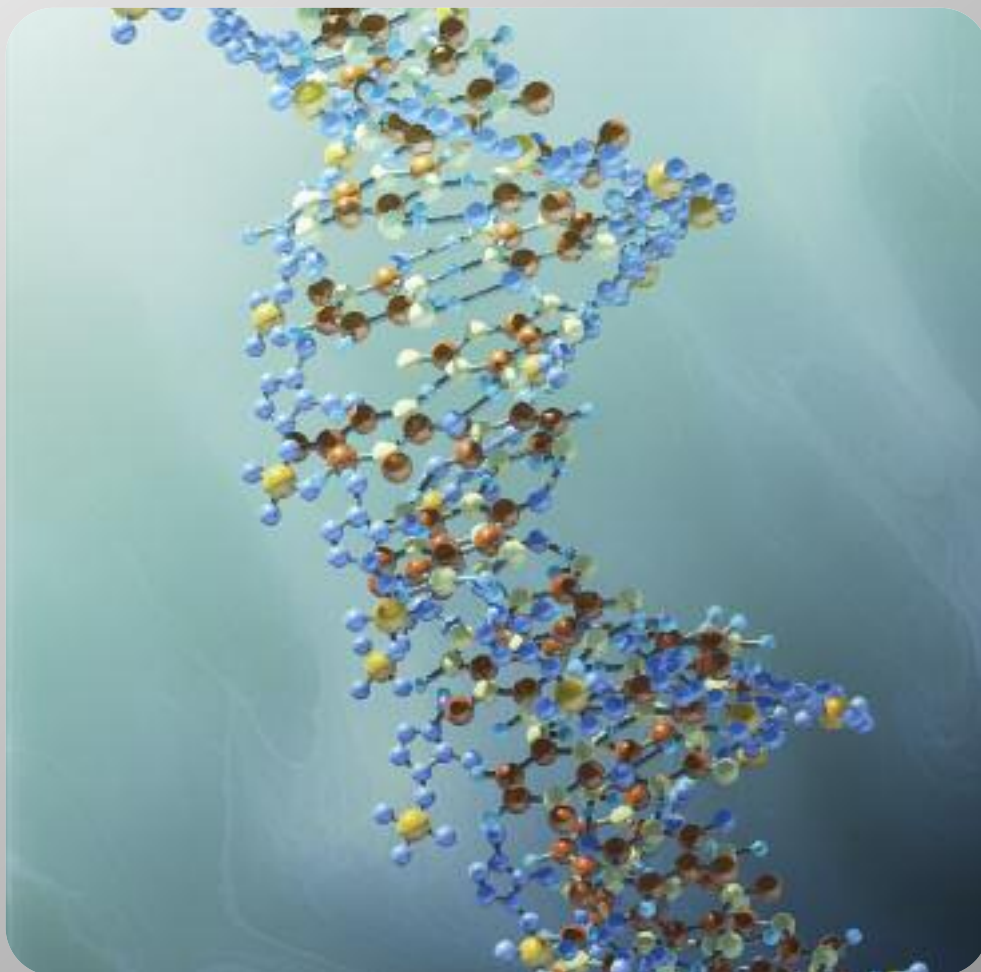


FORUM of CLINICAL ONCOLOGY

Quarterly official publication of the Hellenic Society of Medical Oncology

ISSN: 1792-345X



**Clinical trials in oncology:
 a comprehensive
 scientific, ethical, legal
 and financial overview**

**Ethical issues regarding
 the acquisition and
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 of metastatic bone disease**

**Bisphosphonates: Future perspectives
 and anti-tumor activity in malignant diseases**

Low-grade cribriform cystadenocarcinoma of the parotid gland



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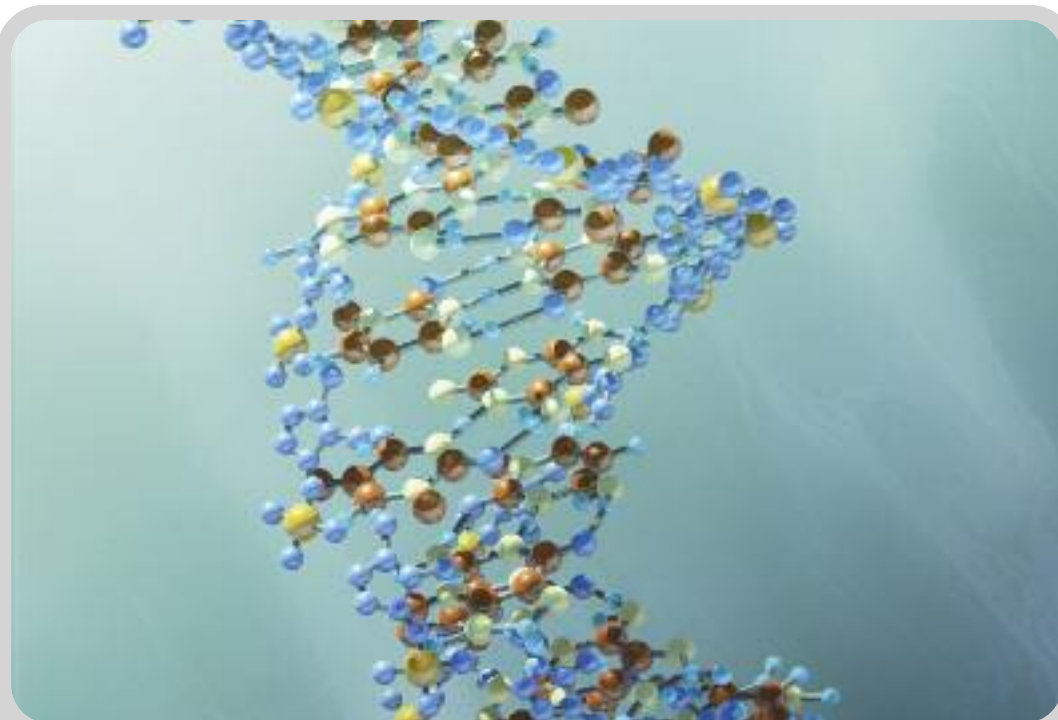


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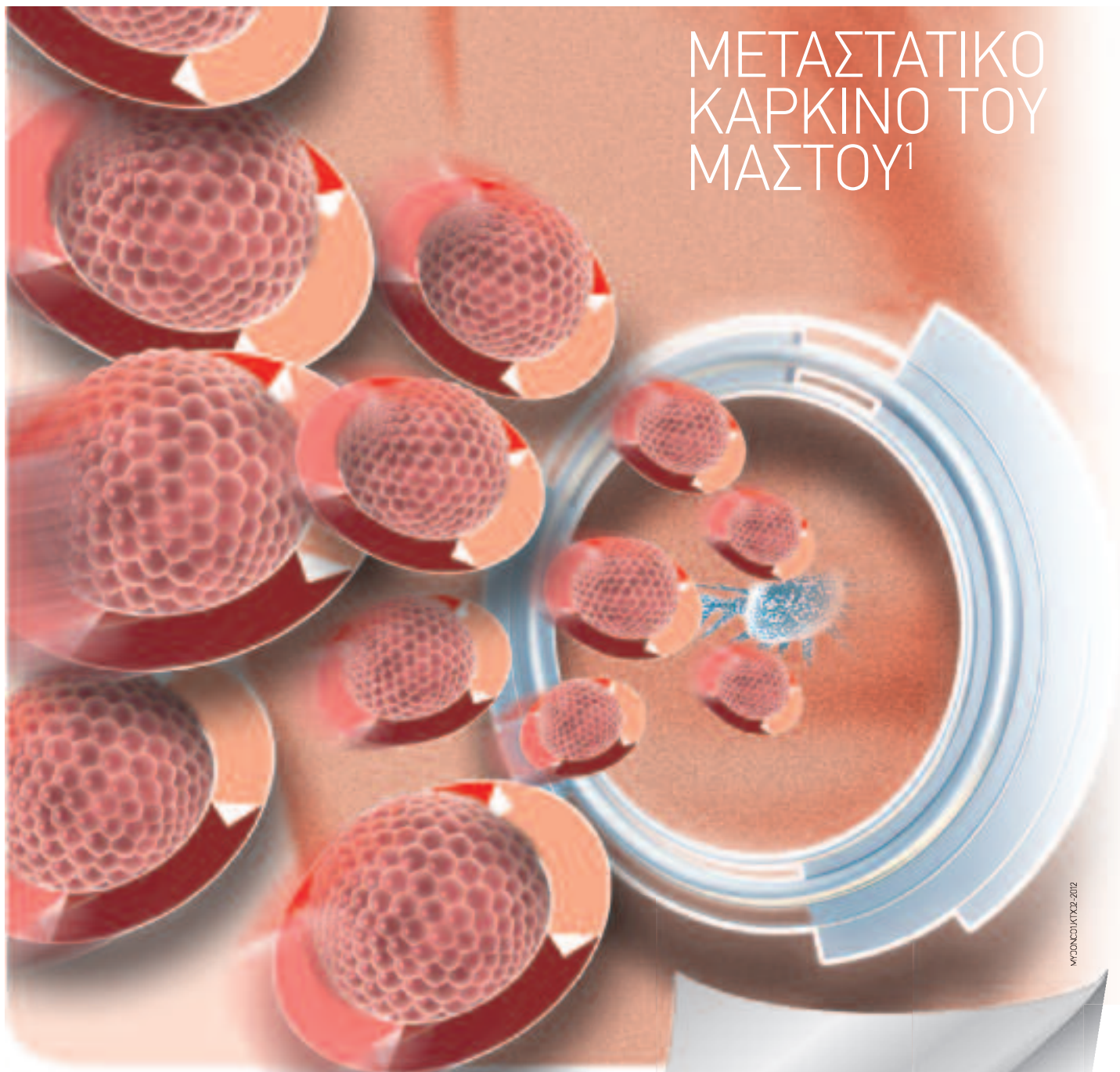
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Diamonds are for ever

Editorial

Vassilios Barbounis

There has been a turmoil regarding excess health expenditure and the barriers in the provision of expensive medicines or novel state-of-the-art pharmaceuticals; In contrast, the value of clinical trials is overshadowed by malicious critique.

The article of Pentheroudakis *et al.* "Clinical trials in oncology: a comprehensive scientific, ethical, legal and financial overview" (FCO 2012; 3(3): 9-13) is a well-documented paper on clinical trials and presents all aspects of the subject: clinical trials are essential to the progress of Oncology; they are governed by strict rules; patients benefit from participating in randomized controlled trials; and last but not least, where trials are conducted there is an additional benefit for the National Health System and the state economy.

The authors point in the right direction guiding health professionals who are involved in cancer research, informing patients as primarily affected and, naturally, regulatory authorities which are responsible both for surveying and enforcing good practice rules as well as creating the appropriate conditions for quick and easy access for patients, far from prohibiting and interminable procedures.

