour period and/or how to respond on a 0-10 scale if they had no speech (i.e. the patients may have had a laryngectomy without ability for speech). Ten percent of the subjects reported difficulty understanding the individual item related to "distress". Ten percent of subjects also reported difficulty understanding the "numbness" item. However, upon cognitive debriefing all three subjects asked for clarification of location of numbness, suggesting that they understood "numbness" but preferred to further characterize this symptom by describing location, rather than strictly assigning a severity rating. Since these items are part of the 13 core items from the MDASI, which has been previously validated in a larger study of Greek-speaking subjects [3], we continue to include these particular items in the G-MDASI-HN.

In conclusion, the G-MDASI-HN is a linguistically valid disease site specific version of the G-MDASI and can be a useful instrument in patient-reported outcomes research and a clinical tool to allow rapid identification of head and neck cancer patient specific symptoms in need of intervention.

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Conflicts of interest

The authors have none to disclose.

REFERENCES

1. Cleeland CS, Sloan JA. Assessing the Symptoms of Cancer Using Patient-Reported Outcomes (ASCPRO): searching for standards. J Pain Symptom Manage 2010 Jun; 39(6):1077-1085.
2. Cleeland CS, Mendoza TR, Wang XS, et al. Assessing symptom distress in cancer patients: the M.D. Anderson Symptom Inventory. Cancer 2000 Oct; 89(7):1634-1646.
3. Mystakidou K, Cleeland C, Tsilika E, et al. Greek M.D. Anderson Symptom Inventory: validation and utility in cancer patients. Oncology 2004; 67(3-4):203-210.
4. Rosenthal DI, Mendoza TR, Chambers MS, et al. Measuring head and neck cancer symptom burden: the development and validation of the M.D. Anderson Symptom Inventory, Head and Neck Module. Head Neck 2007 Oct; 29(10):923-931.
5. Ivanova MO, Ionova TI, Kalyadina SA, et al. Cancer-related symptom assessment in Russia: validation and utility of the Russian M.D. Anderson Symptom Inventory. J Pain Symptom Manage 2005 Nov; 30(5):443-453.
6. Lin C-C, Chang A-P, Cleeland CS, et al. Taiwanese version of the M.D. Anderson Symptom Inventory: symptom assessment in cancer patients. J Pain Symptom Manage 2007 Feb; 33(2):180-188.
7. Okuyama T, Wang XS, Akechi T, et al. Japanese version of the M.D. Anderson Symptom Inventory: a validation study. J Pain Symptom Manage 2003 Dec; 26(6):1093-1104.
8. Wang XS, Wang Y, Guo H, et al. Chinese version of the M.D. Anderson Symptom Inventory: validation and application of symptom measurement in cancer patients. Cancer 2004 Oct; 101(8):1890-1901.
9. Yun YH, Mendoza TR, Kang IO, et al. Validation study of the Korean version of the M.D. Anderson Symptom Inventory. J Pain Symptom Manage 2006 Apr; 31(4):345-352.
10. Wild D, Grove A, Martin M, et al. Principles of Good Practice for the Translation and Cultural Adaptation Process for Patient-Reported Outcomes (PRO) Measures: Report of the ISPOR Task Force for Translation and Cultural Adaptation. Value Health 2005 Apr; 8(2):94-104.
11. Guidance for industry: patient-reported outcome measures: use in medical product development to support labeling claims: draft guidance. Health Qual Life Outcomes 2006; 4:79.

Sleep-wake disturbances in patients with cancer and their informal caregivers: a matter of dyads

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ABSTRACT

Background: Changes in habitual sleep are among the most remarkable and important concerns of both patients with cancer and their informal carers. A dyadic approach in the assessment and management of sleep problems in patients and carers is a promising method of exploring concurrent sleep disturbances and establishing associations between sleep and sleep-impairing factors that may co-vary in the members of the dyad. The purpose of the present mini-review article was to discuss the current evidence, as well as highlight areas where future research is warranted.

Patients & Methods: An electronic search for original peer-reviewed articles published between January 1990 and July 2011 in three research and evidence databases (MedLine, CINAHL, EMBASE) was carried out using a wide range of keywords and free-text terms. Cancer care-related evidence was complemented by additional data derived from studies conducted with married couples or in the context of other chronic illnesses.

Results: Concurrent and comparable nocturnal sleep disruptions might be evident, where poor sleep quality, decreased sleep duration, and multiple awakenings may correlate with each other within the dyad. Care recipients' and caregivers' night and day rest patterns can be synchronised, as caregivers organise their sleep around the patient.

Conclusion: More systematic, dyadic research is warranted to enhance development of intervention protocols for the comprehensive management of sleep disorders in this population throughout the illness experience. These interventions will ensure that sleep patterns are assessed in depth and are managed in a concurrent manner to achieve a concurrent increased level of well-being of patient-caregiver dyads.

Key words: sleep; sleep-wake disturbances; cancer; informal caregivers; dyads; interdependence; dyadic approach.

INTRODUCTION

Sleep is a vital human process known to be essential for health, well-being, and optimal physical and psychological functioning [1, 2]. It is therefore reasonable to argue that sleep-wake disturbances may have serious consequences on the equilibrium of life [3, 4]. Sleep difficulties have been reported as a frequent complication of and are associated with various clinical conditions [5]. Over the last fifteen years, the attention of the scientific community has shifted towards systematic investigation of sleep disorders during the experience of cancer as an important aspect of care.

A cancer diagnosis severely disturbs a person's continuum of life. Sudden changes imposed after the diagnosis and during the ensuing anticancer treatment may profoundly affect the person, resulting in several sources of discomfort, among which sleep-wake disturbances and poor sleep quality [3]. Especially throughout the period of diagnosis and treatment, but also during survivorship or, conversely, during palliative care, people with cancer are in great need of support. To a significant extent this support is expected to be provided by their significant others, family members or friends, whom patients feel they receive support from, and are frequently recognized as their informal caregivers [6]. Their practical and emotional involvement, however, often and in other cases considerably affects the caregivers' own lives [7]. Caregiving can be so demanding and stressful that the burden on these persons may lead to disruptions in their sleep as well [6].

This combined situation of sleep deprivation

may be a reality for some patients and their informal caregivers as they strive to survive health care system demands, and also to effectively cope with illness both as individuals and as members of a relationship. As they share closely their everyday concerns, patients and caregivers may be faced with similar challenges and may manifest most of their needs at the same time. Sleep problems may be prominent for both the patients and their caregivers, even at the same time, possibly over a considerable time period and, in other cases, long after treatment is completed, thus posing an additional short-, mid- or long-term burden on their lives.

Therefore, the purpose of the present mini-review article is to discuss the current evidence regarding the added value of a dyadic approach in the assessment and management of sleep disorders, by including both patients with cancer and their informal caregivers, as well as highlighting areas where future research is warranted. In order to facilitate presentation of related concepts, the article has been divided into three major sections. The first section provides evidence on the magnitude of disrupted sleep patterns in people and families affected by cancer. The second section discusses the benefits of a dyadic approach in health research, whereas the final section analyses the application of this dyadic approach in sleep research and synthesises findings from sleep studies conducted concurrently with cancer patients and their caregivers.

THE EXPERIENCE OF DISRUPTED SLEEP IN THE CONTEXT OF CANCER

Changes in habitual sleep are among the most remarkable and important concerns of patients with cancer [8], and among the most prominent and debilitating symptoms of their caregivers [9]. Patients and caregivers identify sleep-related issues as vital aspects of the experience of cancer. Whereas for healthy people sleep provides a needed refuge from everyday demands, for those affected by cancer it constitutes a form of respite from the ongoing physical discomfort and psychological distress, thus allowing them to meet the next day with renewed energy and motivation [5].

The subjective importance patients with cancer and their caregivers attribute to sleep-wake disruptions has potential consequences for behaviours associated with self-care and identification of symptoms, help-seeking strategies and reporting of disturbances to the health care team, as well as acceptance and compliance with recommended therapeutic interventions [10, 11]. On the other hand, objective significance of sleep disorders includes their potential to strongly influence clinical and care-related outcomes in patients with cancer [2], including fatigue [12-16], performance status [17, 18], mood [19-23], immune function [24], quality of life [23, 25, 26], and survival [27-29]. This reported significance warrants and dictates the need for continuing intervention and relief of patients in times of distress.

Sleep patterns of patients with cancer

The empirical observation of disordered sleep in people with cancer has been supported and boosted by systematic research -especially in the last decade. Current knowledge indicates that disordered sleep is one of the commonest (only second to fatigue) [30] symptoms, twice as prevalent compared to the general population [31]. Total sleep time of less than 50 hours per week [32]; fewer than usual hours of sleep [33]; multiple awakenings in the middle of the night; and difficulty falling sleeping have been reported in varying rates in studies with mixed samples of cancer patients [33, 34]. Moreover, decreased sleep duration and efficiency [35]; very early morning awakening; leg restlessness; interruptions of breathing during sleep [34]; as well as drowsiness [36]; daytime sleepiness [8]; and a need to sleep at unusual hours during the day [33] are frequent complaints. There is some evidence that patients with cancer tend to dream more than usual and to have frightening or unpleasant dreams [8, 37], which may be accompanied by not feeling rested the following day [35], urging the need for use of prescribed hypnotics or over-the-counter sedatives [35, 38, 39]. Although much more research is warranted to shed light on different aspects of disrupted sleep and its meaning for people with different types of cancer, stages of disease, or phases of treatment, this evidence is indicative of a problem that requires the attention of health care professionals.

Sleep patterns of cancer patient caregivers

Sleep research in the context of cancer caregiving has gained some interest over the past 15 years; yet, sleep disturbance remains one of the least assessed symptoms as revealed in a recent review [9] and more systematic investigation is required to fully understand the trends of and influences on sleep patterns of cancer caregivers [6]. Despite the absence of a consistent method of assessment, evidence derived mainly from cross-sectional studies with non-homogeneous samples with regard to phase of cancer experience (palliative care, survivorship, active treatment) or duration of caregiving shows that sleep of cancer patient caregivers also becomes disrupted [9]. In general, difficulty falling and staying asleep; experience of restless and non-restorative sleep; as well as development of insomnia and chronic sleep loss may be common complaints raised by cancer patient caregivers [3, 40]. Albeit poorly explained, some evidence exists that cancer patient caregivers might experience restless sleep and problems staying asleep to a greater extent compared to caregivers of patients with other illnesses such as AIDS or age-related dementias [41], but studies evaluating caregivers of patients with Parkinson's [42, 43] or Alzheimer's [43, 44] disease point to the direction of general similarities in sleep disturbance. Yet, occurrence, frequency and/or severity of these sleep problems may vary widely, mainly but not solely depending on the overall caregiving situation [6]. Existent evidence is indicative of this variability, highlighting the need for a

cautious interpretation when more general conclusions are to be drawn [6].

THE PATIENT-CAREGIVER DYAD: BEYOND INDIVIDUALISM

In the previous section, there was a careful distinction in the account of concept-related and sleep-related research data pertinent to patients with cancer and their caregivers. However, in reality, changes in the lives of the person receiving cancer care and the person providing informal care take place in tandem, and illness is often experienced and managed in the context of a complex network of relationships [45]. In that sense, interdependence between parties of close relationships may exist, and has been accounted as the defining feature of human relationships [46]. At the level of a dyad (otherwise, a pair of closely related persons), interdependence and reciprocal influence can characterise the nature of the relationship and influence the ways in which people communicate, grow and thrive, as well as cope in the wake of major events and challenges [47].

By accepting the probability of complex interactions in their relationship, it is reasonable to argue that patients and their caregivers may react to cancer as a unit and, as a result, both have legitimate interrelated needs for help from health care professionals [48, 49]. There is a general consensus among clinicians and researchers that when patients and caregivers are treated simultaneously, important synergies can be achieved contributing to the well-being of each person [50, 51]. Conversely, when these interrelated and often concurrent needs are neglected, patient-caregiver dyads are denied the opportunity to obtain optimal care. Therefore, Northouse *et al.* [48] and Fletcher *et al.* [47] claim that in order to provide optimal comprehensive cancer care and enhance research, the care plan must focus on these patient-caregiver units.

Several health- and quality of life-related variables have been frequently conceptualised in an individualistic way; however, social contextual models argue that health outcomes are likely to co-vary in close relationships, as in the patient-caregiver relationship. For instance, any change in the functioning of one individual can affect the functioning of his/her significant others, and vice-versa [52]. Similarly, although external factors, such as disease severity and social support, may affect patients' and caregivers' physical and psychosocial well-being directly and unidirectionally, patient and caregiver interdependence may contribute to a bidirectional situation, in which the well-being of each individual in the dyad also affects the well-being of the other [53].

The notion that the patient-caregiver relationship comprises two people, both of whom influence and are influenced by the other, has been stressed as particularly relevant to health care in general [54, 55]. To address and confirm this reciprocity, a shift in cancer research is evident towards inclusion of patient-caregiver dyads rather than merely patients or caregivers alone [47]. In turn, this novel approach promises to enhance care by revealing salient aspects of care existing within the mutuality of the patient-caregiver relationship. Albeit logically reasonable, only relevant research evidence will establish the effects of such dyadic approach.

An overview of the most relevant literature reveals a number of studies dyadically exploring the illness experience of patients and their caregivers [56-68], or testing interventions targeting the dyad [69-74] or the caregiver alone [75] to promote dyadic well-being. There is some weak evidence that during survivorship patients' greater psychological distress might predict significantly poorer physical health in their caregivers, and vice versa [58]. Similarly weak evidence indicates that patients' fear of disease recurrence might affect the carers' own fear of recurrence and distress over time [57], but remains unclear whether this association extends beyond six months post-diagnosis; is influenced by dyadic adjustment to illness; or is true for dyads affected by cancers other than head and neck cancer. Along these lines, examination of the intra- and inter-personal consequences of protective buffering among patients and their partners suggests that the more patients hide cancer-related thoughts and concerns from their partners, and the more they feel that their partner hides their own concerns, the lower their concurrent relationship satisfaction and the poorer their mental health might be [59]. Additionally, mutual avoidance and communication withdrawal can be responsible for poor perceived intimacy, ultimately leading to concurrent psychological distress in heterosexual couples in long-term relationships [60, 61]. Due to absence of proven causality, however, the possibility that dissatisfied or distressed partners might exclude each other from their most intimate thoughts cannot be ruled out. Being partially dissatisfied and not feeling privileged in taking care of the sick spouse have been suggested as possible mediators of incongruence in patient and caregiver perceptions of quality of life [56]. Drawing on some of these findings, education interventions [70, 74] and stress-reduction programmes [71] have targeted the dyad for possible joint effects. In spite of some promising concurrent improvements in psychological distress [70, 71], mood [71, 74] and quality of life [74], there is still an outright need to establish superiority of dyadic interventions not only over control groups, but also over groups in which one member of the dyad receives the intervention (four-group designs); as inconclusive findings indicate [74], this can only happen when methodological rigour supersedes the above-mentioned limitations.

Interestingly, the majority of studies have focused only on bidirectional associations of specifically psychological distress with the dyads' well-being, quality of life, or other external predictors, whereas potentially interrelated bio-behavioural symptoms such as sleep or fatigue have not yet been systematically examined in patient-caregiver dyads. Closely related to this, the association between the dyad's long-term adjustment and interrelated health outcomes has yet to be fully explored. This could be facilitated by conducting

longitudinal, repeated-measures studies over extended periods of time, even one or two years after major events or transitions have taken place. Nonetheless, only a limited number of studies have implemented a truly adequate prospective design to test direction of associations, but this strategy does not necessarily ensure that generalisability is feasible. Furthermore, exploration of dyadic changes of outcome variables has very commonly taken place over select time points thereby unlinked to transition to the different phases of cancer experience, such as prospective re-assessments conducted following diagnosis (e.g., 6- or 12-month follow-ups) or during survivorship or remission. It is, however, interesting for interrelated outcomes to be examined at time points where major events occur, such as post-diagnosis and before, during and after active treatment, during transition from one treatment modality to another, at relapse and related health care decisions, or before, during and after hospice or palliative care. Bearing in mind these important limitations, supporting findings need to be treated as only indicative, but certainly not definitive, of a complex interaction between patient- and caregiver-related outcomes in the context of cancer.

DYADIC APPROACH IN SLEEP RESEARCH: A NOVEL CONCEPT

The onset and maintenance of sleep are dependent on meeting a series of physiological conditions including adequate level of physical comfort, and relative absence of psychological distress and psycho-physiological arousal [5]. Therefore, it has been argued that for the vulnerable state of sleep to occur, persons need to feel physically and emotionally safe and secure to down-regulate vigilance and cease alertness [76, 77]. An adequate social environment may be particularly important for such feelings to emerge [78]. Thus, for humans, sleep is regarded as a fundamental attachment behaviour that may be regulated within and affected by close human relationships [76, 79], one of which is the patient-caregiver one. In that sense, the fact that the science of sleep has tended to view sleep as an entirely individual phenomenon can be described as a rather confined approach, impeding assessment and management of sleep disorders that might manifest themselves especially during periods of adjustment to illness [80]. As described earlier, interdependence is a defining feature of relationships and might also be a defining feature for sleep as seen in the context of a close patient-caregiver relationship [81].

Attachment theory has been implemented to provide a perspective of the link between close relationships and sleep [76]. According to this theory, early interactions with caregivers lead to the development of expectations from them to be responsive to one's needs [76, 82]. Especially in times of real or perceived threat, these key expectations are thought to mediate affect and arousal [78, 83]. This might suggest that the closer the relationship, the greater the odds of a good night's sleep, and vice versa [80]. Although attachment theory has been used thus far to guide research in the field of couples' relationship functioning and sleep [76], it could, to a certain extent, justify the value of concurrent assessment of sleep patterns of patients and their primary family or non-family caregiver [78]. Caregivers who, regardless of their actual caregiving tasks, value their role as important to them and the patient they care for, might be more affectionate towards the patient; this in turn could lead to patients feeling more secure in their relationship and sleeping better [80].

On the other hand, as patients and caregivers go through the experience of illness together, their emotional reactions and distress affect one another in a relatively proportionate manner, adding to one's own concerns and worries when they reach a peak, or relieving from additional distress when they simmer down, and possibly resulting in corresponding changes in sleep patterns. In a similar manner, effective or dysfunctional coping strategies of the dyad might co-affect their sleep through a psycho-behavioural mechanism. Moreover, while it is more than obvious that patient symptom distress can lead to increased caregiving efforts, disrupted caregiver sleep patterns and increased fatigue coupled with daytime sleepiness, increased caregiver burden can equally lead to poor caregiving performance, which might in turn inhibit management of symptoms influencing sleep, or disordered sleep itself. Similarly, although not all patients and caregivers share the same bed or the same room, co-sleeping or cohabitating dyads might be co-affected by poor sleep hygiene practices or by disrupted sleep patterns related to the illness experience. Such sleep mediators might well interfere with the prerequisites necessary for a good night's sleep at a level that transcends the individual.

It has been argued that in a situation involving the co-presence of persons, cooperation is required to promote sleep for both parties [84]. In cohabitating or co-sleeping patients and caregivers, this "cooperation" becomes blurred given that patient symptom experience, caregiver burden and associated frustration can alter sleep habits/rituals or restrict actual sleep of the dyad in a way that concordance might be no longer feasible. Drawing on the above arguments, implementation of a dyadic approach can usefully augment our understanding of co-occurrence of sleep problems in patient-caregiver dyads, trends of concurrent transformation of these sleep problems across time, and covariates/factors that appear to contribute to these patterns within the dyad and across time. Such an approach may prove essential in the development of truly effective treatment strategies [76, 85, 86].

Evidence in the context of couples' research

Despite recognition of the dyadic nature of sleep for most adults, there has been surprisingly little investigation of human sleep patterns in a paired manner. To date, relevant sleep research has focused mainly on the nocturnal sleep patterns and daytime impairments of co-sleeping hetero-

sexual couples either in the absence of a medical illness or in the presence of a primary sleep disorder such as obstructive sleep apnoea (OSA). However, insights from research with couples can be fruitfully incorporated into the patient-caregiver-related research [47].