1. ΟΝΟΜΑΣΙΑ ΤΟΥ ΦΑΡΜΑΚΕΥΤΙΚΟΥ ΠΡΟΪΟΝΤΟΣ Κόνις Myocet 50 mg και υλικό στο στάδιο προ της προέλασης για την παρασκευή πυκνού διαλύματος για λιποσωματική διασπορά προς έγχυση. **2. ΠΟΙΟΤΗΤΑ ΚΑΙ ΠΟΣΗΤΗΤΗ ΣΥΝΘΕΣΗ** Συμπύκνωμα δοξορουβικίνης-κρυστών ενδονυκλικής καρδιακής ανεπάρκειας (HC) δοξορουβικίνης (HC) δοξορουβικίνης. Ένδοξη: Το αντιστοιχείστομο φαρμακευτικό προϊόν περιέχει περίπου 108 mg κόνιου για μία δόση υδροχλωρικής (HC) δοξορουβικίνης 50 mg. **3. ΦΑΡΜΑΚΟΤΕΧΝΙΚΗ ΜΟΡΦΗ** Κόνις και υλικό στο στάδιο προ της προέλασης για την παρασκευή πυκνού διαλύματος για λιποσωματική διασπορά προς έγχυση. Το Myocet διατίθεται με τη μορφή συστημάτων τριών φακών. Υπόλογη (HC) δοξορουβικίνη Myocet είναι μία κόνιου λυοφιλοποιημένη ακατέληκτη/αποσπασμένη Myocet είναι μία λευκή έως υπόλευκη, αδιάλυτη και αμεταβλητή βερνικωτή. Ενδοδοσικό διάλυμα Myocet είναι ένα άχρωμο, αργερό διάλυμα. **4. ΚΛΙΝΙΚΕΣ ΠΛΗΡΟΦΟΡΙΕΣ 4.1 Θεραπευτικές ενδείξεις** Το Myocet, σε συνδυασμό με την κυκλοφωσφamide (CPA), ενδείκνυται για τη θεραπεία πρώτης γραμμής του μεταστατικού καρκίνου του μαστού των ενήλικων γυναικών. **4.2 Δοσολογία και τρόπος χορήγησης** Η χρήση του Myocet πρέπει να περιορίζεται σε μονάδες που είναι εξειδικευμένες στη χορήγηση καταπολέμησης χημειοθεραπείας και η χορήγηση του πρέπει να γίνεται μόνο υπό την επίβλεψη ιατρού που είναι εξειδικευμένος στη χρήση χημειοθεραπείας. Δοσολογία Όταν το Myocet χορηγείται σε συνδυασμό με κυκλοφωσφamide (CPA) (600 mg/m²), η αρχική συνιστώμενη δόση του Myocet είναι 60-75 mg/m² κάθε τρεις εβδομάδες. Ηλικιωμένοι ασθενείς Η ασφαλεία και η αποτελεσματικότητά του Myocet έχουν εκτιμηθεί σε 61 ασθενείς με μεταστατικό καρκίνιο του μαστού, ηλικίας 65 ετών και άνω. Τα δεδομένα από τυχαία επιλεγμένους ελεγχόμενες κλινικές δοκιμές δείχνουν ότι η αποτελεσματικότητά και η ασφαλεία του Myocet έναντι καρδιακών εκδηλώσεων σε αυτό τον πληθυσμό ήταν συγκρίσιμες με αυτές που παρατηρήθηκαν σε ασθενείς ηλικίας κάτω των 65 ετών. Ασθενείς με ηπατική δυσλειτουργία Επίσης η μεταβολική και η απέκκριση της δοξορουβικίνης γίνονται κυρίως από την ηπατοκυτταρική, πρέπει να διενεργείται εκτίμηση της ηπατοκυτταρικής λειτουργίας, πριν και κατά τη διάρκεια της θεραπείας με Myocet. Με βάση περιγραφόμενα στοιχεία ασθενών με ηπατικές μεταστάσεις, συνιστάται επίσης η αρχική δόση του Myocet μειωθεί σύμφωνα με τον ακόλουθο πίνακα

Εξετάσεις ηπατικής λειτουργίας	Δόση
Χολερυθρίνη < ULN και φυσιολογική AST	Συνήθης δόση 60 - 75mg/m ²
Χολερυθρίνη < ULN και αυξημένα AST	Με μελέτη ενδεχόμενη 25% μείωση της δόσης
Χολερυθρίνη > ULN αλλά < 50 μmol/l	50% μείωση της δόσης
Χολερυθρίνη > 50 μmol/l	75% μείωση της δόσης

Αν είναι δυνατόν, το Myocet θα πρέπει να αποφεύγεται σε ασθενείς με χολερυθρίνη > 50 μmol/l καθώς η αύξηση αυτή μπορεί να συμπεραστεί, για μείωση της δόσης λόγω άλλων τοξικών, βλέπε παράγραφο 4.4. Ασθενείς με νεφρική δυσλειτουργία Η δοξορουβικίνη μεταβολίζεται κυρίως από το ήπαρ και απέκκριται στη χολή. Συνεπώς, δεν απαιτούνται προσαρμογές της δόσης σε ασθενείς με νεφρική δυσλειτουργία. Παιδιατρική Η ασφαλεία και η αποτελεσματικότητά του Myocet σε παιδιά ηλικίας έως 17 ετών δεν έχουν τεκμηριωθεί. Δεν υπάρχουν διαθέσιμα δεδομένα. Τρόπος χορήγησης Το Myocet πρέπει να αναμιγνύεται με αραιωμένα περαστήρα πριν από τη χορήγηση. Απαιτείται τελική συγκέντρωση υδροχλωρικής δοξορουβικίνης 0,4 mg/ml έως 1,2 mg/ml. Το Myocet χορηγείται με ενδοφλέβια έγχυση, σε διάστημα 1 ώρας. Το Myocet δεν πρέπει να χορηγείται día της ενδοφλέβιας ή της υποδόριας οδού ή ως εμφύσηση. **4.3 Αντενδείξεις** Υπερσυστροφή στη βρογχική ουσία, στο υλικό στο στάδιο προ της προέλασης ή σε κάποιο από τα εξής: **4.4 Διόσεις προειδοποιήσεων και προφυλάξεις κατά τη χρήση** Μυελοκαταστολή Η ασφαλεία με το Myocet προκαλεί μυελοκαταστολή. Το Myocet δεν πρέπει να χορηγείται σε άτομα με απόλυτο αριθμό ουδετερόφιλων (ANC) μικρότερο από 1.500 κύτταρα/μl ή αριθμό αιμοπεταλίων μικρότερο από 100.000/μl πριν από τον επόμενο κύκλο. Κατά τη διάρκεια της θεραπείας με Myocet, πρέπει να διενεργείται προσεκτική αιματολογική παρακολούθηση πριν να περιλαμβάνει μετρήσεις των λευκών αιμοσφαιρίων και των αιμοπεταλίων, καθώς και της αναιμίας. Μία μετα-ανάλυση έδειξε στατιστικά σημαντική χαμηλότερη ποσοστό ουδετεροπενίας βαθμού 4 (RR = 0,82, p = 0,005) σε ασθενείς που έλαβαν θεραπεία με το Myocet έναντι συμβατικής δοξορουβικίνης. Ωστόσο, δεν διαπιστώθηκαν σημαντικές διαφορές στην εμφάνιση αναιμίας, θρομβοπενίας και επανοδόου ουδετεροπενίας πυρετού. Η μαζολογική τοξικότητα, καθώς και αποδοτικότητα άλλη τοξικότητα, ενδέχεται να απαιτούν μειώσεις ή καθυστερήσεις της δόσης. Οι ακόλουθες προτροπές δοσολογίας συνιστάται κατά τη διάρκεια της θεραπείας και πρέπει να εκτελούνται παράλληλα, τόσο για το Myocet όσο και για την κυκλοφωσφamide. Η δοσολογία που ακολουθεί τη μείωση της δόσης επιβάλλεται στην κρίση του ιατρού που είναι υπεύθυνος για τον ασθενή.

Αιματολογική Τοξικότητα			
Βαθμός	Ελάχιστος Αριθμός ANC (κύτταρα/μl)	Ελάχιστος Αριθμός Αιμοπεταλίων (κύτταρα/μl)	Τροποποίηση
1	1500 - 1900	75.000 - 150.000	Καμία
2	1000 - Λιγότερα από 1500	50.000 - Λιγότερα από 75.000	Καμία
3	500 - 999	25.000 - Λιγότερα από 50.000	Περαιτέρω ωστόσο ο αριθμός των ANC για 1500 ή μεγαλύτερος ή/και ο αριθμός των αιμοπεταλίων για 100.000 ή μεγαλύτερος και κατόπιν επαναχορηγήστε τη δόση μειωνόμενη την κατά 25 %
4	Λιγότερα από 500	Λιγότερα από 25.000	Περαιτέρω ωστόσο ο αριθμός των ANC για 1500 ή/και ο αριθμός των αιμοπεταλίων για 100.000 ή μεγαλύτερος και κατόπιν επαναχορηγήστε τη δόση μειωνόμενη την κατά 50 %

Εάν η μυελοκαταστολή καθυστερήσει τη θεραπεία περαιτέρω από 35 ημέρες μετά τη χορήγηση της πρώτης δόσης του προηγούμενου κύκλου, τότε θα πρέπει να εξεταστεί το ενδεχόμενο διακοπής της θεραπείας.

Βλεννογονιτίδα		
Βαθμός	Συμπτώματα	Τροποποίηση
1	Ανώδυνη ελκί, ερυθρότητα ή ήπια αιμορραγία	Καμία
2	Όδυνηρο ερυθρότητα, οίδημα ή ελκί αλλά ο ασθενής μπορεί να φάει	Περαιτέρω μία εβδομάδα και εάν τα συμπτώματα υποχωρήσουν, επαναχορηγήστε τη δόση μειωνόμενη την κατά 25 %
3	Όδυνηρο ερυθρότητα, οίδημα ή ελκί και ο ασθενής δεν μπορεί να φάει	Περαιτέρω μία εβδομάδα και εάν τα συμπτώματα υποχωρήσουν, επαναχορηγήστε τη δόση μειωνόμενη την κατά 25 %
4	Απώλεια παρεντερικής ή εντερικής υποστήριξης	Περαιτέρω μία εβδομάδα και εάν τα συμπτώματα υποχωρήσουν, επαναχορηγήστε τη δόση μειωνόμενη την κατά 50 %

Σχετικά με τη μείωση της δόσης του Myocet λόγω βλάβης της λειτουργίας του ήπατος, βλέπε παράγραφο 4.2 Καρδιακή τοξικότητα Η δοξορουβικίνη και άλλες ανθρακινικές μπορεί να προκαλέσουν καρδιοτοξικότητα. Ο κίνδυνος τοξικότητας αυξάνει με τις αυξανόμενες αβιοτικές δόσεις αυτών των φαρμακευτικών προϊόντων και είναι υψηλότερος σε άτομα με ιστορικό καρδιοανατομικών ή ακτινοβολιών του μεσοθωρακίου ή προ-υποδοχέας καρδιακής νόσου. Ανάλυση της καρδιοτοξικότητας των κλινικών δοκιμών έχουν δείξει μία στατιστικά σημαντική μείωση των καρδιακών ανεπιθύμητων σε ασθενείς που υποβλήθηκαν σε θεραπεία με Myocet, σε σύγκριση με ασθενείς που υποβλήθηκαν

σε θεραπεία με συμβατική δοξορουβικίνη, στην ίδια δόση σε mg. Μία μετα-ανάλυση έδειξε στατιστικά σημαντική χαμηλότερη ποσοστό τόσο της κλινικής καρδιακής ανεπάρκειας (RR = 0,20, p = 0,02) όσο και της συνδυασμένης κλινικής και υποκλινικής καρδιακής ανεπάρκειας (RR = 0,38, p < 0,0001) σε ασθενείς που έλαβαν θεραπεία με το Myocet έναντι συμβατικής δοξορουβικίνης. Ο μεωμένος κίνδυνος καρδιοτοξικότητας έχει επίσης αποδοθεί σε μια αναδρομική ανάλυση σε ασθενείς που είχαν λάβει προ-γεννητική επικουρική θεραπεία με δοξορουβικίνη (log-rank P = 0,001, άρως κίνδυνος = 5,42). Σε μία μελέτη φάσης III σε συνδυασμό με την κυκλοφωσφamide (CPA), η συγκριση του Myocet (60 mg/m²) + CPA (600 mg/m²) έναντι της δοξορουβικίνης (60 mg/m²) + CPA (600 mg/m²) το 6^ο έναντι του 2^{ου} % των ασθενών αντίστοιχα, ανέπτυξαν σημαντική μείωση στο κλάσμα εξώθησης αρτηρικής κοιλίας (LVEF). Σε μία μελέτη φάσης III, η οποία συγκρίνει το μονοπαραγοντικό Myocet (75 mg/m²) έναντι της μονοπαραγοντικής δοξορουβικίνης (75 mg/m²), το 12 % έναντι του 27 % των ασθενών, αντίστοιχα, ανέπτυξαν σημαντική μείωση του LVEF. Οι αντίστοιχοι αριθμοί για τη συμφορητική καρδιακή ανεπάρκεια (CHF), η οποία εκτιμήθηκε με μικρότερη ακρίβεια, ήταν 0 % για το Myocet + CPA έναντι 3 % για τη δοξορουβικίνη + CPA και 2 % για το Myocet έναντι 8 % για τη δοξορουβικίνη, ο άμεσος χρόνος ζωής αβιοτικής δόσης του Myocet, σε συνδυασμό με την CPA σε ένα καρδιακό βαθμό ήταν > 1.260 mg/m², σε σύγκριση με το 480 mg/m² για τη δοξορουβικίνη σε συνδυασμό με την CPA. Δεν υπάρχει εμπειρία με το Myocet σε ασθενείς με ιστορικό καρδιαγγειακής νόσου, π.χ. εμφραγμα του μυοκαρδίου 6 μήνες πριν από τη θεραπεία. Επομένως, πρέπει να γίνεται προσοχή σε ασθενείς με βλάβη της καρδιακής λειτουργίας. Σε ασθενείς που λαμβάνουν Myocet ταυτόχρονα με τριτογενή μείωση θα πρέπει να παρακολουθείται κατάλληλα η καρδιακή τους λειτουργία όπως περιγράφεται παρακάτω. Η συνολική δόση του Myocet πρέπει επίσης να λαμβάνει υπόψη αποδοτικότητα προηγούμενη ή ονδύη θεραπεία με άλλες καρδιοτοξικές ενώσεις, συμπεριλαμβανομένων των ανθρακινικών και των ανθρακινικών. Πριν από την έναρξη της θεραπείας με Myocet, συνιστάται να εξεταστεί ο συνδυασμός να διενεργηθεί μία μέτρηση του κλάσματος εξώθησης αρτηρικής κοιλίας (LVEF), είτε με Ακτινογραφία Πόλυάξια Εικόνας (MUGA) είτε με ηχοκαρδιογράφημα. Αυτές οι μέθοδοι πρέπει επίσης να εφαρμόζονται ως ρουτίνα, κατά τη διάρκεια με Myocet. Η εκτίμηση της λειτουργίας της αρτηρικής κοιλίας θεωρείται υποχρεωτική πριν από κάθε πρόσθετη χορήγηση του Myocet από τη στιγμή που ο ασθενής υπερβαίνει μια συνολική αβιοτική δόση ανθρακινικής 550 mg/m² ή όπου υπάρχει υποψία καρδιακής ανεπάρκειας. Εάν το LVEF έχει μειωθεί σημαντικά από την αρχική τιμή π.χ. κατά > 20 μονάδες έως τελική τιμή > 50 % ή κατά > 10 μονάδες έως μία τελική τιμή < 50 %, το άρως από τη συνεχή θεραπεία πρέπει να αξιολογηθεί προσεκτικά έναντι του κινδύνου πρόκλησης αμετάκλητης καρδιακής βλάβης. Ωστόσο, θα πρέπει να εξεταστεί το ενδεχόμενο διενέργειας της πλέον καθοριστικής δοκιμασίας για τυχόν βλάβη του μυοκαρδίου από ανθρακινική, δηλαδή της ενδομυοκαρδιακής βιοψίας. Όλα οι ασθενείς που λαμβάνουν Myocet πρέπει επίσης να παρακολουθούνται τακτικά με ΗΚΓ. Οι παρόδους μεταβολές του ΗΚΓ, όπως η επιβράδυνση του κυματός T, η κατάπτωση του τμήματος S-T και οι καθυστερήσεις αρρυθμίες, δεν θεωρούνται υποχρεωτικές ενδείξεις για τη διακοπή της θεραπείας με Myocet. Ωστόσο, η μείωση του συμπλεγμένου QRS θεωρείται πιο ενδεικτική καρδιακής τοξικότητας. Ενδεχεται να επισυμείνουν αιφνίδια συμφορητική καρδιακή ανεπάρκεια εξ αιτίας της καρδιομυοπάθειας, η οποία μπορεί επίσης να παρατηρηθεί μετά τη διακοπή της θεραπείας. Επιδεικνύονται διαταραχές της μετα-ανάλυσης έδειξε στατιστικά σημαντική χαμηλότερη ποσοστό ναυτίας, εμέτου βαθμού ≥ 3 (RR = 0,65, p = 0,04) και διάρροιας βαθμού ≥ 3 (RR = 0,33, p = 0,03) σε ασθενείς που έλαβαν θεραπεία με Myocet έναντι συμβατικής δοξορουβικίνης. Αντιδράσεις στο σημείο της ένεσης Το Myocet πρέπει να θεωρείται ερεθιστική ουσία και να λαμβάνονται προφυλάξεις για την αποφυγή εγγύσεων. Εάν συμβεί εγγύωση, η έγχυση πρέπει να διακοπεί και να τοποθετηθεί νέος στην προφύλαξη. Εάν η εγγύωση περάσει, για 30 λεπτά περίπου. Στη συνέχεια, η έγχυση του Myocet πρέπει να αρχίσει εκ νέου, σε διαφορετική φλέβα από εκείνη στην οποία παρουσιάστηκε εγγύωση. Σημειώστε ότι το Myocet μπορεί να χορηγηθεί διαμέσου κεντρικής ή περιφερικής φλέβας. Στο κλινικό πρόγραμμα, υπήρξαν εννέα περιπτώσεις τυχαίας εγγύωσης του Myocet, καμία από τις οποίες δεν συσχετίστηκε με σοβαρή δερματική βλάβη, εξέλιξη ή νεκρωσία. Αιτιολογία εγγύωσης με την έγχυση. Όταν γίνεται τυχαία έγχυση έχουν αναφερθεί οξείες αντιδράσεις σχετιζόμενες με αιμοσυμμετικές εγγύσεις. Στη αναφερθείσα συμπτωματολογία περιλαμβάνονται το ερυθρόμα, η δύσπνοια, ο πυρετός, το οίδημα προσώπου, η κεφαλαλγία, η ραχιαλγία, το ρίγη, το σφίξιμο στο στήθος και στο φάρυγγα/ή/και η υπόταση. Αυτά τα οξεία φαινόμενα είναι δυνατό να αποφευχθούν με την εφαρμογή έγχυσης διάρκειας 1 ώρας. Άλλα Σχετικά με τις προφυλάξεις που αφορούν τη χρήση του Myocet σε συνδυασμό με άλλα φαρμακευτικά προϊόντα, βλέπε παράγραφο 4.5. Άλλα Σχετικά με άλλα φαρμακευτικά προϊόντα και προϊόντα δοξορουβικίνης, συνδυασμοί αναμενόμενης ακτινοβολίας μπορεί να συμβεί σε περιπτώσεις που έχουν ακτινοβοληθεί στο παρελθόν. Η αποτελεσματικότητά και ασφαλεία του Myocet στην ανσοσυνεχιστική θεραπεία του καρκίνου του μαστού δεν έχουν προδοποιηθεί. Η σημασία των εμφανών διαφορών στην ιατρική κατανομή μεταξύ του Myocet και της συμβατικής δοξορουβικίνης δεν έχει διασαφηνιστεί σε σχέση με τη μακροχρόνια αποτελεσματικότητα αποτελεσματικότητας. **4.5 Αλληλεπιδράσεις με άλλα φαρμακευτικά προϊόντα και άλλες μορφές αλληλεπιδράσεων** Δεν έχουν διεξαχθεί ειδικές μελέτες συμβατικότητας φαρμακευτικών προϊόντων με το Myocet. Το Myocet είναι πιθανό να αλληλεπιδρά με ουσίες που είναι γνωστό ότι αλληλεπιδρούν με τη συμβατική δοξορουβικίνη. Τα επίπεδα της δοξορουβικίνης και του μεταβολίτη της, της δοξορουβικινολίνης στο πλάσμα, ενδέχεται να αυξηθούν όταν χορηγείται η δοξορουβικίνη σε συνδυασμό με την κυκλοφωσφamide, τη βατακινάλη ή με άλλους παράγοντες που αναστέλλουν την Ρ-γλυκοπρωτεΐνη (P-gp). Οι αλληλεπιδράσεις με τη δοξορουβικίνη έχουν επίσης αναφερθεί για τη στερεοϊσοκρίνη, τη φαινοβαρβιτάλη, τη φαινοϊνίνη και τη βαροφαινίνη. Υπάρχει επίσης έλλειψη μελέτων σχετικά με την επίδραση του Myocet σε άλλες ουσίες. Ωστόσο, η δοξορουβικίνη ενδέχεται να ενισχύσει την τοξικότητα των άλλων αντινεοπλασματικών παραγόντων. Η συνδυαστική θεραπεία με άλλες ουσίες που αναφέρονται ως καρδιοτοξικές ή με καρδιολογικές δραστηριότητες (π.χ. ανταγωνιστές αβιοτικής) ενδέχεται να αυξήσει τον κίνδυνο της καρδιοτοξικότητας. Η συνδυαστική θεραπεία με άλλες αιμοσυμμετικές ουσίες ή με ουσίες με συμπλοκά λιπιδίων ή ενδοφλέβια γαλακτωματικά λίπη θα μπορούσε να αλλάξει το φαρμακοκινητικό προφίλ του Myocet. **4.6 Γονιμότητα, κύηση και γαλουχία** Γυναίκες σε αναπαραγωγική ηλικία Γυναίκες σε αναπαραγωγική ηλικία πρέπει να χρησιμοποιούν αποτελεσματική αντισύλληξη κατά τη διάρκεια τουλάχιστον 6 μηνών πριν από την έναρξη της θεραπείας με Myocet και 6 μηνών μετά τη διακοπή της θεραπείας. Εγκυμοσύνη Λόγω των γνωστών κυτταροτοξικών, μεταλλαξιογόνων και εμβρυογενικών ιδιοτήτων της δοξορουβικίνης, το Myocet δεν πρέπει να χρησιμοποιείται κατά τη διάρκεια της εγκυμοσύνης εκτός εάν είναι σαφώς απαραίτητο. Θηλασμός Οι γυναίκες που λαμβάνουν Myocet δεν θα πρέπει να θηλάζουν. **4.7 Επιδράσεις στην ικανότητα οδήγησης και χειρισμού μηχανών** Το Myocet έχει αναφερθεί ότι προκαλεί λιγυρότητα. Οι ασθενείς που πάσχουν από τέτοια συμπτώματα πρέπει να αποφεύγουν την οδήγηση και το χειρισμό μηχανών. **4.8 Αντενδείξεις ενέργειας** Κατά τη διάρκεια κλινικών δοκιμών, οι πιο συχνές ανεπιθύμητες ενέργειες που αναφέρθηκαν ήταν ναυτία/έμετος (73%), λευκοπενία (70%), αλωπεκία (66%), ουδετεροπενία (46%), εξοδονση/κόπωση (46%), στοματίτιδα/βλεννογονιτίδα (42%), θρομβοπενία (31%) και αναιμία (30%). Οι ακόλουθες ανεπιθύμητες ενέργειες έχουν αναφερθεί με το Myocet κατά τη διάρκεια κλινικών μελετών με βάση την εμπειρία μετά την κυκλοφορία του φαρμάκου. Οι ανεπιθύμητες ενέργειες παρατίθενται παρακάτω ανά κατηγορία/οργανικό σύστημα και συχνότητα εμφάνισης με βάση την πρωτομνηστική ορολογία MedDRA (οι συχνότητες καθορίζονται ως < 1%, πολύ συχνές > 1/10, συχνές > 1/100 έως < 1/10, όχι συχνές > 1/1.000 έως < 1/100, μη γνωστές (δεν μπορούν να εκτιμηθούν με βάση τα διαθέσιμα δεδομένα).