In the general population, Meadows *et al.* [81] reported that the variables showing the most significant couple interdependency in cohabitating heterosexual couples were actual bed time, sleep latency, light/dark movement ratio, and wake bouts (the number of nocturnal awakenings). Despite this interesting -yet inconclusive- evidence suggesting a close interrelation in couples' sleep patterns, presence of a bed-partner has been also viewed as a potential source of sleep disturbances: relevant research has demonstrated significantly lower levels of Stage 4 non-rapid eye movement sleep (NREM) [87], a concomitant increase in REM sleep [87], and a greater number of movements during sleep [87, 88] on the nights when participants slept with their partners rather than when they slept alone. In spite of this reciprocal impact on one another's sleep, participants have reported less satisfaction with their sleep when sleeping alone [87, 88]. In a sample of couples without sleep disorders, Pankhurst and Horne [88] observed more movements in men than in women, with women reporting that their sleep was affected by their partners sleep more than did men. Men are also more often loud snorers [89], and the sound of snoring can be a major disturbing factor of their bed-partner's sleep, who might report symptoms of insomnia, morning headache, daytime sleepiness and fatigue [90]. This might be especially true in the context of OSA. OSA has been referred to as a "disease of listeners" [91]; aside from snoring, increased arousals often adversely affect both the bed-partner's and the individual's sleep [90, 92].

Similarly, several efforts have been made to identify a link between reported or observed sleep disturbances within the couple with relationship functioning or quality [93-95] and attachment behaviours [96-98]. Although a positive unidirectional association has been established, evidence is mainly based on either cross-sectional dyadic studies [95, 96] or single-arm studies [93, 94, 97, 98]. Nonetheless, in a very recent longitudinal study of 29 young adult couples, Hasler and Troxel [99] showed the existence of some bidirectional associations between interpersonal interaction and sleep parameters, specifically sleep efficiency and sleep concordance. Women-reported more positive daytime partner interaction was found to predict higher objective perceived sleep efficiency for themselves, as well as higher perceived sleep efficiency of their male partners [99]. These results imply existence of interdependence in night-time sleep and daytime relationships; however, aside from the small study sample and several inconsistencies in data derived from both objective and subjective sleep measures, findings also seem to be largely confined in the limited context of young, happy and childless couples with no concurrent illnesses, who are good sleepers.

Evidence in the context of cancer research

Albeit promising, evidence regarding sleep patterns and sleep-interfering factors in patient-caregiver dyads, irrespective of the context of medical illness, is rather scarce; disappointingly, this is especially true for cancer care. Our systematic search of the relevant literature revealed only two recently published studies, where sleep patterns of patients with cancer and their informal caregivers were evaluated in a dyadic manner [80].

Gibbins *et al.* [100] examined sleep patterns of sixty patients with advanced cancer (lung, breast, prostate, colorectal) and their co-residing family caregivers over a one-week period. In twenty-three per cent of the pairs both reported not sleeping well, while in 45% of the pairs either the patient or the caregiver reported not sleeping well. Disappointingly, sleep parameters within these differing sleep categories were not explored, nor were group differences examined. Forty-seven per cent of patients and 42% of the caregivers reported overall poor sleep. Yet again, use of sleep medication was reported as low, especially for the caregivers (10%). Interestingly, actigraphic data revealed that in only 12% of the patients and 8.3% of the caregivers sleep efficiency was less than 86% over the seven-night period. Nevertheless, sleep fragmentation and movement was high in both patients and caregivers, with patients having at least clinically higher degrees of sleep fragmentation than caregivers throughout assessment. While the average percentage of time awake was largely similar for the dyads over time, a consistently greater variability was revealed for the caregivers, whose wake times varied by a 4-fold compared to those of the patients. Overall, activity levels were consistently higher for caregivers, whereas time immobile in the daytime was greater for patients. Patient poor sleep was associated with higher anxiety and increased body pain. Similarly, caregiver poor sleep was associated with high levels of anxiety and global distress. However, findings were non-existent with regard to potential interacting factors affecting sleep of the dyads; only 28% of the caregivers spontaneously reported being disturbed by the patient.

Approximately one week prior to primary or adjuvant radiation therapy for non-metastatic breast, prostate, lung or brain cancer, Carney *et al.* [101] explored sleep patterns of 102 patient-caregiver dyads. Subjective occurrence of sleep disturbance was similar in both groups (~40% to ~50%), whereas only partial differences regarding use of sleep aids and mid-sleep awakenings were found based on the perceived severity of sleep disturbance. Similarly, objective data revealed no significant differences, except for less mean sleep efficiency in patients compared to caregivers (81.4% v. 84.1%). On the basis of this data, both patients and family caregivers had a significant and concurrent problem with sleep maintenance, which was depicted in their increased and highly correlated number of nocturnal awakenings (~18 per night in both groups) that lasted 3 to 4 minutes; their less than 7 hours sleep; and their below 85% sleep efficiency.

What is more, dyads seemed to synchronise their sleep and wake patterns, as well as their daytime napping. These findings may suggest that if a patient slept poorly, so did his/her caregiver, and vice versa; however, due to the non-prospective nature of the study it is not possible to rule out the possibility that correlations could be merely accidental, rather than implying a causal link. Then again, potential contributing factors were not explored, rendering future research necessary.

Despite the dearth of studies in the field, promising findings have been yielded suggesting bidirectional associations in the sleep of care recipient-caregiver dyads [80]. Converging evidence complemented by studies conducted in the context of dementia [85, 86, 102, 103], Parkinson's disease [42, 104, 105], or ageing [106] suggest that concurrent and comparable nocturnal sleep disruptions might be evident, where poor sleep quality, decreased sleep duration, multiple awakenings, and daytime dysfunction may correlate with each other within the dyad. Care recipients' and caregivers' night and day rest patterns can be synchronised, as caregivers organise their sleep around the patient [80]. As a potential consequence, where the illness is more severe and the overall caregiving situation is more difficult, intense, and prolonged, patient-caregiver dyads may be at greater risk of concurrent sleep disturbances. Especially in dyads sharing a bedroom, a patient's sleep patterns might be a function of the caregiver's sleep, and vice versa. Yet, the effect of sharing a bedroom remains questionable, a field of interference of several influential variables, and answers can only be provided by adequately powered longitudinal studies using predictive models of associations [80].

CONCLUSIONS AND FUTURE IMPLICATIONS

Neither the patient nor the caregiver goes through the experience of cancer independently, but rather as a pair. Several urgent or constant patient needs can lead to disruption of caregiver sleep patterns, whereas increasing caregiver burden can lead to diminished ability to provide care with that resulting to perpetuated disrupted sleep of patients due to unrelieved symptoms or unmet concerns. Disrupted sleep may be so overwhelming that it undermines patients' well-being as well as caregivers' ability to provide efficient care. With these events occurring at the same time, distress due to disrupted sleep patterns in either person becomes even more unbearable. When disturbed nocturnal sleep or daytime dysfunction is evident or suspected, further assessment is warranted to facilitate timely and dyad-tailored interventions.

Longitudinal, repeated-measures research drawing on a combination of self-report (sleep questionnaires, daily sleep logs) and objective (wrist actigraphy, ambulatory polysomnography) sleep measures also is warranted to establish associations between patient and caregiver sleep patterns, as well as qualitative methodologies to reveal salient characteristics of this relationship and underscore the subjective importance of concurrent sleep problems for patients living with cancer and their caregivers. As the majority of studies have thus far aimed at recruiting partners or family members, future research is required to implement a broader definition of the caregiver [80]. Closely related to this trend, with caregiver samples included being women over a mean age of 55, reports of sleep disturbance incidence may have been influenced, as poor sleep might have been the result of associated menopausal symptoms, hyperarousability or past sleep problems, rather than just the caregiving experience itself or patient sleep patterns [80]. Perhaps the inclusion of predominantly or exclusively male caregivers could result in different associations.

Interestingly, evidence as to the nature of factors that co-affect sleep of patients with cancer and their caregivers still remains close to zero [80]. The aetiology of sleep disorders in cancer patients and their caregivers is multidimensional, since multiple factors are likely to alter the normal regulatory processes of sleep [4, 107]. Onset and maintenance of normal or habitual (the one a person considers as normal and "functions" as normal for him/her) sleep is dependent on a host of person- and environment-related prerequisites. Knowledge of the underlying reasons may guide in-depth assessment and targeted treatment of sleep disorders [108], given that care is specifically rather than vaguely focused on the source of the problem, potentially leading to quicker relief and dramatic improvement in sleep quality and sleep-related outcomes. Processing dyadic data on sleep patterns and sleep-impairing covariates with more sophisticated, state-of-the-art analytic models such as the multivariate two-level model for matched pairs' data [109], or the Actor-Partner Interdependence Model (APIM) [46] could permit adequate exploration of inter-dyad effects [47]. In addition, mixed-method studies integrating quantitative and qualitative data [110] could be particularly useful in the clarification of underlying mechanisms in the development of dyadic sleep disturbances.

It is hoped that future research will enhance development of intervention protocols for the comprehensive management of sleep disorders in people with cancer and their informal caregivers throughout their illness experience. These interventions will ensure that sleep patterns are assessed in depth and are managed in a concurrent manner to achieve a simultaneously increased level of well-being for patient-caregiver dyads.

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Conflicts of interest

The authors declare that there are no financial or personal conflicts of interest with regard to the present study.

REFERENCES

1. Kotronoulas G, Stamatakis A, Stylianopoulou F. Hormones, hormonal agents, and neuropeptides involved in the neuroendocrine regulation of sleep in humans. Hormones (Athens) 2009; 8:232-48.
2. Clark J, Cunningham M, McMillan S, Vena C, Parker K. Sleep-wake disturbances in people with cancer part II: evaluating the evidence for clinical decision making. Oncol Nurs Forum 2004; 31:747-71.
3. Berger AM, Parker KP, Young-McCaughan S, Mallory GA, Barsevick AM, Beck SL, et al. Sleep wake disturbances in people with cancer and their caregivers: state of the science. Oncology Nursing Forum 2005; 32:E98-126.
4. Vena C, Parker K, Cunningham M, Clark J, McMillan S. Sleep-wake disturbances in people with cancer part I: an overview of sleep, sleep regulation, and effects of disease and treatment. Oncology Nursing Forum 2004; 31:735-46.
5. Sateia MJ, Santulli RB. Sleep in palliative care. In: Doyle O, Hanks GWC, MacDonald N, editors. Oxford Textbook of Palliative Medicine. 2nd edition ed. New York: Oxford University Press; 1998. p. 731-46.
6. Kotronoulas G, Wengström Y, Kearney N. Sleep patterns and sleep-impairing factors of persons providing informal care for people with cancer: A critical review of the literature. Cancer Nurs 2012, in press.
7. Soothill K, Morris SM, Harman JC, Francis B, Thomas C, McIllmurray MB. Informal carers of cancer patients: what are their unmet psychosocial needs? Health Soc Care Community 2001; 9:464-75.
8. Davidson JR, MacLean AW, Brundage MD, Schulze K. Sleep disturbance in cancer patients. Soc Sci Med 2002; 54:1309-21.
9. Swore Fletcher BA, Dodd MJ, Schumacher KL, Miaskowski C. Symptom experience of family caregivers of patients with cancer. Oncology Nursing Forum 2008; 35:E23-E44.
10. Cobleigh MA. Hormone replacement therapy and nonhormonal control of menopausal symptoms in breast cancer survivors. Cancer Treat Res 1998; 94:209-30.
11. Couzi RJ, Helzlsouer KJ, Fetting JH. Prevalence of menopausal symptoms among women with a history of breast cancer and attitudes toward estrogen replacement therapy. J Clin Oncol 1995; 13:2737-44.
12. Anderson KO, Getto CJ, Mendoza TR, Palmer SN, Wang XS, Reyes-Gibby CC, et al. Fatigue and sleep disturbance in patients with cancer, patients with clinical depression, and community-dwelling adults. J Pain Symptom Manage 2003; 25:307-18.
13. Andrykowski MA, Curran SL, Lightner R. Off-treatment fatigue in breast cancer survivors: a controlled comparison. Journal of Behavioral Medicine 1998; 21:1-18.
14. Broeckel JA, Jacobsen PB, Horton J, Balducci L, Lyman GH. Characteristics and correlates of fatigue after adjuvant chemotherapy for breast cancer. J Clin Oncol 1998; 16:1689-96.
15. Molassiotis A. A correlational evaluation of tiredness and lack of energy in survivors of haematological malignancies. Eur J Cancer Care (Engl) 1999; 8:19-25.
16. Cho MH, Dodd MJ, Lee KA, Padilla G, Slaughter R. Self-reported sleep quality in family caregivers of gastric cancer patients who are receiving chemotherapy in Korea. J Cancer Educ 2006; 21:S37-41.
17. Given B, Given C, Azzouz F, Stommel M. Physical functioning of elderly cancer patients prior to diagnosis and following initial treatment. Nurs Res 2001; 50:222-32.
18. Fletcher BS, Paul SM, Dodd MJ, Schumacher K, West C, Cooper B, et al. Prevalence, severity, and impact of symptoms on female family caregivers of patients at the initiation of radiation therapy for prostate cancer. J Clin Oncol 2008; 26:599-605.
19. Davidson JR, Feldman-Stewart D, Brennenstuhl S, Ram S. How to provide insomnia interventions to people with cancer: insights from patients. Psycho-Oncology 2007; 16:1028-38.
20. Carter PA, Chang BL. Sleep and depression in cancer caregivers. Cancer Nursing 2000; 23:410-5.
21. Carter PA. Family caregivers' sleep loss and depression over time. Cancer Nursing 2003; 26:253-9.
22. Carter PA. A brief behavioral sleep intervention for family caregivers of persons with cancer. Cancer Nurs 2006; 29:95-103.
23. Chang EW, Tsai YY, Chang TW, Tsao CJ. Quality of sleep and quality of life in caregivers of breast cancer patient. Psycho-Oncology 2007; 16:950-5.
24. Savard J, Miller SM, Mills M, O'Leary A, Harding H, Douglas SD, et al. Association between subjective sleep quality and depression on immunocompetence in low-income women at risk for cervical cancer. Psychosom Med 1999; 61:496-507.
25. Berger AM, Sankaranarayanan J, Watanabe-Galloway S. Current methodological approaches to the study of sleep disturbances and quality of life in adults with cancer: a systematic review. Psychooncology 2007; 16:401-20.
26. Fortner BV, Stepanski EJ, Wang SC, Kasprowicz S, Durrence HH. Sleep and quality of life in breast cancer patients. J Pain Symptom Manage 2002; 24:471-80.
27. Degner LF, Sloan JA. Symptom distress in newly diagnosed ambulatory cancer patients and as a predictor of survival in lung cancer. J Pain Symptom Manage 1995; 10:423-31.
28. Earlam S, Glover C, Fordy C, Burke D, Allen-Mersh TG. Relation between tumor size, quality of life, and survival in patients with colorectal liver metastases. J Clin Oncol 1996; 14:171-5.
29. Mystakidou K, Parpa E, Tsilika E, Pathiaki M, Galanos A, Vlahos L. Depression, hopelessness, and sleep in cancer patients' desire for death. Int J Psychiatry Med 2007; 37:201-11.
30. Zhao Y, Wang XS, Li PP. Investigation of common symptoms of cancer and reliability analysis. Chin J Integr Med 2007; 13:195-9.
31. Savard J, Laroche L, Simard S, Ivers H, Morin CM. Chronic insomnia and immune functioning. Psychosom Med 2003; 65:211-21.
32. Kaye J, Kaye K, Madow L. Sleep patterns in patients with cancer and patients with cardiac disease. J Psychol 1983; 114:107-13.
33. Engstrom CA, Strohl RA, Rose L, Lewandowski L, Stefanek ME. Sleep alterations in cancer patients. Cancer Nurs 1999; 22:143-8.
34. Davidson JR, Waisberg JL, Brundage MD, MacLean AW. Nonpharmacologic group treatment of insomnia: a preliminary study with cancer survivors. Psychooncology 2001; 10:389-97.
35. Owen DC, Parker KP, McGuire DB. Comparison of subjective sleep quality in patients with cancer and healthy subjects. Oncol Nurs Forum 1999; 26:1649-51.
36. Portenoy RK, Thaler HT, Kornblith AB, Lepore JM, Friedlander-Klar H, Coyle N, et al. Symptom prevalence, characteristics and distress in a cancer population. Qual Life Res 1994; 3:183-9.
37. Malone M, Harris AL, Luscombe DK. Assessment of the impact of cancer on work, recreation, home management and sleep using a general health status measure. J R Soc Med 1994; 87:386-9.
38. Derogatis LR, Feldstein M, Morrow G, Schmale A, Schmitt M, Gates C, et al. A survey of psychotropic drug prescriptions in an oncology population. Cancer 1979; 44:1919-29.
39. Stiefel FC, Kornblith AB, Holland JC. Changes in the prescription patterns of psychotropic drugs for cancer patients during a 10-year period. Cancer 1990; 65:1048-53.
40. Pellegrino R, Formica V, Portarena I, Mariotti S, Grenga I, Del Monte G, et al. Caregiver distress in the early phases of cancer. Anticancer Res 2010; 30:4657-63.
41. Flaskerud JH, Carter PA, Lee P. Distressing emotions in female caregivers of people with AIDS, age-related dementias, and advanced-stage cancers. Perspect Psychiatr Care 2000; 36:121-30.
42. Happe S, Berger K. The association between caregiver burden and sleep disturbances in partners of patients with Parkinson's disease. Age Ageing 2002; 31:349-54.
43. Teel SC, Press AN. Fatigue among elders in caregiving and non-caregiving roles. Western Journal of Nursing Research 1999; 21:498-520.
44. McCurry S, Teri L. Sleep disturbance in elderly caregivers of dementia patients. Clinical Gerontology 1995; 54B:P189-P98.
45. Illingworth N, Forbat L, Hubbard G, Kearney N. The importance of relationships in the experience of cancer: a re-working of the policy ideal of the whole-systems approach. Eur J Oncol Nurs 2010; 14:23-8.