Όλοι οι Βαθμοί		
Λοιμώξεις και παρασιτώσεις	Βαθμοί >= 3	
Ουδετεροπενικός πυρετός	Πολύ συχνές	Πολύ συχνές
Λοιμώξεις	Πολύ συχνές	Συχνές
Εργασιας/δυσπνοίας	Οχι συχνές	Οχι συχνές
Σζηή	Οχι συχνές	Οχι συχνές
Λοιμώξεις της θέσης ένεσης	Οχι συχνές	Μη γνωστές
Διαταραχές του αιμοποιητικού και του λεμφοτικού συστήματος		

Ουδετεροπενία	Πολύ συχνές	Πολύ συχνές
Θρομβοπενία	Πολύ συχνές	Πολύ συχνές
Αναιμία	Πολύ συχνές	Πολύ συχνές
Λευκοπενία	Πολύ συχνές	Πολύ συχνές
Λευκοπενία	Συχνές	Συχνές
Πανκυτταροπενία	Συχνές	Οχι συχνές
Πανκυτταροπενία	Οχι συχνές	Οχι συχνές
Πορφύρα	Οχι συχνές	Οχι συχνές
Διαταραχές του μεταβολισμού και της θέρμης		
Αναρρέα	Πολύ συχνές	Πολύ συχνές
Αρρυθμία	Συχνές	Πολύ συχνές
Υποκαλιαιμία	Συχνές	Οχι συχνές
Υπερκαλιαιμία	Οχι συχνές	Οχι συχνές
Ψυχιατρικές διαταραχές		
Διέγερση	Οχι συχνές	Μη γνωστές
Διαταραχές του νευρικού συστήματος		
Αιφνίδια	Συχνές	Οχι συχνές
Μη φυσιολογικό βάδισμα	Οχι συχνές	Οχι συχνές
Δυσφωνία	Οχι συχνές	Μη γνωστές
Υπνηλία	Οχι συχνές	Μη γνωστές
Καρδιακές διαταραχές		
Αρρυθμία	Συχνές	Οχι συχνές
Καρδιομυοπάθεια	Συχνές	Συχνές
Συμφορητική καρδιακή ανεπάρκεια	Συχνές	Συχνές
Περικαρδιακή συλλογή	Οχι συχνές	Οχι συχνές
Αγγειακές διαταραχές		
Εμβολίες	Συχνές	Οχι συχνές
Υπόταση	Οχι συχνές	Οχι συχνές
Διαταραχές του αναπνευστικού συστήματος, του θώρακα και του μεσοθωρακίου		
Θωρακικό άλγος	Συχνές	Οχι συχνές
Δυσπνοια	Συχνές	Οχι συχνές
Επιστομή	Συχνές	Οχι συχνές
Ασπύση	Οχι συχνές	Μη γνωστές
Φαρυγγίτιδα	Οχι συχνές	Μη γνωστές
Υπερκαλιαιμία	Οχι συχνές	Οχι συχνές
Πνευμονίτιδα	Οχι συχνές	Οχι συχνές
Διαταραχές του γαστρεντερικού		
Ναυτία/έμετος	Πολύ συχνές	Πολύ συχνές
Σταγυρίτιδα/βλεννογονιτίδα	Πολύ συχνές	Συχνές
Διάρροια	Πολύ συχνές	Συχνές
Δυσκοιλιότητα	Συχνές	Οχι συχνές
Οισοφαγίτιδα	Συχνές	Οχι συχνές
Γαστρικό έλκος	Οχι συχνές	Οχι συχνές
Διαταραχές του ήπατος και του χοληφόρου		
Αυξημένα ηπατικές τρανσαμινάσες	Συχνές	Οχι συχνές
Αυξημένη αλκαλική φωσφοράση	Οχι συχνές	Οχι συχνές
Πτεροσ	Οχι συχνές	Οχι συχνές
Αυξημένη χολερυθρίνη ορού	Οχι συχνές	Μη γνωστές
Διαταραχές του δέρματος και του υποδόριου ιστού		
Ακναιμία	Πολύ συχνές	Συχνές
Εξάνθημα	Συχνές	Μη γνωστές
Διασταλτική αναιμία	Συχνές	Οχι συχνές
Κνηγμός	Οχι συχνές	Οχι συχνές
Θυλακίτιδα	Οχι συχνές	Οχι συχνές
Επιδερμίτιδα	Οχι συχνές	Μη γνωστές
Διαταραχές του μυοσκελετικού συστήματος, των οστών και του συνδετικού ιστού		
Οσφυαλγία	Συχνές	Οχι συχνές
Μυαλγία	Συχνές	Οχι συχνές
Μυϊκή αδυναμία	Οχι συχνές	Οχι συχνές
Διαταραχές των νεφρών και των ουροφόρων οδών		
Αμφοροπτική κυτίτιδα	Οχι συχνές	Οχι συχνές
Ολιγουρία	Οχι συχνές	Οχι συχνές
Γενικές διαταραχές και καταστάσεις της οδού χορήγησης		
Εξοδονση/κόπωση	Πολύ συχνές	Συχνές
Πυρετός	Πολύ συχνές	Συχνές
Άλγος	Πολύ συχνές	Συχνές
Ρίγη	Πολύ συχνές	Οχι συχνές
Ζάλη	Συχνές	Οχι συχνές
Κεφαλαλγία	Συχνές	Οχι συχνές
Απώλεια βάρους	Συχνές	Οχι συχνές
Αντίδραση της θέσης ένεσης	Οχι συχνές	Οχι συχνές
Αίσθημα κακουχίας	Οχι συχνές	Μη γνωστές

4.9 Υπερδοσολογία Η οξεία υπερδοσολογία με το Myocet επιδεινώνει τις τοξικές παρενέργειες. Η θεραπεία της οξείας υπερδοσολογίας πρέπει να επιδιώκεται σε υποστηρικτική φροντίδα για την αντιμετώπιση τοξικότητας και ενδέχεται να περιλαμβάνει νοσηλεία, χορήγηση αντιβιοτικών, μεταγγίσεις αιμοπεταλίων και κοκκοκυτταρικών και συμπτωματική θεραπεία βλεννογονιτίδας. **7. ΚΑΤΟΧΟΣ ΤΗΣ ΑΔΕΙΑΣ ΚΥΚΛΟΦΟΡΙΑΣ** Cephalon Europe S. Rue Charles Marigny 94700 Maisons Alfort (Γαλλία). **8. ΑΡΙΘΜΟΣ(ΟΙ) ΑΔΕΙΑΣ ΚΥΚΛΟΦΟΡΙΑΣ** EU/00/141/001. **ΗΜΕΡΟΜΗΝΙΑ ΠΡΩΤΗΣ ΕΓΚΡΙΣΗΣ/ΑΝΑΝΕΩΣΗΣ ΤΗΣ ΑΔΕΙΑΣ** Ημερομηνία πρώτης έγκρισης: 13/07/2000 Ημερομηνία τελευταίας ανανέωσης: 02/07/2010 **10. ΗΜΕΡΟΜΗΝΙΑ ΑΝΑΘΕΩΡΗΣΗΣ ΤΟΥ ΚΕΙΜΕΝΟΥ** 24.03.2011 Λεπτομέρεια πληροφοριακά στοιχεία για το προϊόν είναι διαθέσιμα στην ιστοσελίδα του Ευρωπαϊκού Οργανισμού Φαρμάκων (EMA) <http://www.ema.europa.eu>. Τρίτος δόστος: Μόνο για Νοσοκομειακή χρήση, Ενδοκτική (N.T.). **MYOCET P.S.** INJ.SOL.SOL. 50MG 2 SET. 980.50€. **ΘΕΛΗΜΑΤΑ** 1. Περιλήψη χαρακτηριστικών Προϊόντος Myocet 2. Προσαρμογή από Balist G. Ramakrishnan G. Sekhar Rao C. et al. Reduced cardiotoxicity and reserved antitumor efficacy of liposome-encapsulated doxorubicin and cyclophosphamide compared with conventional doxorubicin and cyclophosphamide in a randomized, multicenter trial of metastatic breast cancer. J Clin Oncol 2001; 19:1444-54

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Clinical trials in oncology: a comprehensive scientific, ethical, legal and financial overview

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Key words: clinical trials; ethics; finance; patient rights.

INTRODUCTION

In the field of Oncology, progress, development and changes in scientific knowledge occur at a staggering pace.

In its entirety, new knowledge stems from preclinical (laboratory) and clinical research. Clinical research, in turn, is based on clinical trials that are inevitably performed on humans –both patients and healthy volunteers.

This paper shall attempt to stipulate that scientifically sound clinical research, as is currently conducted on the basis of rules and multiple safeguards, yields significant benefits for participating patients; potential benefit for future patients; and has an additional positive impact on researchers, society, health systems and the State.

Why clinical research is scientifically necessary in Oncology

It is a well-accepted maxim that clinical trials are the single most important parameter of medical research, directly resulting in treatment benefits for cancer patients and the community alike. In their vast majority, contemporary treatments are the outcome of knowledge derived from clinical trials. However, a mere 5% of patients with malignancies participate in clinical trials. Most patients that do not, are either unaware of what clinical trials are or were not offered the option. Today, one in three patients with malignancies is cured, whereas the remaining two die as a result of the disease. So, there is no question as to the need for new pharmaceutical substances that will promote effectiveness and safety, as well as contribute to treatment individualisation [1].

Preclinical research offers data related to the effect of a pharmaceutical substance when tested *in vitro* and proffers indications as to its effectiveness, but no evidence as to its efficacy on and safety for humans.

Using *in vivo* experiments, preclinical research may predict the efficacy of a new drug in a more reliable way, but still does not substantiate its effectiveness in humans; on the contrary, clinical trials often compare an established treatment with an innovative and more promising one, aiming at proving the latter to be superior or equal to the former, as far as effectiveness and/or safety is concerned. In this decade, clinical trials are also aimed at improving tailor-made treatments for each oncology patient. Through clinical trials, patients themselves assume an active role in their health management. It should also be stressed that, in this way patients receive additional benefits, since they are granted access to new treatment options that might prolong their survival, before they are made available to the wide public, or by their insurance fund. They are given a chance to contribute to medical research, are mandatorily insured against direct damage to their health as well as against medical errors [2].

Clinical research general supervision and conditions

There are well-established international guidelines to ensure that clinical trials are carried out in a way that is effective, unimpeachable and predominantly safe for its participants. The chief researchers are responsible for effectively and safely executing clinical trials. They are also responsible for designing the trial and authoring the relevant research protocol. The clinical trial protocol states in detail all existing trial data, rationale, aims, design and relevant procedures. The scientific board of the institution that will host the trial decides on its approval. According to each country's legislation, additional approval may be required by the competent Drug Authority and/or Ethics Committee. National Drug Authorities oversee the trials and are responsible for approving a pharmaceutical

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agent or a medical intervention as a therapeutic procedure with specific indications.

The majority of trials in which new drugs or administration strategies are tested and that are expected to change current clinical practice are designed by researchers in close collaboration with the competent regulatory authorities, ultimately responsible for final licensing (FDA and EMEA).

Clinical trials must be held at specialised centres with ample experience in the field of clinical research. It is equally necessary for the staff to have adequate clinical practice training. Research group members participating in any trial stage or procedure must be acknowledged and mentioned in all pertinent trial files by name and full disclosure of their duties and responsibilities.

All trial data files must be made available for review by the competent authorities. Patient records must be fully updated in real time, regarding patient participation, their clinical status and must remain accessible over a 10-year period. Original patient informed consent forms must be filed, bearing the signature of the patients themselves or their proxies [3, 4].

Clinical trial phases

There are three main phases in the clinical development of a pharmaceutical product prior to submitting data for approval by the competent authorities: Phase I, II and III clinical trials, while after the drug enters the market, Phase IV (post marketing) trials are conducted.

Phase I: These trials focus on how experimental drugs or treatments are tolerated, aiming at determining the maximum safe dose. Secondary goals of such trials include the collection of data indicative of drug effectiveness on specific pernicious diseases.

Phase II: Phase II trials investigate initial data concerning the effectiveness and safety of the proposed treatment. They may or may not be comparative and are conducted at one or more research centres. They may be the result of an individual researcher's initiative, that of the academic community or part of a pharmaceutical agent's clinical development sponsored by the pharmaceutical company.

Phase III: These are usually multinational, multicentred trials aimed at confirming the therapeutic value of the proposed pharmaceutical agent or combination. They are contrastive studies comparing the new drug or treatment with the until then considered as acceptable or approved "**standard of care**". Such trials are randomised and typically neither the researchers nor the patients are aware of the treatment administered (**double blind studies**).

ETHICAL AND LEGAL VIEWS ON THE NECESSITY OF CLINICAL RESEARCH IN ONCOLOGY

All necessary guarantees concerning the ethical entrenchment of Clinical Trials in Oncology have been stipulated in

the revised Declaration of Helsinki (59th World Medical Association General Assembly, Seoul, 2008), as well as in the National Commission for the Protection of Human Subjects of Biomedical Research Belmont Report (1979) and are as follows:

1. Potential validity of the null hypothesis on the genuine uncertainty regarding the comparative merits of an experimental over the standard treatment (clinical equipoise).
2. Necessity and importance of the clinical trial: The question that the clinical trial attempts to answer must be both an existing and important one for patient outcome.
3. The anticipated benefits for patients and the society must not outweigh the risks to which the patients shall be exposed. Potential risks must not be excessive and irrational.
4. Patient information and written consent on the potential benefits and possible adverse effects from the administration of the agent studied and ways to counter them [3].
5. To maintain all scientific methodology rules for conducting scientifically and ethically proper clinical trial.

Specific measures and regulations on the ethical and scientific integrity of clinical trials in Oncology include:

- That the clinical trial must be conceived and designed by top physicians/researchers and other scientists.
- The use of optimal scientific methodology as pertains to clinical trial type, randomisation, balancing prognostic factors, statistical design, power, sample size, monitoring.
- Anonymity of participating patients and availability of their biological material to anyone apart from the attending physicians.
- Clinical trial control/approval by an independent authority at the local or national level regarding its ethical and scientific integrity: Hospital Scientific Boards, National Drug Authority/Clinical Trials Department, National Ethics Committee.
- Conflict of Interest Disclosure Statement/Form for regulating authorities and patient information on clinical trial researcher and related foundation Conflicts of Interest, as defined in the American Association of American Medical Colleges (AAMC) "Policy and Guidelines Related to Conflicts of Interest in Human Subjects Research". Conflicts of Interest are defined as researcher/foundation interests that may affect researcher judgement and participation as well as clinical trial scientific and ethical components. Conflicts of Interest may be of scientific, financial or ethical/religious nature.
- Clinical trial treatment efficacy and patient safety data monitoring by an independent authority (Independent Data and Safety Monitoring Committee -IDSMC): Specifically, the IDSMC may be an internal unit of the academic/cooperative team, composed however by researchers other than those involved in the clinical trial; it may be external; or a different institutional body altogether.

- Report of adverse effects, both severe (within 24-72 hours) and non-severe, to overseeing bodies and regulating authorities (researcher team, academic/cooperative team scientific committee, clinical trial sponsor, Independent Data and Safety Monitoring Committee, National Drug Authority, National Ethics Committee) and possibility to modify/discontinue the clinical trial according to safety data [5, 6].

FINANCIAL OVERVIEW OF CLINICAL TRIALS

A significant part of oncology research is funded by the public sector and private organisations. Globally, but mainly in Europe and America, it was estimated that in 2003 this funding amounted to €7 billion, while the research funded by the pharmaceutical industry raised approximately €8 billion, which accounts for 12% of total research costs (about €71 billion). In Europe, the corresponding amounts are €1.4 billion, €3.7 billion and €27 billion, respectively. A large part of research funds that is aimed at the development of new drugs amounts to approximately €2.2-5.4 billion *per annum*, 27% of which is directed to basic research; 57% to clinical research; and the remaining 16% concerns research conducted during or after their approval. In Greece, the per capita public spending on cancer research is virtually non-

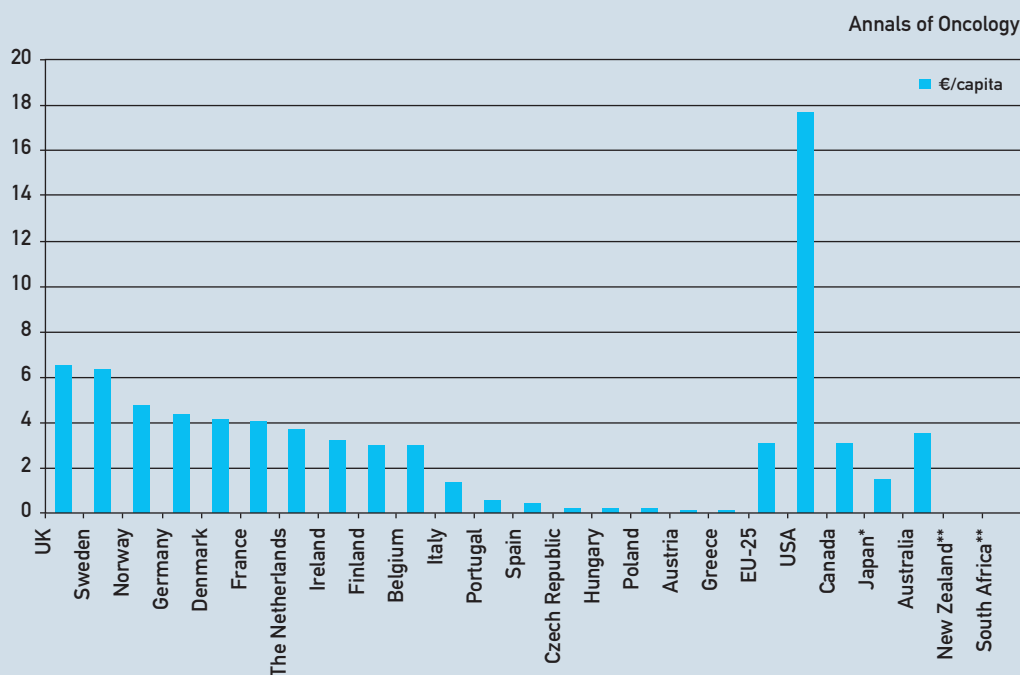
existent, since we generally spend 0.58% of our GDP on research, as compared to an average of 1.7% for other countries (Figure 1). This gap could be covered by the pharmaceutical industry, which -due to the difficulties our country is facing- does not spend amounts comparable to those of other countries or analogous to its sales in Greece. The clinical benefit derived from such spending is indisputable. A typical example is a recent review by researchers at the Karolinska University, Sweden, reporting that a 30% in the reduction of mortality between 1995 and 2003 is a result of new oncology drugs discovered in the framework of clinical trials (Figure 2) [1, 7].

Financial repercussions of clinical research

- **Direct cost:** it concerns health system expenditure on patient prevention, diagnosis, treatment and rehabilitation at various health system levels. The above corresponds to the direct cost of disease, covered by the public or private insurance funds or by the patients themselves (direct patient costs).
- **Indirect cost:** it concerns employee productivity loss as a result of decreased efficiency at work; employment reduction; early retirement; and premature death, as a result of the disease.

Figure 1.

Per capita public spending on cancer research.



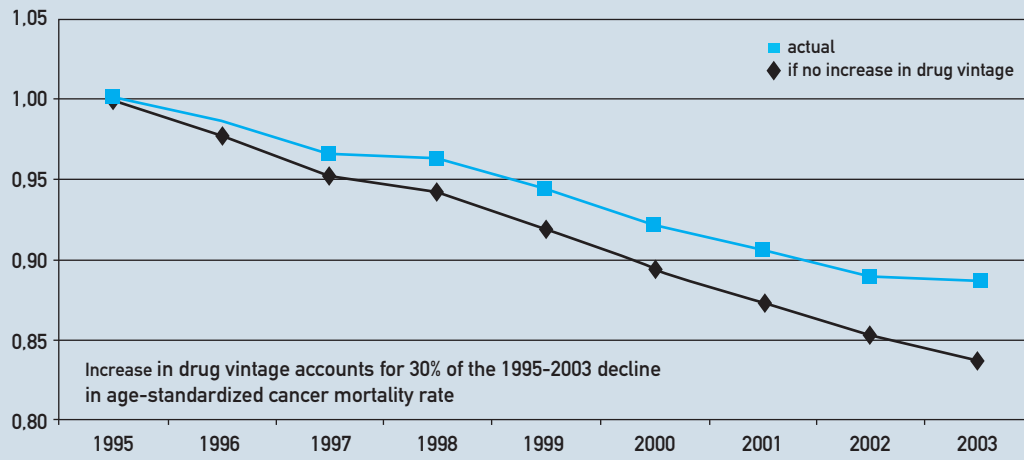
*Include only governmental spend, not charity sector

**Data not available

Estimated national public spending on cancer research per capita in 2003/2004

Figure 2.

Clinical benefit from new anti-cancer drugs.



Contribution of the increase in cancer drug vintage to the decline in the age-adjusted cancer mortality rate

■ **Immaterial cost:** any additional cost, over the sum of direct and indirect costs. It includes emotional and physical pain, as well as the suffering that a disease causes to both patients and their families [8].

Clinical research and drug-treatment cost

In most cases of clinical trials the cost of patient drugs and examinations is covered by the trial sponsors, resulting in significant benefits for health system and social security funds. This is standard operating procedure in Phase I-III, as well as in some Phase IV trials. Consequently, on the one hand patients acquire access to ground-breaking treatments that are not available outside the trials and on the other the health system and social security funds are not burdened with the associated costs. Irrespective of whether the drug cost is covered or not, there are studies to support that, in many cases, patients treated in the framework of clinical trials have a reduced cost. More specifically, an innovative study by the American Association of Cancer Institutes showed the hospitalisation cost of patients treated while participating in a clinical trial was reduced by approximately \$6,000 as compared to that of a matched control patient group treated outside clinical trials [9]. Hospitalisation cost reduction is not always feasible; however, Mayo Clinic studies have shown that even in cases where no reduction in overall patient management cost is achieved, any increase is negligible and most of the time it is offset by clinical benefit.

Clinical research and other financial impacts

A study by the University of Chicago estimated that the financial benefits derived from the increase in life expectancy over the past decades in the US amount to \$2,400 billion

(NIH, 2000). It was also assessed that a 1% reduction in cancer-related deaths results in profits in the region of \$500 billion. Similar results exist for Europe and our country: a study by the London School of Economics showed an average of 30% of economic growth in European countries is due to an increase in life expectancy [10]. Pharmaceutical companies spend €71 billion per year on research, thus supporting employment as well. These funds finance thousands of jobs in the industry itself, as it provides work for researchers of various specialties, analysts, as well as organisation and support staff. At the same time, it creates jobs for numerous scientists and personnel in research study, support and analysis firms. Further, it supports researchers, analysts and administrative staff working in public and private hospitals, universities and laboratories. In these frameworks, there can be a source of competitive advantage, resources and job creation. It should be stressed that the above contribute to better research hospital and laboratory organisation, as well as to upgrading the staff, which is more proficient than the average staff in non-research institutions. In addition to promoting science, it has been found that both organisation and care provision in research units are also of a higher standard [11].

CONCLUSION

Based on both international and Greek data, it is a safe and well-documented fact that clinical trials –and clinical research in general– are currently conducted according to universally accepted scientific and ethical rules, aimed at ensuring that patients are respected as personalities and as individuals. Moreover, “proper” clinical research, as currently carried out in an organised manner, chiefly aims at

benefiting the patients taking part therein. Obviously, all new scientific knowledge stemming from clinical research shall be applied (in the form of improved medical technique) on future patients, resulting in better disease outcomes.

It is expected that moral dilemmas and questions arise from the participation of humans in research procedures, but well-established strict rules and multiple safeguards combined with the anticipated benefit to be derived for patients as a whole, render research that is carried out according to proper clinical practice morally and legally acceptable and desirable.

Apart from the obvious clinical merits and overall promotion of medical knowledge, it has by now become clear that clinical research results in multiple benefits for the scientific community, society as a whole and health systems, in addition to the financial advantages it offers health systems and the State.

The committee members

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Conflict of interest statement

The authors declare no conflict of interest.

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Ethical issues regarding the acquisition and control of genetic information*

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ABSTRACT

Genetic tests for cancer predisposition involve complex issues, not only in terms of expertise and medical potential but also in terms of their moral import on patients or examinees and their families. This paper explores a model of ethical analysis, which aims at the construction of a normative framework within which ethical considerations regarding genetic clinical research, including cancer genetics, can be adequately framed and addressed. It reconsiders and critically assesses the role of fundamental principles in bioethical reasoning, particularly those of respect for personal autonomy, justice, beneficence and nonmaleficence, regarding the acquisition, access and control of genetic information. It investigates their modal structure, on the basis of which it defends an order of priority in cases of conflict between them in actual cases. Reliance on fundamental principles, as the barebones of an adequate moral framework for decision-making, meets hard ethical issues regarding intra-familial dynamics and professional duties, while it also facilitates choices in research settings.

Key words: bioethics; genetic information; data protection; genetic privacy; patient autonomy; informed consent; justice; beneficence; nonmaleficence.