46. Kenny DA, Kashy DA, Cook WL. Dyadic Data Analysis. London: Guilford Press; 2006.
47. Fletcher BS, Miaskowski C, Given B, Schumacher K. The cancer family caregiving experience: An updated and expanded conceptual model. Eur J Oncol Nurs 2011.
48. Northouse LL, Katapodi MC, Song L, Zhang L, Mood DW. Interventions with family caregivers of cancer patients: meta-analysis of randomized trials. CA Cancer J Clin; 60:317-39.
49. Sherman FT. The patient-caregiver dyad: it takes two to tango! Geriatrics 2008; 63:13-4.
50. Hagedoorn M, Sanderman R, Bolks HN, Tuinstra J, Coyne JC. Distress in couples coping with cancer: a meta-analysis and critical review of role and gender effects. Psychol Bull 2008; 134:1-30.
51. Hinnen C, Ranchor AV, Sanderman R, Snijders TA, Hagedoorn M, Coyne JC. Course of distress in breast cancer patients, their partners, and matched control couples. Ann Behav Med 2008; 36:141-8.
52. Siminoff LA, Wilson-Genderson M, Baker S, Jr. Depressive symptoms in lung cancer patients and their family caregivers and the influence of family environment. Psychooncology 2010; 19:1285-93.
53. Lim JW, Zebrack B. Caring for family members with chronic physical illness: a critical review of caregiver literature. Health Qual Life Outcomes 2004; 2:50.
54. Lyons KS, Zarit SH, Sayer AG, Whitlatch CJ. Caregiving as a dyadic process: perspectives from caregiver and receiver. J Gerontol B Psychol Sci Soc Sci 2002; 57:P195-204.
55. Wilson-Genderson M, Pruchno RA, Cartwright FP. Effects of caregiver burden and satisfaction on affect of older end-stage renal disease patients and their spouses. Psychol Aging 2009; 24:955-67.
56. Chen ML, Chu L, Chen HC. Impact of cancer patients' quality of life on that of spouse caregivers. Support Care Cancer 2004; 12:469-75.
57. Hodges LJ, Humphris GM. Fear of recurrence and psychological distress in head and neck cancer patients and their carers. Psychooncology 2009; 18:841-8.
58. Kim Y, Kashy DA, Wellisch DK, Spillers RL, Kaw CK, Smith TG. Quality of life of couples dealing with cancer: dyadic and individual adjustment among breast and prostate cancer survivors and their spousal caregivers. Ann Behav Med 2008; 35:230-8.
59. Langer SL, Brown JD, Syrjala KL. Intrapersonal and interpersonal consequences of protective buffering among cancer patients and caregivers. Cancer 2009; 115:4311-25.
60. Manne S, Badr H. Intimacy processes and psychological distress among couples coping with head and neck or lung cancers. Psychooncology 2010; 19:941-54.
61. Manne S, Badr H, Zaider T, Nelson C, Kissane D. Cancer-related communication, relationship intimacy, and psychological distress among couples coping with localized prostate cancer. J Cancer Surviv 2010; 4:74-85.
62. Manne SL, Ostroff JS, Norton TR, Fox K, Goldstein L, Grana G. Cancer-related relationship communication in couples coping with early stage breast cancer. Psychooncology 2006; 15:234-47.
63. Northouse L, Templin T, Mood D. Couples' adjustment to breast disease during the first year following diagnosis. J Behav Med 2001; 24:115-36.
64. Segrin C, Badger T, Dorros SM, Meek P, Lopez AM. Interdependent anxiety and psychological distress in women with breast cancer and their partners. Psychooncology 2007; 16:634-43.
65. Segrin C, Badger TA, Meek P, Lopez AM, Bonham E, Sieger A. Dyadic interdependence on affect and quality-of-life trajectories among women with breast cancer and their partners. Journal of Social and Personal Relationships 2005; 22:673-89.
66. Sherman DW, Haber J, Hoskins CN, Budin WC, Maislin G, Cater J, et al. Differences in physical, emotional, and social adjustment of intimate, family, and nonfamily patient-partner dyads based on a breast cancer intervention study. Oncol Nurs Forum 2009; 36:E185-97.
67. Tang ST, Chen CC, Tang WR, Liu TW. Determinants of patient-family caregiver congruence on preferred place of death in taiwan. J Pain Symptom Manage 2010; 40:235-45.
68. Zimmermann T, Scott JL, Heinrichs N. Individual and dyadic predictors of body image in women with breast cancer. Psychooncology 2010; 19:1061-8.
69. Baucom DH, Porter LS, Kirby JS, Gremore TM, Wiesenthal N, Aldridge W, et al. A couple-based intervention for female breast cancer. Psychooncology 2009; 18:276-83.
70. Bevans M, Castro K, Prince P, Shelburne N, Prachenko O, Loscalzo M, et al. An individualized dyadic problem-solving education intervention for patients and family caregivers during allogeneic hematopoietic stem cell transplantation: a feasibility study. Cancer Nurs 2010; 33:E24-32.
71. Birnie K, Garland SN, Carlson LE. Psychological benefits for cancer patients and their partners participating in mindfulness-based stress reduction (MBSR). Psychooncology 2010; 19:1004-9.
72. Budin WC, Hoskins CN, Haber J, Sherman DW, Maislin G, Cater JR, et al. Breast cancer: education, counseling, and adjustment among patients and partners: a randomized clinical trial. Nurs Res 2008; 57:199-213.
73. Kayser K, Feldman BN, Borstelmann NA, Daniels AA. Effects of a randomized couple-based intervention on quality of life of breast cancer patients and their partners. Social Work Research 2010; 34:20-32.
74. Ward SE, Serlin RC, Donovan HS, Ameringer SW, Hughes S, Pe-Romashko K, et al. A randomized trial of a representational intervention for cancer pain: does targeting the dyad make a difference? Health Psychol 2009; 28:588-97.
75. Bultz BD, Speca M, Brasher PM, Geggie PH, Page SA. A randomized controlled trial of a brief psychoeducational support group for partners of early stage breast cancer patients. Psychooncology 2000; 9:303-13.
76. Troxel WM. It's more than sex: exploring the dyadic nature of sleep and implications for health. Psychosom Med 2010; 72:578-86.
77. Troxel WM, Robles TF, Hall M, Buysse DJ. Marital quality and the marital bed: examining the covariation between relationship quality and sleep. Sleep Med Rev 2007; 11:389-404.
78. Dahl RE, El-Sheikh M. Considering sleep in a family context: introduction to the special issue. J Fam Psychol 2007; 21:1-3.
79. Dahl RE. The regulation of sleep and arousal: Development and psychopathology. Development and Psychopathology 1996; 8:3-27.
80. Kotronoulas G, Wengström Y, Kearney N. Sleep and sleep-wake disturbances in care recipient-caregiver dyads in the context of a chronic illness: A critical review of the literature. J Pain Symptom Manage 2012, in press.
81. Meadows R, Arber S, Venn S, Hislop J, Stanley N. Exploring the interdependence of couples' rest-wake cycles: an actigraphic study. Chronobiol Int 2009; 26:80-92.
82. Fraley RC, Shaver PR. Adult romantic attachment: theoretical developments, emerging controversies, and unanswered questions. Review of General Psychology 2000; 4:132-54.
83. Sbarra DA, Hazan C. Coregulation, dysregulation, self-regulation: an integrative analysis and empirical agenda for understanding adult attachment, separation, loss, and recovery. Pers Soc Psychol Rev 2008; 12:141-67.
84. Crossley N. Sleep, reflexive embodiment and social networks. Paper presented at the first ESRC "Sleep and Society" seminar; 3 December 2004: University of Warwick; 2004.
85. McCurry SM, Pike KC, Vitiello MV, Logsdon RG, Teri L. Factors associated with concordance and variability of sleep quality in persons with Alzheimer's disease and their caregivers. Sleep 2008; 31:741-8.
86. Pollak CP, Stokes PE. Circadian rest-activity rhythms in demented and nondemented older community residents and their caregivers. J Am Geriatr Soc 1997; 45:446-52.
87. Monroe LJ. Transient changes in EEG sleep patterns of married good sleepers: the effects of altering sleeping arrangement. Psychophysiology 1969; 6:330-7.
88. Pankhurst FP, Horne JA. The influence of bed partners on movement during sleep. Sleep 1994; 17:308-15.
89. Hoffstein V. Snoring and upper airway resistance. In: Kryger MH, Roth T, Dement WC, editors. Principles and Practice of Sleep Medicine. 4th ed. Philadelphia: WB Saunders; 2005. p. 1001-12.
90. Ulfberg J, Carter N, Talback M, Edling C. Adverse health effects among women living with heavy snorers. Health Care Women Int 2000; 21:81-90.
91. Ashtyani H, Hutter DA. Collateral damage: the effects of obstructive sleep apnea on bed partners. Chest 2003; 124:780-1.

92. McArdle N, Kingshott R, Engleman HM, Mackay TW, Douglas NJ. Partners of patients with sleep apnoea/hypopnoea syndrome: effect of CPAP treatment on sleep quality and quality of life. Thorax 2001; 56:513-8.

93. Prigerson HG, Maciejewski PK, Rosenheck RA. The effects of marital dissolution and marital quality on health and health service use among women. Med Care 1999; 37:858-73.

94. Troxel WM, Buysse DJ, Hall M, Matthews KA. Marital happiness and sleep disturbances in a multi-ethnic sample of middle-aged women. Behav Sleep Med 2009; 7:2-19.

95. Strawbridge WJ, Shema SJ, Roberts RE. Impact of spouses' sleep problems on partners. Sleep 2004; 27:527-31.

96. Carmichael CL, Reis HT. Attachment, sleep quality, and depressed affect. Health Psychol 2005; 24:526-31.

97. Troxel WM, Cyranowski JM, Hall M, Frank E, Buysse DJ. Attachment anxiety, relationship context, and sleep in women with recurrent major depression. Psychosom Med 2007; 69:692-9.

98. Niko Verdecias R, Jean-Louis G, Zizi F, Casimir GJ, Browne RC. Attachment styles and sleep measures in a community-based sample of older adults. Sleep Med 2009; 10:664-7.

99. Hasler BP, Troxel WM. Couples' nighttime sleep efficiency and concordance: evidence for bidirectional associations with daytime relationship functioning. Psychosom Med; 72:794-801.

100. Gibbins J, McCoubrie R, Kendrick AH, Senior-Smith G, Davies AN, Hanks GW. Sleep-wake disturbances in patients with advanced cancer and their family carers. J Pain Symptom Manage 2009; 38:860-70.

101. Carney S, Koetters T, Cho M, West C, Paul SM, Dunn L, et al. Differences in sleep disturbance parameters between oncology outpatients and their family caregivers. J Clin Oncol 2011; 29:1001-6.

102. Lee D, Morgan K, Lindesay J. Effect of institutional respite care on the sleep of people with dementia and their primary caregivers. J Am Geriatr Soc 2007; 55:252-8.

103. Castro CM, Lee KA, Bliwise DL, Urizar GG, Woodward SH, King AC. Sleep patterns and sleep-related factors between caregiving and non-caregiving women. Behav Sleep Med 2009; 7:164-79.

104. Smith MC, Ellgring H, Oertel WH. Sleep disturbances in Parkinson's disease patients and spouses. J Am Geriatr Soc 1997; 45:194-9.

105. Pal PK, Thennarasu K, Fleming J, Schulzer M, Brown T, Calne SM. Nocturnal sleep disturbances and daytime dysfunction in patients with Parkinson's disease and in their caregivers. Parkinsonism Relat Disord 2004; 10:157-68.

106. Pollak CP, Stokes PE, Wagner DR. Nocturnal interactions between community elders and caregivers, as measured by cross-correlation of their motor activity. J Geriatr Psychiatry Neurol 1997; 10:168-73.

107. Lee K, Cho M, Miaskowski C, Dodd M. Impaired sleep and rhythms in persons with cancer. Sleep Med Rev 2004; 8:199-212.

108. Savard J, Morin CM. Insomnia in the context of cancer: a review of a neglected problem. Journal of Clinical Oncology 2001; 19:895-908.

109. Lyons KS, Sayer AG. Using multilevel modeling in caregiving research. Aging Ment Health 2005; 9:189-95.

110. Ostlund U, Kidd L, Wengstrom Y, Rowa-Dewar N. Combining qualitative and quantitative research within mixed method research designs: A methodological review. Int J Nurs Stud 2010 Nov 15.

Assessment of older patients in oncology

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ABSTRACT

Cancer is a disease of the elderly with almost 60% of new cancer diagnoses and 70% of cancer deaths occurring in patients over 65 years of age. With population ageing the prevalence of cancer in older patients is expected to rise even further in the future. Choosing the optimal treatment for older cancer patients is challenging since ageing is often related with physiological changes and organ function impairment that can alter anticancer treatment tolerance and efficacy. Ageing is a highly individualized process and chronological age alone cannot accurately define the functional reserve and life expectancy of an individual. A number of methods have been developed for a thorough assessment of older patients in order to help treatment decisions. The comprehensive geriatric assessment of older patients in oncology is presented in this article.

Key words: elderly; cancer; geriatric; assessment.

INTRODUCTION

Although more than half of new cancers occur in the elderly [1], elderly patients are underrepresented in the large randomized trials [2-4], thus limiting applicability of these trials' conclusions on the general elderly population. It is well-recognized that aging is a heterogeneous process and, furthermore, performance status (PS) alone cannot describe the functional status and commonly existing comorbidities in the elderly [5]. Geriatricians have validated standardized tools for assessment of "functional status" as distinct from chronological age, looking for signs of accelerated aging that increase vulnerability to disablement and mortality. These geriatric perspectives have been merged in oncology and it is now recommended that a more thorough and multidimensional evaluation of older cancer patients should be performed in order to better define biological age and individualize treatment in this patient population [6-9]. This multidimensional assessment, often referred to as comprehensive geriatric assessment (CGA) in geriatric oncology literature, includes a compilation of reliable and valid tools to assess geriatric domains such as comorbidity, functional-, cognitive-, psychological- and nutritional status, physical performance, medication review and social support. The tools commonly used within the CGA to evaluate a geriatric cancer patient are summarized in Table 1.

Based on CGA results, four taxonomic groups of older individuals may be defined with different life expectancy, rehabilitative potential and presumed stress tolerance [10] (Table 2). Those in very good condition, labeled "fit", may receive the same treatment as younger patients; those partially impaired, labeled "vulnerable", may require tailored approach and moderate assistance; while the "frail" ones are candidates only for supportive care; and the last category includes those in critical condition, labeled "very frail" or "near death".

FUNCTIONAL ASSESSMENT

The traditional method for functional status assessment in cancer patients is PS. The scales most often used for PS assessment are the Karnofsky Performance Status (KPS) [11] and the Eastern Cooperative Oncology Group (ECOG) score [12]. However, in geriatrics these scales are not considered adequate for an accurate functional assessment and a more extensive evaluation is required [13]. Two methodological approaches for the functional assessment of older patients have been developed. The first method uses questionnaires which describe several activities, patients answer whether they are ca-

Table 1.
Comprehensive geriatric assessment

Comprehensive Geriatric Assessment elements	
Domain	**Instruments used – parameters examined**
Function	Activities of Daily Living (ADL) [15] Instrumental Activities of Daily Living (IADL) [19] "Timed Up and Go" [26]
Comorbidity	Charlson index score [31] Cumulative Illness Rating Scale-Geriatric [33]
Cognitive	Mini Mental State Examination (MMSE) [53]
Emotional	Geriatric Depression Scale-15 (GDS-15) [58]
Nutrition	Mini Nutritional Assessment [42, 44]
Geriatric syndromes	Dementia, delirium, depression, incontinence, osteoporosis with bone fractures, falls, neglect and/or abuse, failure to thrive
Polypharmacy	Number and appropriateness of medications, risk of drug interaction
Socioeconomic status	Economic independence, presence of a reliable caregiver

Table 2.
Taxonomy of elderly patients according to comprehensive geriatric assessment (CGA)

Taxonomy group	CGA parameters	Therapeutic approach
Group 1: "Fit"	No ADL or IADL dependence No severe comorbidity No geriatric syndromes present	Treat as younger patients
Group 2: "Vulnerable"	IADL but no ADL dependence Stable comorbidity No geriatric syndromes present Mild cognitive disorders	Tailored treatment Rehabilitation measures
Group 3: "Frail"	ADL dependence Severe or unstable comorbidity Presence of geriatric syndromes	Supportive care
Group 4: "Very frail"	Critical condition - near death	

pable of performing said activities [14] and it mainly involves evaluation of activities of daily living (ADL) and instrumental activities of daily living (IADL) [7]. ADL include activities that are essential for patients to maintain independence at home and include ability to bathe, feed oneself, dress oneself, maintain continence, use the toilet and functional transfer. The basic scale used for ADL assessment is the Katz scale [15]. ADL assessment has been proved to be a good prognostic factor in older patients in general (not specifically cancer patients) and is strongly associated with one- and two-year mortality following hospital admission [16, 17]. Another study revealed functional status as a stronger predictor of length of stay, mortality, and nursing home placement than principal admitting diagnosis [18]. IADL assessment includes more advanced self-care activities such as the ability to prepare meals, do housework, use the telephone, take medications, manage one's finances and use transportation means [19]. In oncology, IADL dependence has been associated with poorer survival in lung cancer [20] and acute myeloid leukemia patients [21], with increased risk of chemotherapy toxicity in ovarian cancer patients [22] and with higher risk for postoperative complications in older patients undergoing surgical operation [23]. Furthermore, IADL dependence was associated with inferior survival in prospective studies that included patients over 70 years of age with solid tumors [24] and hematological malignancies [25].

The second method of measuring functional status involves having the patient perform some specific activities under physician observation in order to examine what he/she is actually capable of doing. A commonly used tool is the

"Timed Up and Go" tool (measures speed during several functional maneuvers, which include standing up, walking, turning and sitting down) [26]. However, direct functional assessment only moderately correlates with ADL scores and discordance between questionnaire-based and direct functional assessment has been reported [27].

ASSESSMENT OF COMORBIDITY

Older patients present with increased concomitant diseases. Furthermore, comorbidity does not appear to correlate closely with either tumor stage or functional status [5]. Therefore, comorbidity should be assessed independently. Comorbidity may influence cancer patients in many aspects, such as treatment decision, treatment tolerance and finally cancer prognosis [28]. There are only a few clinical trials that incorporate assessment of comorbidity and so it is difficult to define the exact role in each aspect of cancer management [29, 30].

There are many validated tools available to measure comorbidity and each has specific characteristics and differences regarding its easiness of use and validity in measuring comorbidity. Among them, oncology authors most frequently use (in different settings) the Charlson Index [31]; the Cumulative Illness Rate Scale [32] with the Geriatric module (CIRS-G) [33]; the Kaplan-Feinstein Index [34]; and the Adult Comorbidity Evaluation 27 (ACE-27) [35], with Charlson and CIRS-G being the most widely used [36]. The use of validated tools for measuring comorbidity should be preferred instead of general lists of diseases in order to better reproduce and compare the data among different studies.

The Charlson Comorbidity Index

The Charlson Comorbidity Index [31] is a scale with 19 diseases weighted from one to six points. The total score is valid in predicting mortality risk over a period of a few weeks to 10 years and has also been validated in older cancer patients [5]. Potential limitations in oncology include the fact that the index ignores several comorbidities that may be relevant in designing the treatment of cancer patients, such as hematopoietic disorders other than malignancies, polyneuropathy or moderate renal dysfunction. The rating criteria are well defined in the appendix of the original paper [31] and fairly easy for frequent users to memorize.

The Cumulative Illness Rating Scale

The CIRS is aimed at a comprehensive recording of all the comorbid diseases of a patient. Its principle is to classify comorbidities by organ system affected, and rate them according to their severity from 0 to 4, in a way similar to the Common Toxicity Criteria grading (none, mild, moderate, severe, extremely severe/life-threatening). An adaptation that is particularly interesting for geriatric oncologists is the CIRS-Geriatric (CIRS-G) designed by Miller and colleagues, with a multidisciplinary designed rating manual aimed at a geriatric population (and, therefore, detailing several geriatric problems in the list) [33].

NUTRITIONAL STATUS

There are several reports demonstrating the adverse impact of weight loss or low body mass index (BMI) in the general older population [37-39]. Cancer may affect consumption and assimilation of food in many different ways. This is of great importance for older individuals whose functional or financial limitations along with depressed mood may further worsen their capability to maintain adequate caloric intake. The deleterious effect of weight loss on survival was demonstrated in a study of 3047 patients enrolled in 12 ECOG chemotherapy protocols [40]. In this analysis, weight loss was associated with a lower performance status and was an independent prognostic factor for survival. Furthermore, it was associated with a decrease in chemotherapy response rates in women with breast cancer, although this correlation was not present in other tumor types. Even a limited weight loss (0 to 5 percent) can be clinically significant in cancer patients.

The assessment of nutritional state should be a relevant part of CGA, given its numerous implications with tumor prognosis, tolerance to surgery and radio-chemotherapeutic measures, risk of infections, management of comorbidities and most importantly, quality of life [41]. Calculating body mass index (the weight in kilograms divided by the square of height in meters) is an easy and well-known method of monitoring weight in adult populations, with the normal range of 20 (or 18.5 according to the WHO) to 24.9 kg/m^2. However, this parameter has been used mainly to assess prevalence and consequences of obesity rather than to evaluate malnourishment. Some laboratory parameters such as hemoglobin, albumin, transferrin, cholesterol and C-Reactive Protein (CRP) have been proposed as indicators of malnutrition. Unfortunately, in cancer patients, they could hardly be used to follow prospectively the compliance to dietary prescriptions because they may be affected by organ dysfunction as well as by metabolic and immunological deregulation induced by cancer-released cytokines and chemotherapy.

The use of the mini-nutritional assessment (MNA) [42] instrument can better assess nutritional status and identify patients at risk of malnutrition compared with the proportional weight loss [43]. The MNA is an 18-item questionnaire originally validated for use in elderly patients with non-malignant diseases. The instrument is available on-line [44] and should be incorporated in geriatric oncology prospective studies.

GERIATRIC SYNDROMES

An important issue in geriatric oncology is the presence of the so-called "geriatric syndromes" (GS). The definition of this

term includes clinical conditions which appear in the elderly and cannot be classified into discrete disease categories. Common GS are dementia, delirium, depression, falls, neglect and abuse, spontaneous bone fractures and failure to thrive. [45]. Sometimes the presence of GS may complicate cancer treatment, while the side-effects of cancer treatment can worsen underlying GS [46], thus negatively affecting the quality of life of elderly cancer patients. The incidence of GS in elderly cancer population is high ranging from 34% to 51% of patients with different cancer types [47].

Dementia

Dementia is defined as the impairment of two or more fields of cognitive function. These fields are memory, judgment, information recognition and recall. The most common types of dementia are Alzheimer's disease, vascular- and mixed dementia [46]. Dementia may also appear as a result of cancer treatment [48, 49].

Delirium

Delirium is defined as the acute decline in attention and in overall cognitive function which develops in a short time period and fluctuates. The incidence of delirium in outpatients is estimated to be of 10-24% and in inpatients of about 25-60% [46, 50-52]. In 66-76% of patients delirium is unrecognized [51]. It is often difficult to differentiate between dementia and delirium. Whether cancer patients with cognitive function impairment are able to give informed consent is an issue of debate.