Rapid advances in genetics have led to the development of new diagnostic tools, which make it possible to predict the future occurrence of monogenetic diseases or to detect increased susceptibilities to the future development of more complex diseases, such as breast cancer. Genetic tests can be employed to establish probabilities of the occurrence and course of a disease, while the predictive and diagnostic value of the information they provide has been substantially increasing for a number of diseases. Apart from questions regarding their medical potential, the collection and management of genetic data raise a number of ethical, legal, social and public policy issues. The latter require normative analysis, which aims at the clarification and justification of evaluative criteria forming a framework for practical decision-making. Normative inquiry is complex and involves, firstly, an analysis of the diverse ways in which a genetic approach to disease may affect people individually; within their families; and in their social and working spheres. Secondly, it involves the development of a framework of ethical norms for decision-making, which brings out the ethical and professional responsibilities of clinicians as well as those of other agents who may be

directly or indirectly interested in sharing it (other potentially concerned individuals, private or public sector employers, insurance companies, the police, etc). In normative analysis, we must always bear in mind that biology or genetics alone do not determine the social outcome.

A preliminary distinction needs to be made. Genetic knowledge, considered in the abstract, may be taken to refer to claims about the nature and effects of genetic variation, about the respective contributions of genes and the environment to specific outcomes and about the clinical effects of specific genetic variations. What is of particular ethical concern is not genetic knowledge in the abstract, but genetic knowledge *individuated*, associated with genetic data pertaining to particular identifiable *persons*, what is usually described as "genetic information". While genetic knowledge is impersonal, genetic information about individuals is commonly viewed as personal and, in addition, as medical information. This characterization, however, needs to be further qualified. Genetic information is a rather atypical kind of medical information. Unlike the latter, which is normally thought of as intimate rather than publicly available, as cur-

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rent than predictive and as individual rather than shared by a group, a good deal of genetic information is public rather than intimate and not at all medical (e.g. one's skin colour) [1].

As genetic data possess certain idiosyncratic features and characteristically distinguish the data subject from other individuals, there are growing concerns that the information they furnish could become a new tool of discrimination. Concerns are often expressed that gene tests and genetic profiling could be used to keep data subjects deemed at genetic risk of certain diseases banned from getting jobs or health insurance. Additional concerns arise regarding storage of genetic material in biobanks for research. As this kind of research flourishes on the sharing of samples and information, it poses prominent ethical questions: Are there ethical barriers to the sharing of biological resources? How does the advent of large-scale biobanking alter the ways in which ethical issues about genetic data are addressed?

In the light of increasing complexities, it is imperative to approach genetic research and its clinical aspects from a robust ethical perspective, in order to identify core ethical issues emerging, and to draw conclusions regarding the construction of a normative framework, which may also provide directions for certain policy decisions. Moral analysis is part of formulating appropriate policies.

THE CHARACTER OF GENETIC INFORMATION. GENETIC IDENTITY AND "EXCEPTIONALISM"

Inherited genetic traits are part of a person's biological constitution and persist for life. Are they part of one's personal identity and should they, therefore, be treated in a special way? Should genetic information, obtained through genetic testing or genetic screening, be viewed as unique and exceptional, quite unlike other medical or personal information?

Genetic information is commonly seen as sensitive, intimate and strictly personal. However, in the light of an increasing understanding of our genetic make-up, the danger is to fail to recognise the scope and limitation of genetic information as regards the shape of one's identity. While geneticists and medical practitioners clearly state that genes are not the complete story of a human being, the increasing advances in genetic knowledge have given birth to an erroneous social stereotype. The threatening moral hazard in this context is that persons may be categorised on the basis of their genes, and suffer various forms of discrimination. The danger is that increasing reliance on genetics may lead to all sorts of convictions regarding things that are completely out of our control (our genes) to the exclusion of what is within our control, namely, the capacity to adopt and overcome limitations which have been placed upon us by biology.

If the claim is that genes are somehow distinctively the basis of one's identity, this is clearly false. Genetic constitution is not sufficient to specify one's identity, as the case of identical twins indicates. The same genetic make-up does not result

in the same personality. The phrase "genetic identity" is misleading, as it suggests that information about one's lineage and origins will of itself contribute to one's identity or sense of personal identity [2]. This claim does not stand to critical scrutiny. It is imperative that we address society's tendency to oversimplify and exaggerate complex scientific information and adopt analogous unjustified attitudes towards it. Together with robust ethical thinking, what is needed is rigorous public debate and education about the meaning and scope of genetics.

"Genetic exceptionalism" is an over-exaggeration, loaded with unargued metaphysical assumptions. As a general claim about the distinctiveness of genetic information, it is based on controversial, reductive and essentialist, conceptions of genetic identity ("we are our genes", "our genes are us") and presupposes a false methodological claim -that of genetic determinism- which may unjustifiably undermine and distort our very appreciation of moral agency.

Yet, even though genetic exceptionalism is untenable as a general hypothesis, genetic data provide a particularly rich and challenging example of the real ethical challenges that emerge as a result of vital biomedical advances. In the light of immense biotechnological developments regarding the management of genetic information, most profoundly the complex ways in which such information may be collected, used or disclosed, stored or disseminated, its handling offers a paradigm case for a re-examination of, and reflection on, the very character and future of health care ethics and biomedical ethics. Genetic information does seem to raise some issues of special ethical significance.

PROPER USE AND MISUSE - THE NORMATIVE FRAMEWORK

Questions regarding the acquisition, use and control of diagnostic or predictive health information concern the medical potential of such information (in predicting and managing risk predispositions), its ethical evaluation, as well as the legal and regulatory limitations of its use. Arriving at an adequate and sustainable clinical decision requires taking into account diverse considerations, including scientific and medical background, a constantly renewed call for evidence, clinical validity (how well the tests results detect or predict the associated disorder), clinical utility (whether there are preventive measures or therapies that can be adopted to eliminate, reduce or defer the risk of associated disease), psychological and social impact. The mixture of prospective benefits and harms associated with acquiring and using genetic information, both for the individual concerned and family members, calls for robust ethical reasoning as an indispensable parameter in decision-making. A framework needs to be explored for distinguishing morally permissible use from misuse.

Ethical debates concerning the distinction of proper from improper use of medical data, as well as the participation of

individuals in clinical tests, have a long history. Among the ethical principles invoked are the protection of autonomy, justice, beneficence ("doing good") and nonmaleficence ("not doing harm", the no-harm principle) [3]. Respect for autonomy has been treated as the cardinal ethical principle of health care ethics. In its minimal version, it amounts to the claim that it is ethically unacceptable to impose medical decisions on patients or test subjects. As soon as the relevant facts have been presented, it is the patient or the examinee who carries out the decision for a medical act. The practice of medicine should be non-directive and non-paternalistic. The subject concerned should make a rational decision in the light of information concerning medical facts, which health professionals have a duty to provide. The principle of individual autonomy supports the more specific principle of informed consent. The latter has been most widely acknowledged in bioethics discourse applying to clinical research and health care.

However, obtaining data about the presence or absence of specific genetic variations and genetic risks for disease may raise distinctive ethical problems. They characteristically relate to the dual nature of genetic information. On the one hand, it is intensely personal, relating to a person's very biological endowment as an individual. It ought, therefore, to be treated with the greatest respect and sensitivity as private and confidential, not to be disseminated or transmitted to others without the subject's consent. On the other hand, genetic information, by its very nature, pertains to more than one individual; it is familiar. All subjects share their genes with members of their biological family, so that in discovering something about an individual, one may discover something about her relatives, too, and possibly something they do not know about themselves. When subjects taking genetic tests are revealed genetic risks, such as the risk for inheriting mutations in BRCA1 or BRCA2, they can infer that these risks may concern some of their relatives, too. Disclosing information may be ethically problematic just as not disclosing it may be.

If a subject obtains crucial genetic information that is also important for, say, her brother, does she have an obligation to share it with him? Or, conversely, a right not to share it? As it pertains to him too, does he have a right to insist that she seeks his prior consent, or that his refusal to consent should have to restrict or compromise her right to seek this genetic information about herself? Do relatives have a right to limit each others' personal rights to privacy? Discussions turn on the criteria according to which it could be right to disclose information and those of choice in relation to having the tests.

Morally permissible predictive, diagnostic or therapeutic uses of genetic information may be direct, involving the data subject herself, or, in carefully spelt out circumstances, her relatives, but also indirect, in that they may be involved in medical education or clinical research. Particularly, with the establishment of clinical-genomic and biobank research,

with increasing capability of assemblage, storage and use of genetic data at a mass scale, further issues arise. They raise ethical dilemmas, which challenge currently accepted individualistic conceptions of personal autonomy, privacy and informed consent as the ethical milestones in reasoning about action in genetic research and its clinical applications. They have, thus, led to a continuous reviewing and reassessment of the applicability of existing ethical provisions and guidelines and the concomitant legislative responses.

The construction of an appropriate moral framework for decision-making needs to start with an analysis and understanding of constitutive features of the structure of moral agency. Moral requirements are directed towards agents, aim at shaping action and require justification by reasons. Moral ascription presupposes that we are separate beings, whose actions and interactions are mediated by a process of practical reasoning. If such beings are to act at all, each must have some space of action. The conditions of each other's agency must be respected. The fundamental moral insight, in normative analysis, is that the relationship between agents is determined by the reciprocal recognition of each other *as a person* -that is as an autonomous subject capable of self-determining action, who thereby requires respect for the conditions of such action. The core moral axiom is the universal respect for each other's agency, conceptualised as a person's unconditional worth or human dignity. We, thereby, start practical moral deliberation by rejecting those principles that cannot guide the action of all agents, that is, that cannot be principles for all. Fundamental principles follow from the above insight, which ground moral obligations and counterpart rights. The indispensable methodological move, therefore, in developing the appropriate moral framework regarding the use of genetic information, is to determine how it fits within the broader ethical perspective of respect for personality and the fundamental principles derived from it.

THE GROUNDING PRINCIPLES

Fundamental rights of personality. Respect of autonomy, informed consent

Respect for human dignity forms the milestone of our ethical and legal obligations and the starting point of our reasoning for the justification of any particular moral and legal judgements and practices. It is undergirded by the inviolable "intrinsic value" of human beings, it presupposes their freedom (autonomy) and it includes the equality of all human beings, as a matter of principle. The moral obligation of treating a human being as an "end-in-itself" [4] follows necessarily. This means that under no circumstances should a human being be treated as a mere means or instrument for the achievement of any other ends. Human beings, *qua* persons, deserve respect in their individuality. Their physical and psychological integrity ought to be protected by all means. What follows from this is that human subjects cannot be merely reduced to their genetic

traits, nor can they be submitted to discrimination on the basis of their genetic endowment. Fundamental rights of personality constrain every kind of biomedical research and its clinical applications, involving human subjects. The principle of respect for human dignity rules out, *ab initio*, any and every form of exploitation, deception or coercion of a human being, in all contexts. For instance, requesting the consent of a test-subject, after she has been deceived or coerced, violates her autonomy as a person. It constitutes a case of heteronomy and is ethically (and legally) absolutely impermissible.

The core of the fundamental principle of respect for human dignity is the self-determination of a human being. The principle of self-determination (autonomy) forms the inviolable normative point of reference regarding the moral (and legal) assessment of new medical technologies and their use in medical genetics. Autonomy implies that an individual should decide for herself whether to consent to, or dissent from, actions which affect her body, or concern matters which affect her personal sphere of life. It encompasses one's right to decide on the use that one's personal data will be subjected to. Personal autonomy shapes the right of an individual to raise questions about her genetic endowment, including her risk factors, but also to keep confidential sensitive information derived from it, like, for instance, the fact that she carries a mutation that poses high probability of cancerogenesis.

Crucial normative issues pertain to the protection of examinees and patient-subjects from unrestricted and uncontrolled use of their genetic data, as the latter bear information which could touch on the very core of their moral personality in particularly sensitive ways. To the extent that diagnosis, therapy, medical research or education are based on personal data and samples, such practices affect the very core of human autonomy and fundamental rights of personality. The principle of autonomy requires that genetic data should not be collected or used without the prior consent of the data subject, which in turn presupposes her complete information (informed consent).

Furthermore, the knowledge that someone is at risk of developing a serious illness in the future may be psychologically burdensome, generate immense stress and become a source of social stigmatisation and discrimination. Therefore, no one should have such information forced upon oneself against one's will. Protection of the right to self-determination, in this case, entails a right to remain ignorant of one's genetic status (a right to not know). Any claim of a right to not know is, however, complex, in a context where information does not merely pertain to the individual but has implications for other family members as well.

The principle of justice requires informing relatives who are at risk of inheriting the same predisposing factor. A woman with a strong personal and family history of breast or ovarian cancer faces an obligation to provide useful information to her daughter or sister or other relative at risk of inheriting

the same predisposing mutation, as a matter of beneficence and justice. But the latter requirement follows derivatively from the individual's autonomy and right to self-determination. When a person, who has learned of a mutation, expresses disinclination to advise siblings or other relatives who are clearly at risk, subtle moral dilemmas arise. The tension between the rights and interests of the individual, in claiming control of her genetic information, and those of others at-risk, in requiring access to it, may be severe. However, there must be sufficiently compelling reasons to justify the demand of the individual's responsibility to share it [5]. The right to self-determination is overriding and any restriction on it requires robust moral justification.

Overall, it is morally important to ensure that information is not obtained or handled without appropriate consent. The performance of all medical examinations must always be subject to the examinee's consent. Respect for autonomy through informed consent, the examinee's right to informational self-determination, should be safeguarded as far as possible, even in relation to future and currently not clearly defined uses.

But the principle of informed consent cannot be treated as the ultimate or sole principle in decision-making. By itself, it furnishes limited justification for ethical choice, and may furnish even less as new information technologies are used, on an increasing scale, to store and handle genetic data. The central weakness of relying exclusively or primarily on formalized informed consent procedures for ethical justification of certain medical acts is that consent is "referentially opaque" [6]. That is, it is given to specific propositions describing limited aspects of a given situation and does not transfer even to closely related propositions regarding future consequences. Informed consent requirements play their part adequately within a wider net of ethical requirements that determine obligations and rights in scientific and clinical practice. It is important not to lay too much stress on exaggerated, idealised, notions of "fully" informed consent and to take into account the vulnerabilities and specificities of those required to provide their consent, given the complexity of the testing itself, as well as the delicate nature of communicating to them results which are technically complex and anxiety-provoking.

Gathering genetic data in databases creates additional challenges for ethical justification that relies primarily or exclusively on informed consent procedures. This is not because genetic information is somewhat intrinsically exceptional, but because advances in genetic information technologies make it feasible to gather, store and disseminate massive quantities of subtle information in ways which exceed individuals' best efforts and abilities to understand what is at stake, or to give genuinely informed consent or dissent. Regarding future use for scientific research purposes, primarily, the anonymity of data-subjects should be preserved, and the transfer of information in ways which could reveal the subject's personal data, which she

has a right to keep private or to make public when she decides as appropriate, should be strictly forbidden.

Put in a nutshell, the practices of informed consent, however important, may not suffice to secure protection, and they should be constantly scrutinised and revised [7]. In the light of increasing complexities regarding storage and dissemination of massive amounts of information, other ways of safeguarding full protection of patients, data-subjects and relatives than individualised formal consent procedures need to be, additionally, sought. Particularly regarding future use, prior consent is difficult to be obtained, while, on the other hand, seeking case-by-case consent procedures in any future use may be extremely unrealistic. Onora O'Neill [8] has argued convincingly that informed consent needs itself to be analysed as including two distinct stages: i.e. public consent to *systems* for collecting, storing, using and disclosing genetic data, such as biobanks; and individual consent to *particular acts* of collecting, storing, using and disclosing genetic data about individuals. The establishment of background institutions that secure moral standards in medical and scientific practice can provide a safeguard for the particular procedures for which individual consent is sought. Trustworthy institutions are of vast importance.

Confidentiality and genetic privacy

Norms of professional confidentiality and personal privacy stem from the principle of respect for personal autonomy. They are significant since genetic results are directly related to one's characteristic biological endowment and may generate information which touches on the very nature of one's moral personality, in particularly sensitive ways. They are important in health care, medical research but also in contexts of employment or insurance coverage so as to prevent discrimination. These rules require that an individual's genetic information should not be disclosed to third parties. Respecting the privacy of information and securing confidentiality instantiate the ethical principles of respect for persons, their autonomy and their fundamental rights.

At the same time, implications for family members should be taken into account: Genetic information concerns the individual and her future health, but is also significant to family members. A genetic diagnosis/prediction never has implications solely for the examinee, but reflects disease probability and risk factors in other biological relatives. The results of gene testing, including molecular testing in search for mutations, may lead to different reactions among different family members, and some may not wish to have such information. Significantly, genetic testing of clinically healthy relatives may disclose predisposition to disease which may lead to changes in quality of life. Medical professionals, thus, have to cope with further responsibilities if the rights and interests of others, especially biological relatives, are at stake.

In some rare situations, in which the protection of other persons is at stake, a "duty to warn" is also in force. This has been interpreted as a duty to act in prevention of foreseeable harm or injury. But this is a fuzzy area of ethical decision-making. Disclosure against the examinee's will may violate confidentiality rules and discourage individuals from taking the tests. Above all, individuals should be responsible for the dissemination of their own medical information and should be encouraged to do so by the medical staff, on the basis of principles of beneficence, justice and solidarity. However, in cases where individuals resist sharing important information for the health and welfare of others, the physician may be liable to warn the at-risk individuals in specified circumstances -e.g. when serious foreseeable harm is highly likely to occur or disease is preventable or treatable. But the harm due to failure of disclosure should outweigh the harm that may be caused by disclosure.

It must be emphasised that the obligation to warn should be applied with extreme caution, however, for breach of medical confidentiality may have a detrimental effect on the trust placed on genetic counsellors and health care professionals by the individuals concerned. The latter may refuse to seek referral to genetics services altogether, if they deem them untrustworthy, or might provide misleading information about their family history that would obscure the interpretation of their genetic situation.

Deciding what to do in relation to genetic predispositions made available through genetic tests requires close examination of the true as opposed to the feared likelihood that symptoms will develop as well as the subtle weighing of the interests of the individual concerned, other family members and concerned third parties. In such contexts, it is of vital importance for clinicians to discuss with prospective examinees the potential adverse psychological and social consequences of testing, so that they can reach adequately informed decisions whether or not to proceed with testing.

Due to the complexities involved, including the far-reaching implications of test results for both the applicant and her family, genetic counselling is imperative and an integral part of the genetic testing process (pre-test as well as post-test counselling). Particularly, this should be the case as predictive genetic testing, such as that for cancer predisposition genes presents an important psychological challenge. Some people use the information to become proactive, others find the risk revealed frightening, and serious psychological consequences may result, such as anxiety or depression. The importance of pre-test counselling can hardly be exaggerated.

Justice, non-discrimination, non-stigmatisation

Principles of justice are associated with considerations as to whether an individual is treated fairly and equitably. They are vindicated by appealing to a demand of rejecting principles which undermine the exercise of agency and of

causing injury or harm, that cannot be universally adhered to, i.e. that cannot be principles for all. They stem from the equal worth of all human beings *qua* persons.

Justice requires that there should be equality of access to genetic testing, without discrimination. Particularly in cases where there is no universal health care coverage, the cost of genetic testing in search of mutations that put their carriers at high risk of malignancy is considerable. So, given that in many cases reliable insurance coverage is absent or inadequate, the significant economic barriers to seeking useful information are a source of moral concern. Such barriers constitute a violation of the fundamental principle of justice, since they prevent access of the poor to benefits of biotechnology enjoyed by the privileged and the wealthy. These problems are not specific to medical genetics but are detected in every aspect of health care. Questions of distributive justice exist where individuals or groups face disadvantages in enjoying scientific advances and the resources made available. Justice requirements demand that benefits (e.g. access to health care services) and burdens (e.g. taxation) are allocated fairly and equitably. Conversely, we cannot accept inequalities in access (e.g. of diagnosis and treatment) and burdens (allotment of expensive care or of research) for granted and, then, expect to reach ethically justifiable conclusions about genetic testing.

Furthermore, genetic data can be handled in such ways that imply unjustifiably unequal treatment of subjects outside the medical sphere, e.g. when applying for a job or insurance coverage, on the basis of genetic traits. The prohibition of discrimination, whether on grounds of genetic or non-genetic information, follows from the principle of the equal value of all human beings, as conscious self-determining agents, who, therefore, demand respect of their capacity for self-determination, irrespective of medical status and, hence, of their genetic predisposition to health or illness. Discrimination exists where unequal treatment is ethically unjustified. For this reason, it is always indispensable to sound ethical reasoning to seek grounding criteria which justify unequal treatment of persons.

Since accurate foreknowledge is at present unavailable, and may in principle be unattainable, given the complexity of human bodily systems and the effects of their interaction with their environment, a note of caution should be sounded regarding willingness to rely on genetic tests for social purposes. It may become possible to assess individuals' susceptibilities to some common diseases, such as breast cancer or heart disease, stroke and Alzheimer's. Even a crude risk stratification applied to large numbers of individuals could have serious adverse social consequences in limiting the availability of health care resources to some groups as opposed to others. Injustice, stigmatisation and marginalisation may be among the moral hazards provoked.

An issue of vital ethical significance is the protection of data-subjects and their genetic relatives from genetic stigmatisation, which may well be based on irrational overesti-

mation and inadequate understanding of genetic factors. It ought to be rectified with appropriate public discussion and education, rather than with regulation which restricts scientific research. The moral demand for protection against genetic stigmatisation may concern not only individuals but also groups of population as their data are collected and stored and are related to personal information.

Moreover, the issue of commercial use of research has moral import and demands normative assessment and regulation. The possible commercial utilisation of medical findings and genetic research outcomes is a substantial motive for private investment. This is only permissible to the extent that all necessary precautions are provided for the protection of the participants' personal self-determination and fundamental rights.

Regarding use in employment, it should be noted that, when considering whether to employ a candidate, it is legitimate to consider whether at the time of engagement the applicant possesses the physical, mental and health-related fitness required by the relevant activity. Medical examinations are permissible provided that they are necessary to establish that the applicant is fit for the proposed job *at the time of engagement*. More thorough medical examinations for currently symptom-free or predictable conditions may be permissible, if and only if they are necessary, having regard to the principle of proportionality, in order to preclude specific third-party risks inherent in the nature of the activity. Tests of genetic susceptibility to future illness should not be imposed, or genetic information should not be used, except when public safety depends on the good health of the employee and it is needed in order to assess it.

Nonmaleficence, beneficence, solidarity, benefit-sharing

The principle of nonmaleficence (*primum non nocere*) prescribes the avoidance of harm or injury, imposed accidentally and/or systematically, thereby causing adverse effects on someone's rights or interests. Obligations of nonmaleficence (doing no harm) include those of not inflicting actual harm but also of not imposing risks of harm, at least in ways disproportionate to the benefit expected. In cases of risk disposition, it is morally acceptable that a standard of due care determines whether the agent who is causally responsible for the risk is also morally responsible for it. One might counter-argue, at this point, that medical practitioners commonly injure, in order to achieve the greater good of the patient, i.e. with a therapeutic intent. So the rejection of injury cannot be an unconditional principle. However, injury in therapeutic contexts is not gratuitous but intended to limit injury. Likewise, some uses of genetic data may legitimately injure, provided that the injury is not unjustified but only deemed necessary for therapeutic purposes. Unnecessary injury is one that may destroy, damage or degrade a human subject, or, more narrowly, her body and its characteristics. This would be a case of failure to acknowledge respect for human beings and their

moral worth (dignity), and should, therefore, be unconditionally rejected. The principle of nonmaleficence supports more specific moral rules, such as not to kill, not to cause systematic and gratuitous pain or suffering, not to cause offence and not to deprive others of goods contributing to their quality of life [9].

An adequate moral framework for decision-making needs to incorporate normative considerations regarding the well-being of others. These are requirements to support and assist others, particularly those at risk (beneficence). Vulnerable agents (and we are all vulnerable and needy and finite beings) cannot will indifference to others as a universal principle valid for all, because they invariably have plans and life projects which they cannot reasonably hope to achieve without the support of others. In willing indifference as a universal principle, agents would will to put at risk help that may be indispensable for others' activities or projects, including their own. Willing a principle of indifference as a universal principle is incompatible with a commitment to seek effective means for whatever project and life plans agents wish to achieve.