The most commonly cognitive function assessment tool is the *Mini-Mental Status Exam* (MMSE). The MMSE constitutes of a 30 points scale which evaluates time, orientation, attention, calculation, naming, reading, writing and drawing [53].

Depression

Depression is the most frequently present syndrome in cancer patients and is related with decreased overall survival [54, 55]. In general, about 25% of medically ill geriatric patients will develop depression [56]. However, it is often unrecognized by oncologists. One of the main reasons for this phenomenon is the appearance of symptoms like anorexia, weight loss, sleep disorders, energy loss, death thoughts and suicide attempts which could appear either due to depression or the tumor [57].

The Geriatric Depression Scale-15 (GDS-15) is a validated tool for assessing depression. It comprises a clinical rating scale with 15 yes/no answers and is one of the most commonly used instruments for screening cognitively intact older adults [58].

Falls

Falls constitute a significant problem occurring in elderly population which might lead to injuries and hospitalization [45]. Published studies report that about 30-40% of elderly people over 65 years of age suffer from falling [59]. Geriatric cancer patients usually develop symptoms like fatigue and dizziness which significantly increase the risk of falls. Symptoms like these might be also side-effects of cancer therapies. Fall-related fractures are consistent with high healthcare costs and generally, falls prevention programs seem to be cost-effective [60].

FRAILTY

Frailty in the elderly can generally be described as a product of "excess demand imposed upon reduced capacity" [61]. Frail elderly patients have a decreased ability to maintain homeostasis in times of acute stress due to reduced reserves in multiple organ systems. The syndrome is manifested with loss of skeletal muscle mass, abnormal function in inflammatory/neuroendocrine systems, and poor energy regulation [62]. Despite the fact that frailty establishes itself gradually, once the elderly become frail, there is a progressive downward spiral toward failure to thrive and death [63]. The incidence of frailty is reported to be from 2% to 7% between the ages of 65 to 75 years, and increases with age [64]. This percentage increases to 25% for elderly persons in their 80's [65] and is considerably higher among women [66]. According to the Fried definition, which is the most widely accepted, frailty is described as a clinical syndrome in which 3 or more of the following criteria were present: unintentional weight loss (10lbs in past year), self-reported exhaustion, weakness (grip strength), slow walking speed, and low physical activity.

In geriatric oncology, the definition of frailty syndrome may be extremely useful for estimating the risk of side-effects, especially for old or very old patients who are apparently physically active and cognitively intact [67]. Intervention on frailty may minimize the risk of toxicity and substantially improve the prognosis of older cancer patients.

PHARMACOLOGICAL ASPECTS

The term pharmacokinetics describes the course of a certain drug in the body. It includes absorption, distribution across body compartments, metabolism and excretion. Aging results in reduced enzymatic activity and prolongs the process of metabolism and excretion for many drugs with accumulation of their toxic metabolites.

Absorption. Changes in drug absorption are generally mild and probably not clinically relevant. They stem from decrease in the small bowel absorptive area and changes in gastric pH.

Distribution. Changes in the fat and water composition in favor of the former result in increased distribution of highly lipophilic drugs and increased half-life times. Reduced levels of albumin may increase the levels of active compounds due to increased proportion of free unbound drugs.

Hepatic metabolism. Overall, the enzymatic activity of cyto-

chrome P-450 system decreases with age, typically by 30-40% [68], and as such drug doses should be decreased proportionally. On the other hand, clearance by conjugation (e.g. glucuronization) is usually unaffected by age.

Renal elimination. Age results in decrease both in glomerular and tubular function and the use of drugs with primary elimination by the kidneys should be guided by creatinine clearance estimation formulas rather than serum creatinine concentration alone. The latter can be within normal limits despite a decreased glomerular filtration rate due to sarcopenia often present in older individuals.

Although there are no specific prescription guidelines for elderly patients, special care should be given to drug interactions. The elderly usually take many drugs for various medical pre-existing conditions and polypharmacy is quite common nowadays. Drug interactions may occur when prescribed drugs share the same metabolic and excretion systems and also due to pharmacodynamics issues [69].

SHORT SCREENING TOOLS

In routine clinical practice the use of the full Comprehensive Geriatric Assessment (CGA) faces several difficulties. A much more practical and cost-effective approach is to use shorter screening tools. Ideally, these tools could allow the identification of fit patients for whom the complete CGA would not identify relevant age-related problems, while patients with impairment would proceed further to a full multidisciplinary CGA [13].

The *VES-13* is a self-administered questionnaire that consists of 12 items for functional capacity, physical status and patient perception of his health and one question for age [70]. In a pilot study, VES-13 accurately identified elderly prostate cancer patients who were defined as having impairment by CGA. The cutoff score of 3 on the VES-13 had 72.7% sensitivity and 85.7% specificity for CGA deficits and was highly predictive for identifying impairment [71, 72], while other investigators challenged these results with a similar design study that failed to show comparable accuracy between the two methods [73, 74].

The *G8 questionnaire* is a very simple screening tool, which includes seven items from the Mini Nutritional Assessment (MNA) questionnaire, while the eighth item is age score (<80, 80-85, >85), for a total score ranging from 0 (poor score) to 17 (good score) [75].

The abbreviated CGA was developed by Overcash *et al.* and comprises a tool of only 15 items [76]. These 15 items include three questions about ADLs; four questions about IADLs; four questions from the Mini Mental State Examination (MMSE) questionnaire; and four questions from the Geriatric Depression Scale questionnaire.

Finally, Hurria *et al.* developed a brief, self-administered cancer-specific tool which assesses the following domains: functional status, comorbidity, cognition, psychological status, social functioning and support, and nutritional status [77].

THE VALUE OF CGA IN ONCOLOGY

Emerging data in oncology practice demonstrate that CGA can improve the clinical management of elderly cancer patients. One aspect of such a thorough assessment is the detection of unknown health problems that may interfere with treatment [78, 79]. An early intervention could reverse some of these problems and help improve treatment tolerance, quality of life and overall survival.

A CGA can also assist decision making and balance the potential treatment benefit against the likely life expectancy as estimated on the basis of functional status, comorbidity and presence of geriatric syndromes [24, 80-84]. Various domains of the CGA have been proven particularly important in geriatric oncology.

Functional status assessment, especially IADL, can predict survival, chemotherapy toxicity, postoperative morbidity, and mortality as it has been demonstrated from studies of CGA in older cancer patients [20, 22, 23, 85].

Comorbidity is also predictive of both treatment tolerance [86, 87] and survival [86, 88] although the latter was not shown in other studies [22, 89, 90], perhaps as a result of the limitations of the instruments used to measure comorbidity [29].

Depression can also be associated with inferior outcomes in older patients with cancer, as it was shown in large population-based [91] and randomized trials [22, 23].

The nutrition assessment is also important since malnutrition is correlated with higher toxicity and adverse outcome in cancer patients [40, 41].

This data suggests that investigators should develop and use a standardized CGA into studies including a high proportion of older patients and test the impact of CGA and of geriatric variables in decision making, in order to improve the outcome of elderly cancer patients. In addition, use of a CGA can stimulate the development of novel endpoints for elderly-specific clinical trials that address quality of survival and functional independence in addition to traditional endpoints of DFS and OS [29].

Moreover, the adoption of a common language by using the validated tools of CGA is essential both for retrospective evaluation of quality of care and for prospective assessment of outcome in clinical trials [10] and is suggested in the guidelines of several organizations [6, 9].

CONCLUSIONS

Though time consuming, CGA is an important tool for initial assessment and intervention, treatment planning and follow-up of elderly cancer patients. The systematic evaluation of physical, emotional and social aspects of patients increases the possibility of identifying underlying conditions that might compromise their quality of life, complicate cancer treatment and deteriorate its prognosis. Currently, only a few clinical studies have incorporated some type of geriatric assessment prospectively. The many different tools

available for measuring the same aspect (comorbidity, depression scales, etc.), the complexity of the complete model of CGA, as well as the lack of established management guidelines according to results, have hampered its use in routine clinical practice. The short screening tools being developed might be user-friendlier and easily applicable in clinical practice. Until we have study results validating some of these shorter tools, comprehensive geriatric assessment remains the gold standard for the evaluation of older cancer patients.

REFERENCES

1. Yancik R, Ries LA. Cancer in older persons. Cancer 1994; 74:1995-2003.
2. Hutchins LF, Unger JM, Crowley JJ, et al. Underrepresentation of patients 65 years of age or older in cancer-treatment trials. N Engl J Med 1999; 341:2061-67.
3. Lewis JH, Kilgore ML, Goldman DP, et al. Participation of patients 65 years of age or older in cancer clinical trials. J Clin Oncol 2003; 21(7):1383-1389.
4. Talarico L, Chen G, Pazdur R. Enrollment of elderly patients in clinical trials for cancer drug registration: a 7-year experience by the US Food and Drug Administration. J Clin Oncol 2004; 22(22):4626-4631.
5. Extermann M, Overcash J, Lyman GH, et al. Comorbidity and functional status are independent in older cancer patients. J Clin Oncol 1998; 16:1582-1587.
6. Balducci L, Yates J. General guidelines for the management of older patients with cancer. Oncology 2000; 14:221-7.
7. Extermann M. Studies of comprehensive geriatric assessment in patients with cancer. Cancer Control 2003; 10:463-468.
8. Basso U, Monfardini S. Multidimensional geriatric evaluation in elderly cancer patients: a practical approach. Eur J Cancer Care 2004; 13:424-33.
9. Extermann M, Aarpo M, Bernabei R, et al. Use of comprehensive geriatric assessment in older cancer patients: Recommendations from the task force on CGA of the International Society of Geriatric Oncology (SIOG). Crit Rev Oncol Hematol 2005; 55:241-253.
10. Balducci L. Geriatric oncology. Crit Rev Oncol Hematol 2003; 46:211-220.
11. Petermann ML, Karnofsky DA, Hogness KR. Electrophoretic studies on the plasma proteins of patients with neoplastic disease; lymphomas and leukemia. Cancer 1948; 1:109-19.
12. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5:649-55.
13. Pallis AG, Wedding U, Lacombe D, et al. Questionnaires and instruments for a multidimensional assessment of the older cancer patient: what clinicians need to know? Eur J Cancer 2010; 46:1019-25.
14. Garman KS, Cohen HJ. Functional status and the elderly cancer patient. Crit Rev Oncol Hematol 2002; 43:191-208.
15. Katz S, Ford AB, Moskowitz RW, et al. Studies of illness in the aged. The index of ADL: A standardized measure of biological and psychosocial function. JAMA 1963; 185:914-9.
16. Walter LC, Brand RJ, Counsell SR, et al. Development and validation of a prognostic index for 1-year mortality in older adults after hospitalization. JAMA 2001; 285:2987-94.
17. Cohen HJ, Saltz CC, Samsa G, et al. Predictors of two-year post-hospitalization mortality among elderly veterans in a study evaluating a geriatric consultation team. J Am Geriatr Soc 1992; 40:1231-5.
18. Narain P, Rubenstein LZ, Wieland GD, et al. Predictors of immediate and 6-month outcomes in hospitalized elderly patients. The importance of functional status. J Am Geriatr Soc 1988; 36:775-83.
19. Lawton MP. Scales to measure competence in everyday activities. Psychopharmacol Bull 1988; 24:609-614.
20. Maione P, Perrone F, Gallo C, et al. Pretreatment quality of life and functional status assessment significantly predict survival of elderly patients with advanced non-small-cell lung cancer receiving chemotherapy: a prognostic analysis of the multicenter Italian lung cancer in the elderly study. J Clin Oncol 2005; 23:6865-6872.
21. Wedding U, Rohrig B, Klippstein A, et al. Impairment in functional status and survival in patients with acute myeloid leukaemia. J Cancer Res Clin Oncol 2006; 132:665-71.
22. Freyer G, Geay JF, Touzet S, et al. Comprehensive geriatric assessment predicts tolerance to chemotherapy and survival in elderly patients with advanced ovarian carcinoma: a GINECO study. Ann Oncol 2005; 16:1795-800.
23. Audisio RA, Ramesh H, Longo WE, et al. Preoperative assessment of surgical risk in oncogeriatric patients. Oncologist 2005; 10:262-268.
24. Honeker FU, Wedding U, Retting S, et al. Use of the Comprehensive Geriatric Assessment (CGA) in elderly patients (pts) with solid tumors to predict mortality. J Clin Oncol 2009; 27:abstr 9549.
25. Wedding U, Honeker F, Rettig K, et al. Comprehensive Geriatric Assessment (CGA) in Elderly Patients with Hematological Neoplasia: CGA and Not Age Predicts Mortality - Results from in-GHO®-Registry. Blood (ASH Annual Meeting Abstracts) 2009; 112.
26. Podsiadlo D, Richardson S. The timed "Up & Go": a test of basic functional mobility for frail elderly persons. J Am Geriatr Soc 1991; 39:142-8.
27. Joly F, Alibhai SM, Galica J, et al. Impact of androgen deprivation therapy on physical and cognitive function, as well as quality of life of patients with nonmetastatic prostate cancer. J Urol 2006; 176:2443-7.
28. Karampeazis A and Extermann M. Assessment and impact of comorbidity in older adults with cancer. In: "Geriatric Oncology" by Hurria A and Balducci L, Springer US Publishers 2009; 95-111.
29. Extermann M, Hurria A. Comprehensive geriatric assessment for older patients with cancer. J Clin Oncol 2007; 25:1824-1831.
30. Extermann M. Interaction between comorbidity and cancer. Cancer Control 2007; 14:13-22.
31. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987; 40:373-383.
32. Linn BS, Linn MW, Gurel L. Cumulative illness rating scale. J Am Geriatr Soc 1968; 16:622-626.
33. Miller MD, Towers A. A manual of guidelines for scoring the cumulative illness rating scale for geriatrics (CIRS-G). University of Pittsburgh, May 1991.
34. Kaplan MH, Feinstein AR. The importance of classifying initial co-morbidities in evaluating the outcome of diabetes mellitus. J Chron Dis 1974; 27:387-404.
35. Piccirillo JF, Costas I, Claybour P, et al. The measurement of comorbidity by cancer registries. J Registry Manage 2003; 30:8-14.
36. Extermann M. Measuring comorbidity in older cancer patients. Eur J Cancer 2000; 36:453-471.
37. Newman AB, Yanez D, Harris T, et al. Weight change in old age and its association with mortality. J Am Geriatr Soc 2001; 49:1309.
38. Grabowski DC, Ellis JE. High body mass index does not predict mortality in older people: analysis of the Longitudinal Study of Aging. J Am Geriatr Soc 2001; 49:968.
39. Wallace JI, Schwartz RS, LaCroix AZ, et al. Involuntary weight loss in older outpatients: incidence and clinical significance. J Am Geriatr Soc 1995; 43:329.
40. Dewys WD, Begg C, Lavin PT, et al. Prognostic effect of weight loss prior to chemotherapy in cancer patients. Eastern Cooperative Oncology Group. Am J Med 1980; 69:491.
41. Slaviero KA, Read JA, Clarke SJ, Rivory LP. Baseline nutritional assessment in advanced cancer patients receiving palliative chemotherapy. Nutr Cancer 2003; 46:148-57.
42. Guigoz Y, Lauque S, Vellas BJ. Identifying the elderly at risk for malnutrition. The Mini Nutritional Assessment. Clin Geriatr Med 2002; 18:737-57.
43. Gioulbasanis I, Baracos VE, Giannousi Z, et al. Baseline nutritional evaluation in metastatic lung cancer patients: Mini Nutritional Assessment versus wei-

ght loss history. Ann Oncol 2011; 4:835-41.
44. http://www.mna-elderly.com/forms/MNA_english.pdf
45. Inouye S, Studenski S, Tinetti M, et al. Geriatric syndromes: clinical, research, and policy implications of a core geriatric concept. J Am Geriatr Soc 2007; 55:780-791.
46. Naeim A, Reuben D. Geriatric syndromes and assessment in older cancer patients. Oncology 2001; 15:1-14.
47. Koroukian S, Murray P, Madigan E. Comorbidity, disability and geriatric syndromes in elderly cancer patients receiving home health care. J Clin Oncol 2006; 24:2304-2310.
48. Vigliani M, Duyckaerts C, Hauw J, et al. Dementia following treatment of brain tumors with radiotherapy administered alone or in combination with nitrosourea-based chemotherapy: A clinical and pathological study. J Neurooncol 1999; 41:137-149.
49. Schagen S, Van Dam F, Muller M, et al. Cognitive deficits after postoperative adjuvant chemotherapy for breast carcinoma. Cancer 1999; 85:640-650.
50. Elie M, Rousseau F, Cole M, et al. Prevalence and detection of delirium in elderly emergency department patients. CMAJ 2000; 163:977-981.
51. Inouye S, Rushing J, Foreman M, et al. Does delirium contribute to poor hospital outcomes? A three-site epidemiologic study. J Gen Intern Med 1998; 13:234-242.
52. Inouye S, Leo-Summers L, Zhang Y, et al. A chart-based method for identification of delirium: Validation compared with interviewer ratings using the confusion assessment method. J Am Geriatr Soc 2005; 53:312-318.
53. Folstein M, Folstein S, McHugh P. "Mini-Mental": A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975; 12:189-198.
54. Zabora J, Brintzenhofe, Szoc K, Curbow B, et al. The prevalence of psychological distress by cancer site. Psychooncology 2001; 10:19-28.
55. Jacobsen P, Donovan K, Trast P, et al. Screening for psychologic distress in ambulatory cancer patients. Cancer 2005; 103:1494-1502.
56. Nelson C, Chao C, Berk A, et al. Are gold standard depression measures appropriate for use in geriatric cancer patients? A systemic evaluation of self-report depression instruments used with geriatric, cancer, and geriatric cancer samples. J Clin Oncol 2010; 28(2):348-356.
57. Lebowitz B, Pearson J, Snheider L, et al. Diagnosis and treatment of depression in late life. Consensus statement update. JAMA 1997; 278:1186-1190.
58. Friedman B, Heisel M, Delevan R. Psychometric properties of the 15-item geriatric depression scale in functionally impaired, cognitively intact, community-dwelling elderly primary care patients. J Am Geriatr Soc 2005; 53:1570-1576.
59. Tinneti M, Speechley M, Ginter S. Risk factors for falls among elderly persons living in the community. N Eng J Med 1988; 319:1701-1707.
60. Guideline for the prevention of falls in older persons. American Geriatric Society, British Geriatrics Society and American Academy of Orthopaedic Surgeons Panel on Falls Prevention. J Am Geriatr Soc 2001; 49:664-672.
61. Powell C. Frailty: help or hindrance? J R Soc Med 1997; 90(S32):23-6.
62. Ahmed N, Mandel R, Fain MJ. Frailty: an emerging geriatric syndrome. Am J Med 2007; 120:748-53.
63. Hamerman D. Toward an understanding of frailty. Ann Intern Med 1999; 130:945-50.
64. Walston J, McBurnie MA, Newman A, et al. Frailty and activation of the inflammation and coagulation systems with and without clinical comorbidities: results from the Cardiovascular Health Study. Arch Intern Med 2002; 162:2333-41.
65. Wilson JF. Frailty -and its dangerous effects- might be preventable. Ann Intern Med 2004; 141:489-92.
66. Walston J, Fried LP. Frailty and the older man. Med Clin North America 1999; 83:1173-94.
67. Ferrucci L, Guralnik JM, Cavazzini C, et al. The frailty syndrome: a critical issue in geriatric oncology. Crit Rev Oncol Hematol 2003; 46:127-37.
68. Sotaniemi EA, Arranto AJ, Pelkonen O, et al. Age and cytochrome P450-linked drug metabolism in humans: an analysis of 226 subjects with equal histopathologic conditions. Clin Pharmacol Ther 1997; 61:331-339.
69. Delafuente JC. Understanding and preventing drug interactions in elderly patients. Crit Rev Hem Oncol 2003; 48:133-143.
70. Saliba D, Elliott M, Rubenstein LZ, et al. The Vulnerable Elders Survey: a tool for identifying vulnerable older people in the community. J Am Geriatr Soc 2001; 49:1691-9.
71. Mohile S, Bylow K, Dale W, et al. A pilot study of the Vulnerable Elders Survey-13 compared with the comprehensive geriatric assessment for identifying disability in older patients with prostate cancer who receive androgen ablation. Cancer 2007; 109:802-10.
72. Luciani A, Ascione G, Bertuzzi C, et al. Detecting disabilities in older patients with cancer: comparison between comprehensive geriatric assessment and the vulnerable elders survey-13. J Clin Oncol 2010; 12:2046-50.
73. Falci C, Basso U, Fiduccia P, et al. Is vulnerable elders survey-13 (VES-13) a sensitive and specific tool for identifying vulnerable/frail elderly cancer patients compared to full comprehensive geriatric assessment (CGA)? Crit Rev Onc Hemat 2009; 72:S19-S20.
74. Monfardini S, Basso U, Fiduccia P, et al. Can the short screening test vulnerable elders survey-13 (VES-13) substitute for the time-consuming comprehensive geriatric assessment (CGA) to identify vulnerable/frail elderly breast cancer patients? J Clin Oncol 2010; 28:15s.
75. Soubeyran P, Bellera CA, Gregoire F, et al. Validation of a screening test for elderly patients in oncology. J Clin Oncol 2008; 26:abstr 20568.
76. Overcash JA, Beckstead J, Extermann M, et al. The abbreviated comprehensive geriatric assessment (aCGA): a retrospective analysis. Crit Rev Oncol Hematol 2005; 54:129-36.
77. Hurria A, Gupta S, Zauderer M, et al. Developing a cancer-specific geriatric assessment: a feasibility study. Cancer 2005; 104:1998-2005.
78. Terret C, Albrand G, Droz JP, et al. Geriatric assessment in elderly patients with prostate cancer. Clin Prostate Cancer 2004; 2:236-240.
79. Extermann M, Meyer J, McGinnis M, et al. A comprehensive geriatric assessment detects multiple problems in older breast cancer patients. Crit Rev Oncol Hematol 2004; 49:69-75.
80. Reuben DB, Rubenstein LV, Hirch SH, et al. Value of functional status as predictor of mortality. Am J Med 1992; 93:663-669.
81. Satariano W, Ragland D. The effect of comorbidity on 3-years survival of women with primary breast cancer. Ann Int Med 1994; 120:104-110.
82. Bruce M, Hoff R, Jacobs S, et al. The effect of cognitive impairment on 9-year mortality in a community sample. J Gerontol 1995; 50B:289-296.
83. Covinsky K, Kahana E, Chin M, et al. Depressive symptoms and three year mortality in older hospitalized medical patients. Ann Int Med 1999; 130:563-569.
84. Hurria A, Togawa K, Mohile S, et al. Predicting chemotherapy toxicity in older adults with cancer: A prospective multicenter study. J Clin Oncol 2011; 29:3457-3465.
85. Karampeazis A, Vamvakas L, Pallis AG, et al. Docetaxel (D) plus gemcitabine (G) compared with G in elderly patients with advanced non-small cell lung cancer (NSCLC): Preliminary results of a randomized phase III Hellenic Oncology Research Group trial. J Clin Oncol, 2010 ASCO Annual Meeting Proceedings, Vol 28:7s (abstr 7605).
86. Frasci G, Lorusso V, Panza N, et al. Gemcitabine plus vinorelbine versus vinorelbine alone in elderly patients with advanced non-small-cell lung cancer. J Clin Oncol 2000; 18:2529-2536.
87. Birim O, Kappetein A, van Klaveren R, et al. Prognostic factors in non-small cell lung cancer surgery. Eur J Surg Oncol 2006; 32:12-23.
88. Steyerberg E, Neville B, Koppet L, et al. Surgical mortality in patients with esophageal cancer: Development and validation of a simple risk score. J Clin Oncol 2006; 24:4277-4284.
89. Houterman S, Janssen-Heijnen M, Verheij C, et al. Greater influence of age than co-morbidity on primary treatment and complications of prostate cancer patients: An in-depth population-based study. Prostate Cancer Prostatic Dis 2006; 9:179-184.
90. Karampeazis A, Vamvakas L, Agelaki S, et al. Baseline comprehensive geriatric assessment (CGA) and prediction of toxicity in elderly non-small cell lung cancer (NSCLC) patients receiving chemotherapy. J Clin Oncol, 2011 ASCO Annual Meeting Proceedings (abstr e19656).
91. Goodwin J, Zsang D, Ostir G, et al. Effect of depression on diagnosis, treatment and survival of older women with breast cancer. J Am Ger Soc 2004; 52:106-111.

Thrombotic thrombocytopenic purpura in a patient with lung adenocarcinoma: A case report and literature review

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ABSTRACT

Thrombotic Thrombocytopenic Purpura (TTP) or Moschowitz disease is a rare hematologic disorder characterized by microangiopathic hemolytic anemia and thrombocytopenia similar to hemolytic-uremic syndrome and disseminated intravascular coagulation. The syndrome can rarely be triggered by the progression of a solid tumor or anticancer chemotherapy. We report a patient with lung adenocarcinoma who, after an initial response to systemic chemotherapy, presented disease progression with brain metastases; at the same time, the patient developed clinical and laboratory findings of TTP; bronchoalveolar hemorrhage and respiratory failure complicated the syndrome leading to the patient's death.

Key words: TTP; Moschowitz syndrome; thrombocytopenia; hemolysis; adenocarcinoma; non-small-cell carcinoma.

INTRODUCTION

Thrombotic Thrombocytopenic Purpura (TTP) and hemolytic uremic syndrome are both acute syndromes with abnormalities in multiple organ systems and evidencing microangiopathic hemolytic anemia and thrombocytopenia [1]. TTP was first described by Moschowitz in 1925 as a new disease characterized by the presence of hyaline thrombi in different organs [2]. The classical pentad for clinical diagnosis is the presence of thrombocytopenia, microangiopathic hemolytic anemia, neurological symptoms and signs, renal function abnormalities and fever [3]. However, in practice, the presence of otherwise unexplained thrombocytopenia and microangiopathic hemolytic anemia is sufficient to establish TTP diagnosis and initiate treatment [4].

The cause and mechanism for platelet consumption in some patients with TTP has been elucidated. Indeed, normal plasma contains large Von Willebrand factor (VWf) multimers which are degraded in the circulation into the normal size range of VWf multimers by a specific von Willebrand factor-cleaving protease (or cleaving metalloproteinase, now called ADAMTS13 – A Disintegrin-like And Metalloprotease with ThromboSpondin type 1 repeats) [5-6]. In subsequent genetic studies in four pedigrees with congenital TTP, a locus was identified on chromosome 9q34, an area containing a gene that encodes for a metalloproteinase thought to be the cleaving protease [7]. This study identified 12 mutations in the ADAMTS13 gene, accounting for 14 of the 15 disease alleles studied in individuals with a congenital deficiency of ADAMTS13 activity (2 to 7 percent of normal activity). So far, several mutations in the ADAMTS13 gene have been described [8].

Among the different pathologic situations which may trigger the consumption of platelets in the periphery and the development of thrombotic microangiopathic hemolytic anemia is disseminated cancer [9-10] and cancer chemotherapy [11-13]. Early initiation of plasma exchange (PE) allows more than 80% of patients with idiopathic TTP to achieve remission and mandates urgency in diagnosis and therapy; however, this is not the case for the microangiopathic hemolytic anemia with thrombocytopenia which is associated with metastatic cancer. Here, we report a rare case of a patient with metastatic lung adenocarcinoma who developed clinical signs of TTP during the progress of his disease after an initial response to systemic chemotherapy.

CASE PRESENTATION

A 59 year-old man, ex-smoker (40 pack-years) presented in July 2008 with shortness

of breath and left pleuritic pain. His chest X-ray revealed a left-sided pneumothorax and a chest tube catheter was immediately inserted. After 10 days of thoracic drainage the pneumothorax was not absorbed and he underwent an open thoracotomy. A suspicious left upper lobe nodule was found, enabling an excisional biopsy and the removal of two hilar lymph nodes.

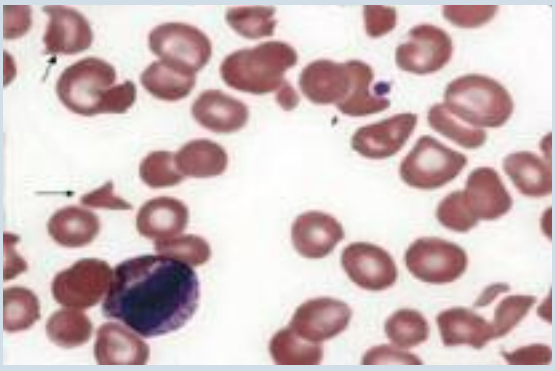
Histological examination of the obtained material identified a poorly differentiated lung adenocarcinoma with visceral pleural invasion. The hilar lymph nodes were not involved in the disease.

A thorax CT scan that was performed after the biopsy, revealed the presence of enlarged left paratracheal lymph nodes (the largest being 1.6cm) and left pleuritic fluid. A CT scan of the upper abdomen and brain, as well as a whole bone scan were negative for secondary metastatic disease.

The patient was considered to have a stage IV disease (cytologically positive pleural effusion; M1a) and combination chemotherapy with paclitaxel/carboplatin was initiated. After 4 chemotherapy cycles, thorax CT-scans demonstrated an almost 95% reduction in initial lesion dimensions. The patient refused further treatment and remained asymptomatic and in good general condition for 2 months when he was admitted to the hospital due to epileptic seizures. A brain CT scan demonstrated the presence of a single metastatic lesion on the left parietal lobe, whereas a thorax CT scan revealed multiple bilateral pulmonary nodules and mediastinal lymph node enlargement; the patient was referred to the radiotherapy department for CyberKnife and whole brain RT. Post-radiotherapy, 2nd line pemetrexed was given but imaging and clinical evaluation after 4 cycles demonstrated a clear progressive disease (PD). One month after completion of the second line chemotherapy, he developed low grade fever, confusion and deterioration of his general condition leading to his admission to the hospital. Laboratory results showed grade IV thrombocytopenia (platelets= 8000K/μl), grade IV anemia (Hb=7g/dl), increased serum levels of d-dimers (d-d: 51μg/ml) accompanied with low fibrinogen levels (value of 191μg/dl). Prothrombin time and partial thromboplastin time levels were normal (INR: 1.17 and aPTT: 29). Blood biochemistry revealed marginally deteriorated renal function (Urea: 67mg/dl and creatinine: 1.2mg/dl). Other biochemical values were within normal limits (LDH: 139U/l, tbil: 0.5mg/dl, Na: 138mEq/l, K: 3.8mEq/l, total protein: 5.2g/dl). Chest X-ray upon admission did not show any difference compared to his previous one and he had no signs of infection. A brain CT scan excluded brain hemorrhage, as well as progression of his already known metastatic disease and a spiral thorax CT scan ruled out the possibility of pulmonary embolism.

The study of peripheral blood smears identified the presence of red blood schistocytes (Figure 1) and combined with the negative results of direct Coombs test and the increased serum levels of d-dimers, diagnosis had to be differentiated between the causes of microangiopathic hemolytic anemia and, mainly, between disseminated intravascular coagulation and thrombotic thrombocytopenic purpura.

Figure 1.
Schistocytes in the patient's peripheral blood smear



Since the patient presented a progressively deteriorated neurological symptomatology and normal prothrombin and partial thromboplastin time values, clinical diagnosis was in favor of the TTP rather than of the DIC. Since the diagnosis was made on the basis of clinical picture and simple blood tests including complete blood count (CBC), prothrombin time (PT) and partial thromboplastin time (APTT), a diagnostic bone marrow aspiration was not performed.

The patient underwent a plasmapheresis course and, immediately after, presented some clinical improvement in consciousness and a slight increase in platelet count (platelets=18,000K/μl). However, on his 2nd day of hospitalization, the patient's general condition deteriorated, the number of platelets dropped (platelets=5,000K/μl) and, clinically, the patient was markedly hemorrhagic from all body orifices as well as the venous puncture sites. He underwent a second course of plasmapheresis, without any improvement of his clinical status. The patient died on the 2nd day of hospitalization from respiratory failure due to massive bronchioalveolar hemorrhaging.

DISCUSSION

TTP is characterized by arteriolar thrombotic lesions in various organs resulting in thrombocytopenia and hemolytic anemia due to red cell fragmentation. It affects individuals of all ages but primarily young adults and more often women [14]. The classical clinical pentad of TTP occurs variably, depending upon number and sites of arteriolar lesions. Anemia may be very mild to very severe and is associated with severe thrombocytopenia [1]. The neurological and renal symptoms are usually seen when the platelet count is significantly decreased (<20,000-30,000K/μL). Fever may also accompany the syndrome. The onset of TTP may be acute but its course spans days to weeks in most patients and

occasionally neurological symptoms such as changes in mental status occur (confusion, delirium or altered state of consciousness as well as seizures, hemiparesis, aphasia and visual field defects). These neurological symptoms may escalate leading to coma [14]. Coagulation tests, such as prothrombin time, partial thromboplastin time, fibrinogen concentration and the level of fibrinogen degradation products, are usually normal or mildly abnormal. If the coagulation tests indicate a major consumption of procoagulants, TTP diagnosis is doubtful. This actually constitutes the major difference between TTP and DIC, a condition in which coagulation cascade is activated resulting in a major change in PT/PTT [1, 2, 6]. The clinical manifestations of the disease can be explained by the obstruction of arterioles by hyaline material, presumably fibrin and platelets, leading to tissue destruction and organ dysfunction [15]. In idiopathic TTP, thrombus formation seems to be the result of a specific protease deficiency (ADAMTS13) which leads to von Willebrand Factor (vWF) misbehaving.

ADAMTS13 is a metalloproteinase that cleaves the big vWF multimers down to size. In idiopathic TTP this proteinase is missing -either under-produced due to genetic defect [6-7] or coated by inhibitory autoantibodies [16]. Without ADAMTS13 the unusually large vWF remain Ultra Large vWF (ULvWF) attracting platelets in huge clumps and, thus, creating intravascular thrombi. This results in increased intravascular coagulation at the sites of arteriolar wall injury, leading to an increased amount of red blood cells being trapped in the meshwork and fragmented by the force of blood pressure leading to intravascular hemolysis [15].

Apart from the idiopathic TTP, there are several other pathological conditions that can lead to the development of this syndrome (secondary TTP). Among these causes are both disseminated cancer and cancer chemotherapy. Disseminated malignancy is an important consideration in the differential diagnosis of TTP, since cancer has been well described for many years as a cause of microangiopathic hemolytic anemia and thrombocytopenia [17-21] (Table 1).

The incidence of TTP in cancer patients is very low. The importance of prompt diagnosis of the systemic malignancy is to provide an opportunity for treatment with appropriate chemotherapy -Francis *et al.* [10] recently reported that 10 (3%) out of 351 patients who were initially diagnosed with TTP and began treatment with plasma exchange were subsequently diagnosed to have systemic malignancy (breast cancer, renal cancer, non-small-cell lung cancer, pancreatic cancer, Kaposi's sarcoma, Non-Hodgkin's Lymphoma and Acute Lymphoblastic Leukemia); in six of these patients disseminated malignancy was diagnosed by bone marrow biopsy. Simultaneously, the authors conducted a systemic review of the literature and reported 19 patients in whom cancer was not initially apparent and TTP or HUS was suspected as the etiology for microangiopathic hemolytic anemia and thrombocytopenia; the diagnoses for these patients were gastric carcinoma (five patients), prostate carcinoma (four patients), carcinoma of unknown primary (three patients), anal squamous cell carcinoma (two patients), and colon carcinoma and multiple endocrine neoplasia type I (one patient each) [10]. Similarly, Chang and Nagvi [17] described that nine out of 93 patients with the established diagnosis of thrombotic microangiopathy diagnosed in their institution from 01/1981-12/2002 had active cancer. Six of these patients, diagnosed with breast cancer, lung cancer and stomach cancer, had extensive bone marrow metastasis and secondary myelofibrosis. Four patients were treated with exchange plasmapheresis (EP) and two patients were treated with chemotherapy; three patients achieved complete remission of TTP, one with EP alone and two with chemotherapy. The other three patients treated with EP alone died within 2 months after TTP diagnosis [22]. The following table presents described cases of TTP in literature, that are related to solid tumors (Table 2).

Cancer chemotherapy may also be associated with TTP. Among the drugs implicated is mitomycin C, cisplatin [14], gemcitabine [11, 13], docetaxel [36], carboplatin [12], or any high-dose regimen combined with radiation (for bone marrow transplantation).

Diagnosis of disseminated malignancy excludes diagnosis of idiopathic TTP [37-38] since the former is a pathologically and clinically distinct disorder. It can cause microangiopathic hemolytic anemia and thrombocytopenia, in the absence of

Table 1.
General characteristics of microangiopathic syndromes

	HUS	TTP	DIC
Age	Mainly in children	Adults	Adults
Hematologic picture	Anemia	Anemia and thrombocytopenia	Anemia and thrombocytopenia
Peripheral blood smear	Schistocytes	Schistocytes	Schistocytes
Clinical picture	Mainly renal failure	Mainly CNS involvement	Underlying disease
Treatment	Supportive	Plasmapheresis	Blood products, heparin
Prognosis	Good	Without intensive treatment, fatal	Generally poor

Table 2.
Presenting features and clinical course of 14 previously reported patients with systemic malignancy, initially diagnosed as TTP

Presenting symptoms	Neurological abnormality	Hct (%)	Plt (103/μl)	Final diagnosis
Weakness	Right-side weakness, dysphasia	11	65	Anal squamous carcinoma [23]
Epistaxis	Vertigo, blurred vision	22	32	Gastric Carcinoma [24]
Epistaxis, intestinal bleeding	None	11	20	Gastric Carcinoma [25]
Weakness, bone pain	None	24	100	Gastric Carcinoma [26]
Abdominal and back pain	None	19	66	Gastric Carcinoma [27]
Abdominal and back pain, jaundice	None	32	86	Gastric Carcinoma [28]
—	—	37	20	Prostate Carcinoma [29]
Oliguria, hematuria	Transient right side weakness	35	21	Prostate Carcinoma [30]
Back pain	None	36	4	Prostate Carcinoma [31]
Abdominal and back pain, jaundice	Confusion	29	23	Colon Carcinoma [32]
Fever, weight loss, jaw pain	Disorientation, left hemiparesis	26	70	Non-small cell lung cancer [33]
Dyspnea	None	37	34	Breast Carcinoma [34]
Abdominal pain, jaundice	No	23	80	Carcinoma, unknown origin [28]
—	None	23	124	Carcinoma, unknown origin [35]

DIC by microvascular tumor emboli, as has been observed with diffuse microscopic pulmonary involvement [39]. ADAMTS13 activity is not severely deficient [40] but may be lower than normal in some patients with disseminated malignancy -something that does not exist in idiopathic TTP, where levels of ADAMTS 13 are significantly lower. Prompt diagnosis of systemic malignancy is also important in avoiding unnecessary risks of plasma exchange treatment for TTP, since plasma exchange has practically no role in its management when a malignant disorder is recognized.

In conclusion, the presentation of this rare case of cancer-associated TTP underlines the importance of clinical features for the establishment of diagnosis, since laboratory tests for ADAMTS13 deficiency or inhibitors are not readily available and lack standardization; in parallel, diagnosis of this syndrome clearly represents a dismal clinical development which is associated with a high incidence of fatal outcomes. Microangiopathic hemolytic anemia and thrombocytopenia caused by systemic malignancies have been well described, but it is uncommon for microangiopathic hemolytic anemia and thrombocytopenia to be the predominant presenting clinical features in patients whose systemic malignancy is not initially apparent. In our case the predominant triggering factor seems to be disseminated cancer of the lung rather than pemetrexed therapy complication, since the event evolved one month after completion of the treatment.

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REFERENCES

1. Georgoulis I. Haematology, Greek edition, fourth edition, 2007.
2. Moschowitz E. An acute febrile pleiochromic anemia with hyaline thrombosis of the terminal arterioles and capillaries. Arch Intern Med 1925; 36:89.
3. Amorosi E, Ultmann J. Thrombotic thrombocytopenic purpura: Report of 16 cases and review of the literature. Medicine 1966; 45:139.
4. Moake JL. Thrombotic microangiopathies. N Engl J Med 2002; 347:589.
5. Veyradier A, Obert B, Houllier A, et al. Specific von Willebrand factor-cleaving protease in thrombotic microangiopathies: a study of 111 cases. Blood 2001; 98:1765.
6. Remuzzi G, Galbusera M, Noris M, et al. Von Willebrand factor cleaving protease (ADAMTS13) is deficient in recurrent and familial thrombotic thrombocytopenic purpura and hemolytic uremic syndrome. Blood 2002; 100:778.
7. Levy GG, Nichols WC, Lian EC, et al. Mutations in a member of the ADAMTS gene family cause thrombotic thrombocytopenic purpura. Nature 2001; 413:488.
8. Kremer Hovinga JA, Studt JD, Lämmle B. The von Willebrand factor-cleaving protease (ADAMTS-13) and the diagnosis of thrombotic thrombocytopenic purpura (TTP). Pathophysiol Haemost Thromb 2003; 33:417.
9. Elliott MA, Letendre L, Gastineau DA, Winters JL, Pruthi RK, Heit JA. Cancer-associated microangiopathic hemolytic anemia with thrombocytopenia: an important diagnostic consideration. Eur J Haematol 2010 Jul; 85(1):43-50.
10. Francis KK, Kalyanam N, Terrell DR, Vesely SK, George JN. Disseminated malignancy misdiagnosed as thrombotic thrombocytopenic purpura: A report of 10 patients and a systematic review of published cases. Oncologist 2007 Jan; 12(1):11-9.

11. Robinson A, Clark WF. A case report of gemcitabine treatment for duodenal cancer: the good (a sustained response) and the bad (life threatening refractory thrombotic thrombocytopenic purpura). J Gastrointest Cancer 2010 Mar; 41(1):71-4.

12. Karim M, Vaux E, Davies DR, Mason PD. Renal failure due to scleroderma with thrombotic microangiopathy developing in a woman treated with carboplatin for ovarian cancer. Clin Nephrol 2002 Nov; 58(5):384-8.

13. Teixeira L, Debourdeau P, Zammit C, Estival JL, Pavic M, Colle B. Gemcitabine-induced thrombotic microangiopathy. Presse Med 2002 Apr 27; 31(16):740-2.

14. Harrison's Principles and Practice of internal medicine.

15. Nabhan C, Kwaan HC. Current concepts in the diagnosis and management of thrombotic thrombocytopenic purpura. Hematol Oncol Clin North Am 2003 Feb; 17(1):177-99.

16. Rieger M, Mannucci PM, Kremer Hovinga JA, et al. ADAMTS13 autoantibodies in patients with thrombotic microangiopathies and other immunomediated diseases. Blood 2005; 106(4):1262.

17. Waugh TR. Hemolytic anemia in carcinomatosis of the bone marrow. Am J Med Sci 1936; 191:160-169.

18. Brain MC, Dacie JV, Hourihane OB. Microangiopathic hemolytic anemia: The possible role of vascular lesions in pathogenesis. Br J Haematol 1962; 8:358-374.

19. Forshaw J, Harwood L. Poikilocytosis associated with carcinoma. Arch Intern Med 1966; 117:203-205.

20. Lohrmann HP, Adam W, Heymer B, et al. Microangiopathic hemolytic anemia in metastatic carcinoma. Ann Int Med 1973; 79:368-375.

21. Antman KH, Skarin AT, Mayer RJ, et al. Microangiopathic hemolytic anemia and cancer: A review. Medicine 1979; 58:377-384. http://theoncologist.alphamedpress.org/external-ref?access_num=10.1046/j.1365-2141.2001.02704.x&link_type=DOI.

22. Chang JC, Naqvi T. Thrombotic thrombocytopenic purpura associated with bone marrow metastasis and secondary myelofibrosis in cancer. Oncologist 2003; 8(4):375-80.

23. Tapp E, Ralson A. Thrombotic microangiopathy associated with squamous carcinoma. Brit Med J 1969; 4:209-210.

24. Brook J, Konwaler BE. Thrombotic thrombocytopenic purpura. Association with metastatic gastric carcinoma and a possible auto-immune disorder. Calif Med 1965; 102:222-226.

25. Aksoy M, Erdem S, Tahsinglu M, et al. Microangiopathic hemolytic anemia due to adenocarcinoma of the stomach. New Istanbul Contrib Clin Sci 1975; 11:103-107.

26. Hansen RM, Hanson GA. Gastric carcinoma in young people. A case report and review of the literature. Am J Gastroenterol 1980; 74:497-503.

27. Gonzalez N, Rios E, Martin-Noya A, et al. Thrombotic thrombocytopenic purpura and bone marrow necrosis as a complication of gastric neoplasm. Haematologia 2002; 87:ECR01.

28. Arkenau HT, Mussig O, Buhr T, et al. Microangiopathic hemolytic anemia (MAHA) as paraneoplastic syndrome in metastasized signet ring cell carcinomas: Case reports and review of the literature. Z Gastroenterol 2005; 43:719-722.

29. Eugene M, Deray G, Cacoub P, et al. Hemolytic uremic syndrome and prostatic adenocarcinoma. Clin Nephrol 1987; 27:46.

30. Van der Merwe WM, Collins JF. The haemolytic uraemic syndrome and prostatic carcinoma. N Z Med J 1987; 100:483-485.

31. Perkovic V, Came NA, Grigg AP, et al. Haemolytic uraemic syndrome and prostatic cancer. N Z J Med 1999; 29:383-384.

32. Lee JL, Lee JH, Kim MK. A case of bone marrow necrosis with thrombotic thrombocytopenic purpura as a manifestation of occult colon cancer. JpnJ Clin Oncol 2004; 34:476-480.

33. Podzamczer D, Carreras L, Condom E, et al. Microangiopathic hemolytic anemia associated with pulmonary adenocarcinoma. JAMA 1985; 254:2554-2555.

34. Systrom DM, Mark EJ. Case records of the Massachusetts Hospital: A 55-year-old woman with acute respiratory failure and radiographically clear lungs. New Eng J Med 1995; 332:1700-1708.

35. Pirrotta MT, Bucalossi A, Forconi F, et al. Thrombotic thrombocytopenic purpura secondary to an occult adenocarcinoma. The Oncologist 2005; 10:299-300.

36. Siau K, Varughese M. Thrombotic microangiopathy following docetaxel and trastuzumab chemotherapy: a case report. Med Oncol 2010 Dec; 27(4):1057-9.

37. Allford S, Hunt BJ, Rose P, et al. Guidelines on the diagnosis and management of the thrombotic microangiopathic haemolytic anemias. Br J Haematol 2003; 120:556-573.

38. Veyradier A, Meyer D. Thrombotic thrombocytopenic purpura and its diagnosis. J Thromb Haemost 2005; 3:2420-2427.

39. Systrom DM, Mark EJ. Case records of the Massachusetts Hospital: A 55-year-old woman with acute respiratory failure and radiographically clear lungs. New Eng J Med 1995; 332:1700-1708.

40. Fontana S, Gerritsen HE, Hovinga JK, et al. Microangiopathic haemolytic anaemia in metastasizing malignant tumours is not associated with a severe deficiency of the von Willebrand factor-cleaving protease. Br J Haematol 2001; 113:100-102.

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ΚΛΙΝΙΚΕΣ ΠΛΗΡΟΦΟΡΙΕΣ: 4.1 Θεραπευτικές ενδείξεις:** Το YERVOY ενδείκνυται για τη θεραπεία του προχωρημένου (μη χειρουργήσιμου ή μεταστατικού) μελανώματος σε ενηλίκους που έχουν λάβει προηγούμενη θεραπεία. **4.3 Αντενδείξεις:** Υπερευαισθησία στη δραστική ουσία ή σε κάποιο από τα έκδοχα. **4.4 Ειδικές προειδοποιήσεις και προφυλάξεις κατά τη χρήση:** Το YERVOY σχετίζεται με φλεγμονώδεις ανεπιθύμητες αντιδράσεις που προκύπτουν από αυξημένη ή εκτεταμένη δραστηριότητα του ανοσοποιητικού (ανεπιθύμητες αντιδράσεις που συνδέονται με το ανοσοποιητικό) και πιθανόν σχετίζονται με το μηχανισμό δράσης του. Ανεπιθύμητες αντιδράσεις που συνδέονται με το ανοσοποιητικό που μπορεί να είναι σοβαρές ή απειλητικές για τη ζωή, είναι πιθανό να συμπεριλαμβάνουν γαστρεντερικές, ηπατικές, δερματικές, νευρολογικές, ενδοκρινολογικές ή άλλων οργανικών συστημάτων. Ενώ οι περισσότερες ανεπιθύμητες αντιδράσεις που συνδέονται με το ανοσοποιητικό εμφανίστηκαν κατά την περίοδο επαγωγής έχει επίσης αναφερθεί εκδήλωση μήνες μετά από την τελευταία δόση του YERVOY. Εκτός αν προσδιοριστεί διαφορετική αιτιολογία, η διάρροια, η αυξημένη συχνότητα κενώσεων, το αίμα στα κόπρανα, οι αυξήσεις LFT, το εξάνθημα και η ενδοκρινοπάθεια πρέπει να θεωρηθούν φλεγμονώδεις και να συνδέονται με το YERVOY. Η πρώιμη διάγνωση και η κατάλληλη διαχείριση είναι απαραίτητες για την ελαχιστοποίηση απειλητικών για τη ζωή επιπλοκών. Συστηματική εισαγωγή υψηλών δόσεων κορτικοστεροειδών με ή χωρίς επιπρόσθετη ανοσοκατασταλτική θεραπεία είναι πιθανό να απαιτηθεί για την αντιμετώπιση σοβαρών ανεπιθύμητων αντιδράσεων που συνδέονται με το ανοσοποιητικό. Ειδικές για το YERVOY κατευθυντήριες γραμμές για την αντιμετώπιση ανεπιθύμητων αντιδράσεων που συνδέονται με το ανοσοποιητικό περιγράφονται παρακάτω. Γαστρεντερικές αντιδράσεις που συνδέονται με το ανοσοποιητικό: Το YERVOY σχετίζεται με σοβαρές γαστρεντερικές αντιδράσεις που συνδέονται με το ανοσοποιητικό. Θανατηφόρα περιστατικά λόγω διάτρησης του γαστρεντερικού σωλήνα έχουν αναφερθεί σε κλινικές δοκιμές (βλέπε παράγραφο 4.8). Σε ασθενείς που έλαβαν μονοθεραπεία με YERVOY 3 mg/kg σε μια μελέτη προχωρημένου (μη χειρουργήσιμου ή μεταστατικού) μελανώματος Φάσης 3 (MDX01020, βλέπε παράγραφο 5.1) ο διάμεσος χρόνος έως την εκδήλωση σοβαρών ή θανατηφόρων (Βαθμού 35) γαστρεντερικών αντιδράσεων που συνδέονται με το ανοσοποιητικό ήταν 8 εβδομάδες (εύρος 5 έως 13 εβδομάδες) από την αρχή της θεραπείας. Με κατευθυντήριες γραμμές για την αντιμετώπιση σχετιζόμενες με το πρωτόκολλο, η υποχώρηση (ορίζεται ως βελτίωση σε ήπια [Βαθμού 1] ή λιγότερο ή στη σοβαρότητα κατά την έναρξη) σημειώθηκε στις περισσότερες περιπτώσεις (90%) σε διάμεσο χρόνο από την εκδήλωση έως την υποχώρηση 4 εβδομάδες (εύρος 0,6 έως 22 εβδομάδες). Οι ασθενείς πρέπει να παρακολουθούνται για γαστρεντερικά σημεία και συμπτώματα που είναι πιθανό να υποδεικνύουν κολίτιδα σχετιζόμενη με το ανοσοποιητικό ή διάτρηση του γαστρεντερικού σωλήνα. Στην κλινική εικόνα είναι πιθανό να συμπεριλαμβάνεται διάρροια, αυξημένη συχνότητα εντερικών κινήσεων, κοιλιακό άλγος ή αιματοχεσία, με ή χωρίς πυρετό. Διάρροια ή κολίτιδα που εμφανίζεται μετά από την έναρξη του YERVOY πρέπει να αξιολογείται έγκαιρα για τον αποκλεισμό λοιμώδους ή άλλης εναλλακτικής αιτιολογίας. Σε κλινικές δοκιμές, κολίτιδα σχετιζόμενη με το ανοσοποιητικό συσχετίστηκε με στοιχεία φλεγμονής του βλεννογόνου, με ή χωρίς εξελκώσεις και λεμφοκυτταρική και ουδετεροφιλική διήθηση. Συστάσεις για την αντιμετώπιση της διάρροιας ή της κολίτιδας βασίζονται στην βαρύτητα των συμπτωμάτων (σύμφωνα με την ταξινόμηση της βαθμολόγησης της βαρύτητας κατά NCICTCAE v3). Ασθενείς με ήπια έως μέτρια (Βαθμού 1 ή 2) διάρροια (αύξηση έως 6 κενώσεις την ημέρα) ή πιθανολογούμενη ήπια έως μέτρια κολίτιδα (π.χ. κοιλιακό άλγος ή αίμα στα κόπρανα), είναι πιθανό να παραμείνουν στο YERVOY. Συνιστάται συμπτωματική θεραπεία (π.χ. λοπεραμίδη, υποκατάσταση υγρών) και προσεκτική παρακολούθηση. Εάν τα ήπια έως μέτρια συμπτώματα υποτροπιάσουν ή επιμείνουν για 57 ημέρες, η προγραμματισμένη δόση του YERVOY θα πρέπει να παραλείπεται και θα πρέπει να ξεκινήσει θεραπεία με κορτικοστεροειδή (π.χ. πρεδνιζόνη 1 mg/kg από το στόμα άπαξ ημερησίως ή ισοδύναμο). Εάν παρουσιαστεί υποχώρηση σε Βαθμό 01 ή επιστροφή στην έναρξη, το YERVOY μπορεί να ξαναρχίσει στην επόμενη προγραμματισμένη δόση. Δόσεις που παραλείπονται λόγω ανεπιθύμητων αντιδράσεων δεν πρέπει να υποκαθίστανται (βλέπε παράγραφο 4.2). Το YERVOY πρέπει να διακόπτεται οριστικά σε ασθενείς με σοβαρή (Βαθμού 3 ή 4) διάρροια ή κολίτιδα (βλέπε παράγραφο 4.2),και πρέπει να ξεκινήσει αμέσως υψηλής δόσης ενδοφλέβια θεραπεία με κορτικοστεροειδή. (Σε κλινικές δοκιμές έχει χρησιμοποιηθεί μεθυλπρεδνιζολόνη 2 mg/kg/ημέρα). Όταν ελέγχεται η διάρροια και άλλα συμπτώματα, η έναρξη βαθμιαίας μείωσης και διακοπής των κορτικοστεροειδών πρέπει να βασίζεται σε κλινική απόφαση. Σε κλινικές δοκιμές, η ταχεία βαθμιαία μείωση και διακοπή (σε διαστήματα < 1 μήνα) οδήγησε στην υποτροπή της διάρροιας ή της κολίτιδας σε ορισμένους ασθενείς. Οι ασθενείς πρέπει να αξιολογούνται για στοιχεία διάτρησης του γαστρεντερικού σωλήνα ή περιτονίτιδας. Η εμπειρία από κλινικές δοκιμές σχετικά με την αντιμετώπιση διάρροιας ανθεκτικής σε κορτικοστεροειδή ή κολίτιδας είναι περιορισμένη. Ωστόσο, είναι δυνατόν να ληφθεί υπόψη η προσθήκη ενός εναλλακτικού ανοσοκατασταλτικού παράγοντα στο σχήμα με κορτικοστεροειδή. Σε κλινικές δοκιμές, προστέθηκε εφάπαξ δόση infliximab 5 mg/kg, εκτός εάν ήταν αντένδειξη. Δεν πρέπει να χρησιμοποιείται infliximab εάν πιθανολογείται διάτρηση του γαστρεντερικού σωλήνα ή σηψαιμία (βλέπε την Περίληψη Χαρακτηριστικών του Προϊόντος για το infliximab). Ηπατοτοξικότητα που συνδέεται με το ανοσοποιητικό: Το YERVOY σχετίζεται με σοβαρή ηπατοτοξικότητα σχετιζόμενη με το ανοσοποιητικό. Θανατηφόρος ηπατική ανεπάρκεια έχει αναφερθεί σε κλινικές δοκιμές (βλέπε παράγραφο 4.8). Σε ασθενείς που έλαβαν μονοθεραπεία με YERVOY 3 mg/kg στην MDX01020, ο χρόνος έως την εκδήλωση μέτριας έως σοβαρής ή θανατηφόρου (Βαθμού 25) ηπατοτοξικότητας που συνδέεται με το ανοσοποιητικό κυμάνθηκε από 3 έως 9 εβδομάδες από την έναρξη της θεραπείας. Με κατευθυντήριες γραμμές για την αντιμετώπιση σχετιζόμενες με το πρωτόκολλο, ο χρόνος έως την υποχώρηση κυμάνθηκε από 0,7 έως 2 εβδομάδες. Οι ηπατικές τρανσαμινάσες και η χολερυθρίνη πρέπει να αξιολογούνται πριν από κάθε δόση του YERVOY, καθώς πρόωρες εργαστηριακές μεταβολές μπορεί να υποδεικνύουν αναπτυσσόμενη ηπατίτιδα σχετιζόμενη με το ανοσοποιητικό (βλέπε παράγραφο 4.2). Αυξήσεις σε LFT είναι πιθανό να αναπτυχθούν απουσία κλινικών συμπτωμάτων. Πρέπει να αξιολογούνται αυξήσεις της AST και της ALT ή της ολικής χολερυθρίνης προς αποκλεισμό λοιπών αιτιών κάκωσης του ήπατος, συμπεριλαμβανομένων λοιμώξεων, εξέλιξης της νόσου ή φαρμακευτικών προϊόντων και να παρακολουθούνται έως την υποχώρησή τους. Βιοψίες ήπατος από ασθενείς που είχαν ηπατοτοξικότητα σχετιζόμενη με το ανοσοποιητικό, κατέδειξαν στοιχεία οξείας φλεγμονής (ουδετερόφιλα, λεμφοκύτταρα και μακροφάγα). Για ασθενείς με αυξημένη AST ή ALT στο εύρος των > 5-≤ 8 x ULN ή ολική χολερυθρίνη στο εύρος των > 3-≤ 5 x ULN που πιθανολογείται ότι σχετίζεται με το YERVOY, πρέπει να παραλειφθεί η προγραμματισμένη δόση του YERVOY και πρέπει να παρακολουθούνται οι LFT έως την υποχώρηση. Όταν βελτιωθούν τα επίπεδα LFT (AST και ALT ≤ 5 x ULN και ολική χολερυθρίνη ≤ 3 x ULN), το YERVOY μπορεί να ξαναρχίσει στην επόμενη προγραμματισμένη δόση. Δόσεις που παραλείπονται λόγω ανεπιθύμητων αντιδράσεων, δεν πρέπει να υποκαθίστανται (βλέπε παράγραφο 4.2). Για ασθενείς με αυξήσεις της AST ή της ALT > 8 x ULN που πιθανολογείται ότι σχετίζονται με το YERVOY, η θεραπεία πρέπει να διακόπτεται οριστικά (βλέπε παράγραφο 4.2) και πρέπει να ξεκινήσει αμέσως συστηματική ενδοφλέβια θεραπεία με κορτικοστεροειδή υψηλής δόσης (π.χ. μεθυλπρεδνιζολόνη 2 mg/kg ημερησίως ή ισοδύναμο). Σε αυτούς τους ασθενείς, πρέπει να παρακολουθούνται οι LFT έως την ομαλοποίηση. Όταν υποχωρούν τα συμπτώματα και ομαλοποιηθούν οι αυξήσεις των LFT, η έναρξη βαθμιαίας μείωσης και διακοπής των κορτικοστεροειδών πρέπει να βασίζεται στην κλινική απόφαση. Η βαθμιαία μείωση και διακοπή πρέπει να γίνεται μέσα σε διάστημα τουλάχιστον 1 μήνα. Αυξήσεις των LFTs κατά τη βαθμιαία μείωση και διακοπή είναι δυνατόν να αντιμετωπιστούν με αύξηση της δόσης του κορτικοστεροειδούς και βραδύτερη βαθμιαία μείωση και διακοπή. Για ασθενείς με σημαντικές αυξήσεις των LFT που είναι ανθεκτικές σε θεραπεία με κορτικοστεροειδή, είναι δυνατόν να εξεταστεί η προσθήκη ενός εναλλακτικού ανοσοκατασταλτικού παράγοντα στο σχήμα με κορτικοστεροειδή. Σε κλινικές δοκιμές, χρησιμοποιήθηκε μυκοφαινολική μοφετίλη σε ασθενείς χωρίς ανταπόκριση σε θεραπεία με κορτικοστεροειδή ή που παρουσίασαν αύξηση του LFT κατά την βαθμιαία μείωση και διακοπή κορτικοστεροειδών που δεν ανταποκρίνονταν σε αύξηση της δόσης των κορτικοστεροειδών (βλέπε την Περίληψη Χαρακτηριστικών του Προϊόντος για τη μυκοφαινολική μοφετίλη). Δερματικές ανεπιθύμητες αντιδράσεις που συνδέονται με το ανοσοποιητικό: Το YERVOY σχετίζεται με σοβαρές δερματικές ανεπιθύμητες αντιδράσεις που μπορεί να συνδέονται με το ανοσοποιητικό. Θανατηφόρος τοξική επιδερμική νεκρόλυση έχει αναφερθεί σε κλινικές δοκιμές (βλέπε παράγραφο 4.8). Εξάνθημα και κνησμός επαγόμενα από YERVOY ήταν κυρίως ήπια ή μέτρια (Βαθμού 1 ή 2) και ανταποκρίνονταν σε συμπτωματική θεραπεία. Σε ασθενείς που έλαβαν μονοθεραπεία με YERVOY 3 mg/kg στην MDX01020, ο διάμεσος χρόνος έως την εκδήλωση μέτριων έως σοβαρών ή θανατηφόρων (Βαθμού 25) δερματικών ανεπιθύμητων αντιδράσεων ήταν 3 εβδομάδες (εύρος 0,9 έως 16 εβδομάδες) από την έναρξη της θεραπείας. Με ειδικές για το πρωτόκολλο κατευθυντήριες γραμμές για την αντιμετώπιση, παρουσιάστηκε υποχώρηση στις περισσότερες περιπτώσεις (87%), σε διάμεσο χρόνο από την εκδήλωση έως την υποχώρηση 5 εβδομάδες (εύρος 0,6 έως 29 εβδομάδες). Εξάνθημα και κνησμός επαγόμενα από YERVOY πρέπει να αντιμετωπίζεται με βάση τη σοβαρότητα. Ασθενείς με μια ήπια έως μέτρια (Βαθμού 1 έως 2) δερματική ανεπιθύμητη αντίδραση μπορούν να παραμείνουν σε θεραπεία με YERVOY με συμπτωματική θεραπεία (π.χ. αντισταμινικά). Για ήπιο έως μέτριο εξάνθημα ή κνησμό που εμμένει για 1 έως 2 εβδομάδες και δεν βελτιώνεται με τοπικά κορτικοστεροειδή, πρέπει να ξεκινήσει η από του στόματος θεραπεία με κορτικοστεροειδή (π.χ. πρεδνιζόνη 1 mg/kg άπαξ ημερησίως ή ισοδύναμο). Για ασθενείς με μια σοβαρή (βαθμού 3) δερματική ανεπιθύμητη αντίδραση, η προγραμματισμένη δόση του YERVOY θα πρέπει να παραλειφθεί. Εάν βελτιωθούν τα αρχικά συμπτώματα σε ήπια (Βαθμού 1) ή υποχωρήσουν, η θεραπεία με YERVOY μπορεί να συνεχιστεί και πάλι στην επόμενη προγραμματισμένη δόση. Δόσεις που παραλείπονται λόγω μιας ανεπιθύμητης αντίδρασης, δεν πρέπει να υποκαθίστανται (βλέπε παράγραφο 4.2). Το YERVOY πρέπει να διακόπτεται οριστικά σε ασθενείς με ένα πολύ σοβαρό (Βαθμού 4) εξάνθημα ή σοβαρό (Βαθμού 3) κνησμό (βλέπε παράγραφο 4.2) και θα πρέπει να ξεκινήσει αμέσως συστηματική ενδοφλέβια θεραπεία με υψηλές δόσεις κορτικοστεροειδών (π.χ. μεθυλπρεδνιζολόνη 2 mg/kg/ημέρα). Όταν ελεγχθεί το εξάνθημα ή ο κνησμός, η έναρξη της βαθμιαίας μείωσης και διακοπής των κορτικοστεροειδών πρέπει να βασίζεται στην κλινική απόφαση. Η βαθμιαία μείωση και διακοπή πρέπει να γίνεται μέσα σε διάστημα τουλάχιστον 1 μήνα. Νευρολογικές ανεπιθύμητες αντιδράσεις που συνδέονται με το ανοσοποιητικό: Το YERVOY σχετίζεται με σοβαρές νευρολογικές ανεπιθύμητες αντιδράσεις που συνδέονται με το ανοσοποιητικό. Θανατηφόρο σύνδρομο Guillain-Barré έχει αναφερθεί σε κλινικές δοκιμές (βλέπε παράγραφο 4.8). Έχουν επίσης αναφερθεί συμπτώματα ομοιάζοντα με μυασθένεια gravis. Οι ασθενείς μπορεί να παρουσιάσουν μυϊκή αδυναμία. Μπορεί ακόμη να παρουσιαστεί αισθητική νευροπάθεια. Ανεξήγητη κινητική νευροπάθεια, μυϊκή αδυναμία ή αισθητική νευροπάθεια που διαρκεί > 4 ημέρες πρέπει να αξιολογείται και θα πρέπει να αποκλειστούν μη φλεγμονώδη αίτια, όπως εξέλιξη της νόσου, λοιμώξεις, μεταβολικά σύνδρομα και φαρμακευτικά προϊόντα. Για ασθενείς με μέτρια (Βαθμού 2) νευροπάθεια (κινητική με ή χωρίς αισθητική) που πιθανόν σχετίζεται με το YERVOY, θα πρέπει να παραλείπεται η προγραμματισμένη δόση. Εάν τα νευρολογικά συμπτώματα υποχωρήσουν στην έναρξη, ο ασθενής μπορεί να ξαναρχίσει το YERVOY στην επόμενη προγραμματισμένη δόση. Δόσεις που παραλείπονται λόγω μιας ανεπιθύμητης αντίδρασης δεν πρέπει να υποκαθίστανται (βλέπε παράγραφο 4.2). Το YERVOY πρέπει να διακόπτεται οριστικά σε ασθενείς με σοβαρή (Βαθμού 3 ή 4) αισθητική νευροπάθεια που πιθανολογείται ότι συνδέεται με το YERVOY (βλέπε παράγραφο 4.2). Οι ασθενείς πρέπει να αντιμετωπίζονται σύμφωνα με τις κατευθυντήριες γραμμές του ιδρύματος για την διαχείριση αισθητικής νευθροπάθειας και πρέπει να ξεκινήσουν αμέσως ενδοφλέβια θεραπεία με κορτικοστεροειδή (π.χ. μεθυλπρεδνιζολόνη 2 mg/kg/ημέρα). Προοδευτικά σημάδια κινητικής νευροπάθειας θα πρέπει να θεωρείται ότι σχετίζονται με το ανοσοποιητικό και να αντιμετωπίζονται ανάλογα. Το YERVOY πρέπει να διακόπτεται οριστικά σε ασθενείς με σοβαρή (Βαθμού 3 ή 4) κινητική νευροπάθεια ανεξαρτήτως αιτιολογίας (βλέπε παράγραφο 4.2). Ενδοκρινοπάθεια που συνδέεται με το ανοσοποιητικό: Το YERVOY μπορεί να προκαλέσει φλεγμονή των οργάνων του ενδοκρινικού συστήματος, συγκεκριμένα υποφυσίτιδα, υποϋποφυσισμό, επινεφριδιακή ανεπάρκεια και υποθυρεοειδισμό και οι ασθενείς μπορεί να παρουσιάσουν μη ειδικά συμπτώματα, τα οποία μπορεί να μοιάζουν με άλλα αίτια, όπως μετάσταση στον εγκέφαλο ή υποκείμενη νόσο. Στη συχνότερη κλινική εικόνα συμπεριλαμβάνεται η κεφαλαλγία και η κόπωση. Στα συμπτώματα μπορεί να συμπεριλαμβάνονται ελλείμματα του οπτικού πεδίου, αλλαγές της συμπεριφοράς, διαταραχές των ηλεκτρολυτών και υπόταση. Επινεφριδιακή κρίση ως αίτιο των συμπτωμάτων του ασθενούς πρέπει να αποκλείεται. Η κλινική εμπειρία με ενδοκρινοπάθεια σχετιζόμενη με το YERVOY είναι περιορισμένη. Για ασθενείς που έλαβαν μονοθεραπεία με YERVOY 3 mg/kg στην MDX01020, ο χρόνος έως την εκδήλωση μέτριας έως πολύ σοβαρής (Βαθμού 24) ενδοκρινοπάθειας σχετιζόμενης με το ανοσοποιητικό κυμάνθηκε από 7 έως περίπου 20 εβδομάδες από την έναρξη της θεραπείας. Ενδοκρινοπάθεια που συνδέεται με το ανοσοποιητικό που παρατηρήθηκε σε κλινικές δοκιμές, ήταν γενικώς ελεγχόμενη με ανοσοκατασταλτική θεραπεία και θεραπεία υποκατάστασης ορμονών. Εάν υπάρχουν οποιαδήποτε σημεία επινεφριδιακής κρίσης, όπως σοβαρή αφυδάτωση, υπόταση ή καταπληξία, συνιστάται άμεση χορήγηση ενδοφλέβιων κορτικοστεροειδών με αλατοκορτικοειδική δράση και ο ασθενής θα πρέπει να αξιολογηθεί για την παρουσία σηψαιμίας ή λοιμώξεων. Εάν υπάρχουν σημεία επινεφριδιακής ανεπάρκειας, αλλά ο ασθενής δεν βρίσκεται σε επινεφριδιακή κρίση, πρέπει να εξεταστούν περαιτέρω παρακλινικές εξετάσεις στις οποίες συμπεριλαμβάνεται η αξιολόγηση εργαστηριακών και απεικονιστικών ελέγχων. Η αξιολόγηση των αποτελεσμάτων των εργαστηριακών ελέγχων για την έλεγχο της ενδοκρινούς λειτουργίας πρέπει να πραγματοποιείται πριν από την έναρξη θεραπείας με κορτικοστεροειδή. Εάν οι απεικονιστικοί έλεγχοι της υπόφυσης ή εργαστηριακοί έλεγχοι της ενδοκρινούς λειτουργίας είναι μη φυσιολογικοί, συνιστάται βραχύ σχήμα θεραπείας με υψηλές δόσεις κορτικοστεροειδών (π.χ. δεξαμεθαζόνη 4 mg ανά 6 ώρες ή ισοδύναμο) ώστε να αντιμετωπιστεί η φλεγμονή του προσβεβλημένου αδένα και η προγραμματισμένη δόση του YERVOY θα πρέπει να παραλειφθεί (βλέπε παράγραφο 4.2). Αυτή τη στιγμή είναι άγνωστο εάν η θεραπεία με κορτικοστεροειδή αναστρέφει την αδενική δυσλειτουργία. Θα πρέπει επίσης να ξεκινήσει κατάλληλη υποκατάσταση ορμονών. Είναι πιθανό να είναι απαραίτητη μακροχρόνια θεραπεία με υποκατάσταση ορμονών. Όταν τεθούν υπό έλεγχο τα συμπτώματα ή οι μη φυσιολογικές εργαστηριακές τιμές και είναι εμφανής η βελτίωση του ασθενούς συνολικά, μπορεί να συνεχιστεί η θεραπεία με YERVOY και η έναρξη της βαθμιαίας μείωσης και διακοπής των κορτικοστεροειδών πρέπει να βασίζεται στην κλινική απόφαση. Η βαθμιαία μείωση και διακοπή πρέπει να γίνεται μέσα σε διάστημα τουλάχιστον 1 μήνα. Άλλες ανεπιθύμητες αντιδράσεις που συνδέονται με το ανοσοποιητικό: Οι παρακάτω ανεπιθύμητες αντιδράσεις που πιθανολογείται ότι συνδέονται με το ανοσοποιητικό, έχουν αναφερθεί σε ασθενείς που έλαβαν μονοθεραπεία με YERVOY 3 mg/kg στην MDX01020: ραγοειδίτιδα, ηωσινοφιλία, αύξηση λιπάσης και σπειραματονεφρίτιδα. Επιπροσθέτως, ιρίτιδα, αιμολυτική αναιμία, αυξήσεις αμυλάσης, πολυοργανική ανεπάρκεια και πνευμονίτιδα έχουν αναφερθεί σε ασθενείς που έλαβαν πεπτιδικό εμβόλιο με YERVOY 3 mg/kg + gp100 στην MDX01020 (βλέπε παράγραφο 4.8). Αν οι αντιδράσεις είναι σοβαρές (Βαθμού 3 ή 4) είναι πιθανό να απαιτηθεί άμεσα θεραπεία με υψηλές δόσεις κορτικοστεροειδών και διακοπή του YERVOY (βλέπε παράγραφο 4.2). Για ραγοειδίτιδα, ιρίτιδα ή επισκληρίτιδα που συνδέεται με το YERVOY, θα πρέπει να εξετάζεται η χρήση τοπικών κορτικοστεροειδών στη μορφή των οφθαλμικών σταγόνων όπως ενδείκνυται ιατρικά. Ειδικοί πληθυσμοί: Ασθενείς με οφθαλμικό μελάνωμα, πρωτοπαθές μελάνωμα του ΚΝΣ και ενεργές μεταστάσεις του εγκεφάλου δεν συμπεριελήφθησαν στην πιλοτική κλινική δοκιμή (βλέπε παράγραφο 5.1). Αντίδραση στην έγχυση: Υπήρχαν μεμονωμένες αναφορές σοβαρών αντιδράσεων στην έγχυση σε κλινικές δοκιμές. Σε περίπτωση σοβαρής αντίδρασης στην έγχυση, η έγχυση YERVOY πρέπει να διακόπτεται και να χορηγείται κατάλληλη ιατρική θεραπεία. Ασθενείς με ήπια ή μέτρια αντίδραση στην έγχυση, μπορούν να λάβουν YERVOY με προσεκτική παρακολούθηση. Μπορεί να ληφθεί υπόψη η προφαρμακευτική αγωγή με αντιπυρετικό και αντισταμινικό. Ασθενείς με αυτοάνοση νόσο: Ασθενείς με ιστορικό αυτοάνοσης νόσου (εκτός από λεύκη και επαρκώς ελεγχόμενη ανεπάρκεια ενδοκρίνης, όπως υποθυρεοειδισμός), συμπεριλαμβανομένων αυτών για τους οποίους απαιτείται συστηματική ανοσοκατασταλτική θεραπεία για προϋπάρχουσα ενεργό αυτοάνοση νόσο ή για διατήρηση μοσχεύματος μετά από μεταμόσχευση οργάνου, δεν αξιολογήθηκαν σε κλινικές δοκιμές. Το ipilimumab είναι ενισχυτής των Τκυττάρων που καθιστά δυνατή την ανοσολογική ανταπόκριση (βλέπε παράγραφο 5.1) και είναι πιθανό να παρέμβει στην ανοσοκατασταλτική θεραπεία, γεγονός που οδηγεί σε παροξυσμό της υποκείμενης νόσου ή αυξημένο κίνδυνο απόρριψης του μοσχεύματος. Το YERVOY πρέπει να αποφεύγεται σε ασθενείς με σοβαρή ενεργό αυτοάνοση νόσο, σε περιπτώσεις στις οποίες περαιτέρω ενεργοποίηση του ανοσοποιητικού είναι ενδεχομένως άμεσα απειλητική για τη ζωή και χρησιμοποιείται με προσοχή σε άλλους ασθενείς με ιστορικό αυτοάνοσης νόσου, μετά από προσεκτική εξέταση του ενδεχόμενου κινδύνου-οφέλους σε ατομική βάση. Ασθενείς που ακολουθούν δίαιτα με ελεγχόμενη περιεκτικότητα σε νάτριο. Κάθε ml αυτού του φαρμακευτικού προϊόντος περιέχει 0,1 mmol (ή 2,30 mg) νατρίου. Θα πρέπει να λαμβάνεται υπόψη κατά την θεραπεία ασθενών που ακολουθούν δίαιτα με ελεγχόμενη περιεκτικότητα σε νάτριο. **4.8 Ανεπιθύμητες ενέργειες: Περίληψη του προφίλ ασφάλειας:** Το YERVOY έχει χορηγηθεί σε > 3.000 ασθενείς σε ένα κλινικό πρόγραμμα το οποίο αξιολόγησε τη χρήση του με διάφορες δόσεις και τύπους όγκων. Εκτός εάν ορίζεται διαφορετικά, τα δεδομένα παρακάτω αποτυπώνουν την έκθεση σε YERVOY στα 3 mg/kg σε κλινικές δοκιμές μελανώματος. Στη μελέτη Φάσης 3 MDX01020, (βλέπε παράγραφο 5.1), οι ασθενείς έλαβαν ένα διάμεσο 4 δόσεων (εύρος 14). Το YERVOY σχετίζεται πολύ συχνά με ανεπιθύμητες ενέργειες που προκύπτουν από αυξημένη ή εντεταμένη δράση του ανοσοποιητικού. Οι περισσότερες από αυτές, στις οποίες συμπεριλαμβάνονται σοβαρές αντιδράσεις, υποχώρησαν μετά από την έναρξη κατάλληλης ιατρικής θεραπείας ή τη διακοπή του YERVOY (βλέπε παράγραφο 4.4 για την αντιμετώπιση ανεπιθύμητων αντιδράσεων που συνδέονται με το ανοσοποιητικό). Σε ασθενείς που έλαβαν μονοθεραπεία με YERVOY 3 mg/kg στην MDX01020, οι ανεπιθύμητες ενέργειες που αναφέρθηκαν συχνότερα (≥ 10% των ασθενών), ήταν διάρροια, εξάνθημα, κνησμός, κόπωση, ναυτία, έμετος, μειωμένη όρεξη και κοιλιακό άλγος. Στην πλειονότητά τους ήταν ήπιες έως μέτριες (Βαθμού 1 ή 2). Η θεραπεία με YERVOY διακόπηκε λόγω ανεπιθύμητων ενεργειών στο 10% των ασθενών. Κατάλογος ανεπιθύμητων ενεργειών σε πίνακα: Ανεπιθύμητες ενέργειες που αναφέρθηκαν σε ασθενείς με προχωρημένο μελάνωμα, οι οποίοι έλαβαν YERVOY 3 mg/kg σε κλινικές δοκιμές (n = 767), παρουσιάζονται στον Πίνακα 2. Αυτές οι αντιδράσεις παρουσιάζονται ανά κατηγορία συστήματος οργάνων σύμφωνα με την συχνότητα. Η συχνότητα ορίζεται ως εξής: πολύ συχνές (≥ 1/10), συχνές (≥ 1/100 έως < 1/10), όχι συχνές (≥ 1/1.000 έως < 1/100), σπάνιες (≥ 1/10.000 έως < 1/1.000), πολύ σπάνιες (< 1/10.000). Εντός κάθε κατηγορίας συχνότητας εμφάνισης, οι ανεπιθύμητες ενέργειες εμφανίζονται κατά φθίνουσα σειρά σοβαρότητας. Τα ποσοστά ανεπιθύμητων αντιδράσεων που συνδέονται με το ανοσοποιητικό σε HLAA2*0201 θετικούς ασθενείς οι οποίοι έλαβαν YERVOY στην MDX01020, ήταν παρόμοια με εκείνα που παρατηρήθηκαν στο κλινικό πρόγραμμα συνολικά.

Πίνακας 2: Ανεπιθύμητες ενέργειες σε ασθενείς με προχωρημένο μελάνωμα που έλαβαν YERVOY 3 mg/kg (n = 767)[α]	
Λοιμώξεις και παρασιτώσεις	
Όχι συχνές	σηψαιμία[β], σηπτική καταπληξία[β], μηνιγγίτιδα, γαστρεντερίτιδα, εκκολπωματίτιδα, ουρολοίμωξη, λοίμωξη του ανώτερου αναπνευστικού συστήματος, λοίμωξη του κατώτερου αναπνευστικού συστήματος
Νεοπλάσματα καλοήθη, κακοήθη και μη καθορισμένα (περιλαμβάνονται κύστεις και πολύποδες)	
Συχνές	πόνος από όγκο
Όχι συχνές	παρανεοπλασματικό σύνδρομο
Διαταραχές του αιμοποιητικού και του λεμφικού συστήματος	
Συχνές	αναιμία, λεμφοπενία
Όχι συχνές	αιμολυτική αναιμία[β], θρομβοπενία, ηωσινοφιλία, ουδετεροπενία
Διαταραχές του ανοσοποιητικού συστήματος	
Όχι συχνές	υπερευαισθησία
Διαταραχές του ενδοκρινικού συστήματος	
Συχνές	υποϋποφυσισμός (συμπεριλαμβάνεται η υποφυσίτιδα)[γ], υποθυρεοειδισμός[γ]
Όχι συχνές	επινεφριδιακή ανεπάρκεια[γ], υπερθυρεοειδισμός[γ], υπογοναδισμός
Διαταραχές του μεταβολισμού και της θρέψης	
Πολύ συχνές	μειωμένη όρεξη
Συχνές	αφυδάτωση, υποκαλιαιμία
Όχι συχνές	υπονατριαιμία, αλκάλωση, υποφωσφοραιμία, σύνδρομο λύσης όγκου
Ψυχιατρικές διαταραχές	
Συχνές	συγχυτική κατάσταση
Όχι συχνές	μεταβολές της νοητικής κατάστασης, κατάθλιψη, μειωμένη γενετήσια ορμή
Διαταραχές του νευρικού συστήματος	
Συχνές	περιφερική αισθητική νευροπάθεια, ζάλη, κεφαλαλγία, λήθαργος
Όχι συχνές	σύνδρομο Guillain-Barré[β,γ], συγκοπή, κρανιακή νευροπάθεια, εγκεφαλικό οίδημα, περιφερική νευροπάθεια, αταξία, τρόμος, μυόκλωνος, δυσαρθρία
Οφθαλμικές διαταραχές	
Συχνές	θαμπή όραση, πόνος του οφθαλμού
Όχι συχνές	ραγοειδίτιδα[γ], αιμορραγία του υαλοειδούς σώματος, ιρίτιδα[γ], μειωμένη οπτική οξύτητα, αίσθημα ξένου σώματος στους οφθαλμούς, επιπεφυκίτιδα
Καρδιακές διαταραχές	
Όχι συχνές	αρρυθμία, κολπική μαρμαρυγή
Αγγειακές διαταραχές	
Συχνές	υπόταση, έξαψη
Όχι συχνές	αγγειίτιδα, αγγειοπάθεια[β], περιφερική ισχαιμία, ορθοστατική υπόταση
Διαταραχές του αναπνευστικού συστήματος, του θώρακα και του μεσοθωρακίου	
Συχνές	δύσπνοια, βήχας
Όχι συχνές	αναπνευστική ανεπάρκεια, σύνδρομο οξείας αναπνευστικής δυσχέρειας[β], διήθηση πνεύμονα, πνευμονικό οίδημα, πνευμονίτιδα, αλλεργική ρινίτιδα
Διαταραχές του γαστρεντερικού	
Πολύ συχνές	διάρροια[γ], έμετος, ναυτία
Συχνές	γαστρεντερική αιμορραγία, κολίτιδα[β,γ], δυσκοιλιότητα, γαστροοισοφαγική παλινδρόμηση, κοιλιακό άλγος
Όχι συχνές	διάτρηση του γαστρεντερικού σωλήνα[β,γ], διάτρηση του παχέος εντέρου[β,γ], διάτρηση του εντέρου[β,γ], περιτονίτιδα[β], παγκρεατίτιδα, εντεροκολίτιδα, γαστρικό έλκος, έλκος του παχέος εντέρου, οισοφαγίτιδα, ειλεός[δ]
Διαταραχές του ήπατος και των χοληφόρων	
Συχνές	μη φυσιολογική ηπατική λειτουργία
Όχι συχνές	ηπατική ανεπάρκεια[β,γ], ηπατίτιδα, ηπατομεγαλία, ίκτερος
Διαταραχές του δέρματος και του υποδόριου ιστού	
Πολύ συχνές	εξάνθημα[γ], κνησμός[γ]
Συχνές	δερματίτιδα, ερύθημα, λεύκη, κνίδωση, αλωπεκία, νυκτερινοί ιδρώτες, ξηροδερμία
Όχι συχνές	τοξική επιδερμική νεκρόλυση[β,γ], λευκοκυτταροκλαστική αγγειίτιδα, αποφολίδωση δέρματος
Διαταραχές του μυοσκελετικού συστήματος και του συνδετικού ιστού	
Συχνές	αρθραλγία, μυαλγία, μυοσκελετικός πόνος, μυϊκοί σπασμοί
Όχι συχνές	ρευματική πολυμυαλγία, αρθρίτιδα-
Διαταραχές των νεφρών και των ουροφόρων οδών	
Όχι συχνές	νεφρική ανεπάρκεια[β], σπειραματονεφρίτιδα[γ], νεφρική σωληναριακή οξέωση
Διαταραχές του αναπαραγωγικού συστήματος και του μαστού	
Όχι συχνές	αμηνόρροια
Γενικές διαταραχές και καταστάσεις της οδού χορήγησης	
Πολύ συχνές	κόπωση, αντίδραση της θέσης ένεσης, πυρεξία
Συχνές	ρίγη, εξασθένιση, οίδημα, άλγος
Όχι συχνές	πολυοργανική ανεπάρκεια[β,γ], σχετιζόμενη με την έγχυση αντίδραση
Παρακλινικές εξετάσεις	
Συχνές	αυξημένη αμινοτρανσφεράση της αλανίνης[γ], αυξημένη ασπαρτική αμινοτρανσφεράση[γ], αυξημένη χολερυθρίνη αίματος, μειωμένο σωματικό βάρος
Όχι συχνές	μη φυσιολογικές δοκιμασίες ηπατικής λειτουργίας, αυξημένη κρεατινίνη αίματος, αυξημένη θυρεοειδοτρόπος ορμόνη αίματος, μειωμένη κορτιζόλη αίματος, μειωμένη κορτικοτροφίνη αίματος, αυξημένη λιπάση[γ], αυξημένη αμυλάση αίματος[γ], μειωμένη τεστοστερόνη αίματος

α Οι συχνότητες βασίζονται σε συγκεντρωτικά στοιχεία από 9 κλινικές δοκιμές που εξέτασαν το YERVOY 3 mg/kg δόση σε μελάνωμα.

β Συμπεριλαμβάνεται η θανατηφόρος έκβαση.

γ Πρόσθετες πληροφορίες σχετικά με αυτές τις πιθανώς φλεγμονώδεις ανεπιθύμητες ενέργειες παρέχονται στην «Περιγραφή επιλεγμένων ανεπιθύμητων ενεργειών» και την παράγραφο 4.4. Τα δεδομένα που παρουσιάζονται σε αυτές τις παραγράφους αποτυπώνουν κυρίως την εμπειρία από μια μελέτη Φάσης 3, την MDX01020.

δ Αναφέρονται σε πρόσφατες μελέτες εκτός των ολοκληρωμένων κλινικών δοκιμών στο μελάνωμα.

Πρόσθετες ανεπιθύμητες ενέργειες που δεν αναφέρονται στον Πίνακα 2 έχουν αναφερθεί σε ασθενείς που έλαβαν άλλες δόσεις (είτε < ή > 3 mg/kg) YERVOY σε κλινικές δοκιμές μελανώματος. Αυτές οι πρόσθετες αντιδράσεις παρουσιάστηκαν όλες σε συχνότητα < 1%: μηνιγγισμός, μυοκαρδίτιδα, καρδιομυοπάθεια, αυτοάνοση ηπατίτιδα, πολύμορφο ερύθημα, αυτοάνοση νεφρίτιδα, συμπτώματα ομοιάζοντα με μυασθένεια gravis, αυτοάνοση θυρεοειδίτιδα, υπερυποφυσισμός, δευτεροπαθής ανεπάρκεια του φλοιού των επινεφριδίων, υποπαραθυρεοειδισμός, θυρεοειδίτιδα, επισκληρίτιδα, βλεφαρίτιδα, οίδημα του οφθαλμού, σκληρίτιδα, κροταφική αρτηρίτιδα, φαινόμενο Raynaud, πρωκτίτιδα, σύνδρομο παλαμοπελματιαίας ερυθροδυσαισθησίας, ψωρίαση, αιματουρία, πρωτεϊνουρία, μειωμένη θυρεοειδοτρόπος ορμόνη αίματος, μειωμένη γοναδοτροφίνη αίματος, μειωμένη θυροξίνη, λευκοπενία και πολυκυτταραιμία. Περιγραφή επιλεγμένων ανεπιθύμητων ενεργειών: Με εξαίρεση τις περιπτώσεις στις οποίες επισημαίνεται, τα δεδομένα για τις παρακάτω επιλεγμένες ανεπιθύμητες ενέργειες βασίζονται σε ασθενείς που έλαβαν μονοθεραπεία με YERVOY 3 mg/kg (n = 131) ή YERVOY 3 mg/kg σε συνδυασμό με gp100 (n = 380) σε μια μελέτη Φάσης 3 του προχωρημένου (μη χειρουργήσιμου ή μεταστατικού) μελανώματος (MDX01020, βλέπε παράγραφο 5.1). Οι κατευθυντήριες γραμμές για την αντιμετώπιση αυτών των ανεπιθύμητων ενεργειών περιγράφονται στην παράγραφο 4.4. Γαστρεντερικές αντιδράσεις που συνδέονται με το ανοσοποιητικό. Το YERVOY σχετίζεται με σοβαρές γαστρεντερικές αντιδράσεις που συνδέονται με το ανοσοποιητικό. Θανατηφόρα περιστατικά λόγω διάτρησης του γαστρεντερικού σωλήνα έχουν αναφερθεί σε < 1% των ασθενών που έλαβαν YERVOY 3 mg/kg σε συνδυασμό με gp100. Στην ομάδα με μονοθεραπεία με YERVOY 3 mg/kg, αναφέρθηκε διάρροια και κολίτιδα οποιασδήποτε βαρύτητας στο 27% και το 8% αντίστοιχα. Η συχνότητα σοβαρής (Βαθμού 3 ή 4) διάρροιας και σοβαρής (Βαθμού 3 ή 4) κολίτιδας ήταν 5% για το καθένα. Ο διάμεσος χρόνος έως την εκδήλωση σοβαρών ή θανατηφόρων (Βαθμού 3 έως 5) γαστρεντερικών αντιδράσεων που συνδέονται με το ανοσοποιητικό ήταν 8 εβδομάδες (εύρος 5 έως 13 εβδομάδες) από την αρχή της θεραπείας. Με κατευθυντήριες γραμμές για την αντιμετώπιση σχετιζόμενες με το πρωτόκολλο η υποχώρηση παρουσιάστηκε στις περισσότερες περιπτώσεις (90%), με διάμεσο χρόνο από την εκδήλωση έως την υποχώρηση (ορίζεται ως βελτίωση σε ήπια [Βαθμού 1] ή λιγότερο ή στη σοβαρότητα κατά την έναρξη) 4 εβδομάδες (εύρος 0,6 έως 22 εβδομάδες). Σε κλινικές δοκιμές η κολίτιδα που συνδέεται με το ανοσοποιητικό συσχετίστηκε με στοιχεία φλεγμονής του βλεννογόνου, με ή χωρίς εξελκώσεις και λεμφοκυτταρική και ουδετεροφιλική διήθηση. Ηπατοτοξικότητα που συνδέεται με το ανοσοποιητικό. Το YERVOY σχετίζεται με σοβαρή ηπατοτοξικότητα που συνδέεται με το ανοσοποιητικό. Θανατηφόρος ηπατική ανεπάρκεια έχει αναφερθεί σε < 1% των ασθενών που έλαβαν μονοθεραπεία με YERVOY 3 mg/kg. Αυξήσεις της AST και της ALT οποιασδήποτε βαρύτητας αναφέρθηκαν στο 1% και το 2% των ασθενών αντίστοιχα. Δεν υπήρχαν αναφορές σοβαρής (Βαθμού 3 ή 4) αύξησης της AST ή της ALT. Ο χρόνος έως την εκδήλωση μέτριας έως σοβαρής ή θανατηφόρου (Βαθμού 2 έως 5) ηπατοτοξικότητας που συνδέεται με το ανοσοποιητικό κυμάνθηκε από 3 έως 9 εβδομάδες από την αρχή της θεραπείας. Με κατευθυντήριες γραμμές για την αντιμετώπιση σχετιζόμενες με το πρωτόκολλο, ο χρόνος έως την υποχώρηση κυμάνθηκε από 0,7 έως 2 εβδομάδες. Σε κλινικές δοκιμές, βιοψίες ήπατος από ασθενείς που είχαν ηπατοτοξικότητα σχετιζόμενη με το ανοσοποιητικό, εμφάνισαν στοιχεία οξείας φλεγμονής (ουδετερόφιλα, λεμφοκύτταρα και μακροφάγα). Δερματικές ανεπιθύμητες αντιδράσεις που συνδέονται με το ανοσοποιητικό. Το YERVOY σχετίζεται με σοβαρές δερματικές ανεπιθύμητες αντιδράσεις που μπορεί να συνδέονται με το ανοσοποιητικό. Θανατηφόρος τοξική επιδερμική νεκρόλυση έχει αναφερθεί σε < 1% των ασθενών που έλαβαν YERVOY σε συνδυασμό με gp100 (βλέπε παράγραφο 5.1). Στην ομάδα με μονοθεραπεία με YERVOY 3 mg/kg, αναφέρθηκε εξάνθημα και κνησμός διαφορετικής βαρύτητας, το καθένα στο 27% των ασθενών. Εξάνθημα και κνησμός επαγόμενο από YERVOY ήταν κυρίως ήπια (Βαθμού 1) ή μέτρια (Βαθμού 2) και ανταποκρίνονταν σε συμπτωματική θεραπεία. Ο διάμεσος χρόνος έως την εκδήλωση μέτριων έως σοβαρών ή θανατηφόρων (Βαθμού 2 έως 5) δερματικών ανεπιθύμητων αντιδράσεων ήταν 3 εβδομάδες από την αρχή της θεραπείας (εύρος 0,9 έως 16 εβδομάδες). Με κατευθυντήριες γραμμές για την αντιμετώπιση σχετιζόμενες με το πρωτόκολλο, υποχώρηση παρουσιάστηκε στις περισσότερες περιπτώσεις (87%), με διάμεσο χρόνο από την εκδήλωση έως την υποχώρηση 5 εβδομάδες (εύρος 0,6 έως 29 εβδομάδες). Νευρολογικές ανεπιθύμητες αντιδράσεις που συνδέονται με το ανοσοποιητικό. Το YERVOY σχετίζεται με σοβαρές νευρολογικές αντιδράσεις που συνδέονται με το ανοσοποιητικό. Θανατηφόρο σύνδρομο Guillain-Barré έχει αναφερθεί σε < 1% των ασθενών που έλαβαν YERVOY 3 mg/kg σε συνδυασμό με gp100. Συμπτώματα ομοιάζοντα με μυασθένεια gravis έχουν επίσης αναφερθεί σε < 1% των ασθενών που έλαβαν υψηλότερες δόσεις YERVOY σε κλινικές δοκιμές. Ενδοκρινοπάθεια που συνδέονται με το ανοσοποιητικό. Στην ομάδα με μονοθεραπεία με YERVOY 3 mg/kg, υποϋποφυσισμός οποιασδήποτε βαρύτητας αναφέρθηκε στο 4% των ασθενών. Επινεφριδιακή ανεπάρκεια, υπερθυρεοειδισμός και υποθυρεοειδισμός οποιασδήποτε βαρύτητας αναφέρθηκε το καθένα στο 2% των ασθενών. Η συχνότητα σοβαρού (Βαθμού 3 ή 4) υποϋποφυσισμού αναφέρθηκε στο 3% των ασθενών. Δεν υπήρχαν αναφορές σοβαρής ή πολύ σοβαρής (Βαθμού 3 ή 4) επινεφριδιακής ανεπάρκειας, υπερθυρεοειδισμού ή υποθυρεοειδισμού. Ο χρόνος έως την εκδήλωση μέτριας έως πολύ σοβαρής (Βαθμού 2 έως 4) σχετιζόμενης με το ανοσοποιητικό ενδοκρινοπάθειας κυμάνθηκε από 7 έως περίπου 20 εβδομάδες από την αρχή της θεραπείας. Ενδοκρινοπάθεια σχετιζόμενη με το ανοσοποιητικό που παρατηρήθηκε σε κλινικές δοκιμές, ήταν γενικώς ελεγχόμενη με θεραπεία υποκατάστασης ορμονών. Άλλες ανεπιθύμητες αντιδράσεις που συνδέονται με το ανοσοποιητικό. Οι παρακάτω ανεπιθύμητες αντιδράσεις που πιθανολογείται ότι συνδέονται με το ανοσοποιητικό, έχουν αναφερθεί σε < 2% των ασθενών που έλαβαν μονοθεραπεία με YERVOY 3 mg/kg: ραγοειδίτιδα, ηωσινοφιλία, αύξηση λιπάσης και σπειραματονεφρίτιδα. Επιπροσθέτως, ιρίτιδα, αιμολυτική αναιμία, αυξήσεις αμυλάσης, πολυοργανική ανεπάρκεια και πνευμονίτιδα έχουν αναφερθεί σε ασθενείς που έλαβαν YERVOY 3 mg/kg σε συνδυασμό με πεπτιδικό εμβόλιο gp100. YERVOY 5 mg/ml πυκνό διάλυμα για παρασκευή διαλύματος προς έγχυση – Συσκευασία: 1 Φιαλίδιο (γυάλινο) x 10 ml με ενδεικτική Νοσοκομειακή τιμή 3.887,16 €, και ενδεικτική Χονδρική τιμή τιμή 4.468,00 €. YERVOY 5 mg/ml πυκνό διάλυμα για παρασκευή διαλύματος προς έγχυση – Συσκευασία: 1 Φιαλίδιο (γυάλινο) x 40 ml με ενδεικτική Νοσοκομειακή τιμή 15.548,65 €, και ενδεικτική Χονδρική τιμή τιμή 17.872,01 €.

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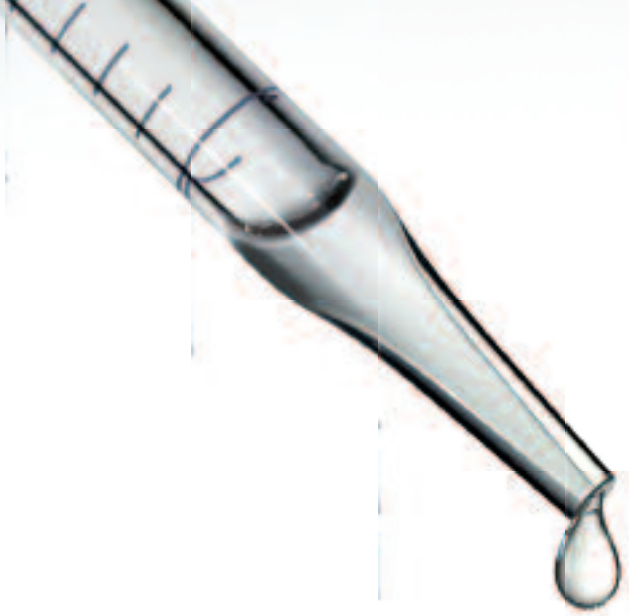

ΚΑΙ ΤΩΡΑ ΕΓΚΕΚΡΙΜΕΝΟ

Το YERVOY™ (ipilimumab) ενδείκνυται για τη θεραπεία του προχωρημένου (ανεγχείρητου ή μεταστατικού) μελανώματος σε ενηλίκους που έχουν λάβει προηγούμενη θεραπεία.[1]

ΠΡΟΟΔΟΣ ΤΗΣ ΕΠΙΣΤΗΜΗΣ
ΣΤΟ ΜΕΤΑΣΤΑΤΙΚΟ ΜΕΛΑΝΩΜΑ

Η δύναμη του ανοσοποιητικού συστήματος

Η σπουδαιότητα της παρατεταμένης επιβίωσης

- **YERVOY™: Ο πρώτος εγκεκριμένος παράγοντας που παρατείνει σημαντικά τη συνολική επιβίωση σε ασθενείς με προχωρημένο μελάνωμα*[2]**
- **YERVOY™: Μια νέα θεραπεία ενίσχυσης των Τ-κυττάρων που ενεργοποιεί το ανοσοποιητικό σύστημα ώστε αυτό να καταστρέφει τους καρκινικούς όγκους.[1]**

Για σημαντικές πληροφορίες ασφάλειας, ανατρέξτε στην Περίληψη Χαρακτηριστικών Προϊόντος του YERVOY™

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YERVOY™ (ipilimumab)
πυκνό διάλυμα για παρασκευή διαλύματος προς έγχυση

*Σε μια τυχαιοποιημένη, ελεγχόμενη δοκιμή φάσης 3.

1. Περίληψη Χαρακτηριστικών Προϊόντος του YERVOY™. 2. Hodi FS *et al. N Engl J Med.* 2010;363(8):711-723.