The duty to assist others may be interpreted in clinical genetics (including cancer genetics) as a duty to provide information which may be significant in facilitating the empowerment of individuals to think for themselves and take charge of their lives. It, thus, makes their autonomy possible. The positive obligations of beneficence (to do good) complement in this way the negative moral obligation not to harm others (the no harm principle).

Genetic research and its clinical applications, particularly the use of stored genetic data, may lead to the improvement of diagnostic tools for the prediction and diagnosis of diseases, the development of techniques for prevention and cure, individualised medicine, and so on. In this sense, research based on genetic material is of interest to society at large, as health is a public good, the protection of which is of universal value. Therefore, the improvement of health needs to be protected, from the perspective of public interest. From the perspective of individual data-subjects, the use of genetic data has to be assessed morally, not only on the basis of avoiding harm and the protection of their fundamental rights, but also on the basis of responsibility and a moral claim for social solidarity (an obligation to assist those in need).

The use of genetic information in medical research and education may substantially contribute to the improvement of public health, by facilitating the establishment of the right health policies for large samples of the population. In this context, the voluntary and informed consent for the participation of individuals constitutes an act of social solidarity and ought to be promoted. "Because of shared vulnerabilities, people have common interests and moral responsibilities to each other. Willingness to share information and to participate in research is a praiseworthy contribution to society" [10].

In moral analysis, there is a growing emphasis on the significance of information *sharing* rather than the protection strictly of individual "genetic" rights. The claims of rights to know and to not know have to be constantly renegotiated in the light of such considerations.

Put in a nutshell, binding normative requirements should be in place in order to safeguard the protection of patients or data subjects' personal autonomy and fundamental rights. The principles of respect for autonomy, justice, beneficence and nonmaleficence, particularly in the form of the protection of the life and health of individuals, form the "ethical minimum" of any normative evaluation of the uses of genetic information. In addition, there are other norms that are relevant in decision-making, which include those of promoting collective goods, such as scientific knowledge and public health. There is a responsibility to promote the genetic health of the population and to help those at risk, whereas the protection of freedom of research (and its quality), related to public interest, is also to be promoted. But these requirements are structured in an order of priority, such that the latter require adherence on the condition that the former are not violated. That is, however important the purpose of the use of genetic data may be, no such use can legitimise or justify, the violation of the fundamental rights of patients or individual data-subjects or the generation of harm to them. The protection of human subjects is overriding and no genetics research, however useful to society, can be morally permitted to interfere with or postpone the appropriate therapeutic interventions for individual patients.

Freedom from injury or harm, and from disrespect as well as respect for personal autonomy are overriding principles. Proper use ought not to inflict systematic or gratuitous harm or injury, and it ought not to override the consent of those whose data are being used.

CONCLUSION

Advances in genetic research lead to improvements in knowledge of the factors related to predisposition to various diseases as well to associations between genes, way of life and the environment. This new knowledge carries with it a powerful potential for combating disease, promoting health and improving the quality of life. Its utilisation, however, should not be exaggerated or idealised. Providing genetic analysis for susceptibility to diseases should take into account, minimally, test limitations (particularly for multifactorial ones), including the fact that they are probabilistic and based on current research results, which may be revised. Test results should not be used by themselves for medical decision-making, given their bounded and qualified clinical validity and utility. In addition, integrating genetic information into medical practice raises a distinct set of ethical challenges. Ethical questions may take the form of issues related to the care of individuals or families, but may also take the form of societal and public health concerns, such as those related to biobank research, which may

include policy making from the point of view of public interest and society at large.

To address such issues, it is essential to start moral reflection with fundamental ethical principles, for which sound normative justification can be provided. However, bioethical analysis is not merely a matter of identifying and grounding the appropriate moral principles. It is also concerned with their practical application; it is equally policy-oriented. Emphasis on ethical principles can hardly be sufficient without their contextualisation. One of the aims of bioethical debate is to ensure that fundamental ethical principles can be assimilated by professional and regulatory practices, and where required, by governmental policy. The role of medical education is of special significance. Organisations responsible for the education of healthcare professionals are required to train the latter with sensitivity to ethical principles and norms of best practice in the areas of giving advice about personal genetic testing or profiling.

A bioethical policy-oriented approach on issues as complex and as rapidly changing as the scientific and clinical uses of genetic information will be an ongoing and delicate process. This paper's methodological strategy has been to identify

robust ethical principles, for which sound justificatory arguments can be given. After establishing the framework of principles, we may begin to argue for guidelines, which can be of practical interest to medical practitioners, professional, educational and regulatory bodies and research ethics committees, which will make decisions concerning specific uses of genetic data.

There is no simple way of applying moral principles, either algorithmically or mechanistically. Particularly in the field of cancer genetics, the complexity and delicacy of handling genetic information, including practices of seeking to control health risks, require continuous assessment of cases and possibilities, in the light of the best available scientific evidence and in combination with rigorous ethical arguments.

Conflict of interest statement

The author declares no conflict of interest.

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Treatment compliance, tolerance and efficacy in elderly and non-elderly patients with metastatic colorectal cancer: A single institution comparative study

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ABSTRACT

Background: Elderly patients with metastatic colorectal cancer (mCRC) have been reported to receive chemotherapy of suboptimal intensity and duration, mainly due to fears of poor compliance and/or excessive toxicity.

Patients & Methods: We retrospectively evaluated all patients who received first-line chemotherapy for metastatic colorectal cancer at our institution between January 2007 and December 2011. Using the cut-off of 70 years, we compared elderly patients with their younger counterparts in terms of treatment delivery and tolerance (type, dose intensity [DI], related dose intensity [RDI], duration), chemotherapy toxicity and treatment efficacy (objective response rate [ORR], overall survival [OS] and progression-free survival [PFS]).

Results: Among 94 eligible patients, full data was available for 72 (76.6%), among which 38 (52.8%) were elderly. As compared to their younger counterparts, elderly patients were more likely to receive single-agent chemotherapy (13.1% vs. 0%, $p < 0.001$). The mean number of chemotherapy sessions was 6.2 for the elderly and 8.3 for the non-elderly patients who received either the FOLFOX or the FOLFIRI regimen ($p = 0.142$), and 5.1 vs. 5.0 for the patients who received either the XELOX or XELIRI regimen, respectively ($p = 0.831$). In oxaliplatin-containing regimens, elderly patients received 42.8% of the planned dose, as compared to 78.4% for the younger ones ($p = 0.012$); whereas in irinotecan-containing regimens, the corresponding values were 52.8% and 62.7% ($p = 0.170$), respectively. DI for oxaliplatin was greater in non-elderly than in the elderly (46.66 mg/m²/week vs. 32.47 mg/m²/week, $p = 0.008$); whereas for irinotecan, no significant difference was noted (69.62 vs. 62.81 mg/m²/week, $p = 0.165$). No difference was observed in the rate of severe (grade III-IV) toxicities. ORR, PFS and OS were similar between the two groups.

Conclusions: Despite the inferior intensity and duration of chemotherapy, elderly patients derived similar clinical benefit to their younger counterparts. These data further support the use of optimal chemotherapy in elderly patients with mCRC.

Key words: metastatic colorectal cancer; elderly; tolerance; toxicity; efficacy; chemotherapy.

INTRODUCTION

Cancer mostly affects older patients [1-3] and aging has been proven to be the most important risk factor for carcinogenesis [1]. The chronological time-point that separates elderly from non-elderly cancer patients is not clearly defined and although there is no consensus [4, 5], most of the published trials in oncology use the cut-off of 65 or 70 years for this purpose [6]. However, it is important to note that biological age alone is not the

decisive factor that distinguishes the two groups [7]. Moreover, in the past decades a trend has been recorded for less aggressive therapeutic strategy in elderly patients [6, 8, 9]. Possible explanations for this include the presence of substantial comorbidities; poly-pharmacy; decreased physiological hepatic and/or renal reserves which compromise treatment tolerance; poor compliance; physician's reluctance; and barriers in the elderly person's access to medical care [10].

Colorectal cancer is the most common gastrointestinal tumor in Western countries and its frequency is increasing in elderly patients [11]. Despite the fact that the median age of diagnosis is 71 years and nearly 70% of new cases are over 65 years of age [12], elderly patients are under-represented and often excluded from clinical trials [13, 14]. Furthermore, population-based analyses [8, 9] report a trend for suboptimal treatment of elderly patients with colorectal cancer, despite the fact that meta-analyses and reports of pooled study populations [11, 15] do not suggest different outcomes in terms of toxicity or efficacy.

In order to assess whether elderly patients with metastatic colorectal cancer are treated differently from their younger counterparts in the Hellenic clinical setting, we undertook a retrospective analysis of all patients who received first-line chemotherapy for colorectal cancer in our institution in the past five years and compared treatment delivery, tolerance and efficacy between the two groups.

PATIENTS & METHODS

Adult patients with a diagnosis of advanced (recurrent or metastatic) colorectal cancer; with measurable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST) [16]; with an Eastern Cooperative Oncology Group (ECOG) status of 2 or less; who had received first-line chemotherapy between January 2007 and December 2011; were eligible for the analysis.

For all eligible patients, we collected clinicopathological data, treatment-related characteristics (chemotherapy regimen, duration, dose intensity and related dose intensity for all administered agents) and information on treatment and patient outcome (objective response rate [ORR], overall survival [OS], progression-free survival [PFS] and toxicities). Dose intensity (DI) was calculated as the dose delivered per square meter per week for each chemotherapeutic agent (expressed as mg/m²/week) and relative dose intensity (RDI) was calculated as the ratio of administered to the planned dose intensity (expressed as percentage %) for each pharmacological agent. We opted not to perform analysis on molecular targeted agents (monoclonal antibodies against the epidermal growth factor receptor [EGFR] and the vascular endothelial growth factor receptor [VEGFR]), since these biological agents were not universally available in 2007 and their indications evolved from 2007 to 2011 resulting in a complexity that obscured comparative analysis between elderly and non-elderly patients.

STATISTICAL CONSIDERATIONS

Categorical variables were compared in the two study groups with the chi-square test. Continuous variables were analyzed with the student's t-test or the Wilcoxon test where appropriate. Survival curves (PFS and OS) were plotted with the Kaplan-Meier method and were compared between the two study groups with the Log Rank test. Data were analyzed using SPSS version 17.1.

Table 1.

Clinicopathological characteristics of the patient population.

		Total	Elderly (N=38)	Non-elderly (N=34)
Age				
Median (Range)		72.0 (34-88)	76.6 (70-88)	57.4 (34-69)
Gender	Male (%)	45 (62.5)	24 (63.2)	21 (61.8)
	Female (%)	27 (37.5)	14 (36.8)	13 (38.2)
Initial Duke's stage	B	12 (16.7)	8 (21.1)	4 (11.8)
	C	26 (36.1)	15 (39.5)	11 (32.4)
	D	34 (47.2)	15 (39.5)	19 (55.9)
Grade	I	6 (8.3)	2 (5.3)	4 (11.8)
	II	55 (76.4)	32 (84.2)	23 (67.6)
	III	11 (15.3)	4 (10.5)	7 (20.6)
Location	Ascending colon	23 (31.9)	11 (28.9)	12 (35.3)
	Descending colon	9 (12.5)	5 (13.2)	4 (11.8)
	Sigmoid	19 (26.4)	8 (23.5)	11 (28.9)
	Rectal	21 (29.2)	11 (28.9)	10 (29.4)
Adjuvant chemotherapy	Yes	12 (31.6)	9 (26.5)	21 (29.2)
	No	26 (68.5)	25 (73.5)	51 (70.80)
Surgery	Yes	28 (73.7)	24 (70.6)	52 (72.2)
	No	10 (26.3)	10 (29.4)	20 (27.8)

Table 2.

Dose intensity (DI) and relative dose intensity (RDI) for oxaliplatin and irinotecan.

		Non-elderly	Elderly	P (two-sided)
OXALIPLATIN N=15	DI (mg/m ² /week)	46.66	32.47	0.008
	RDI (%)	78.4	42.8	0.012
IRINOTECAN N=49	DI (mg/m ² /week)	69.62	62.81	0.165
	RDI (%)	52.80	62.70	0.170

Table 3.

Toxicity data.

	Non-elderly (N=34)	Elderly (N=38)	Total (N=72)
Neutropenia	3 (8.8%)	1 (2.6%)	4 (5.6%)
Anemia	1 (2.9%)	0 (0%)	1 (1.4%)
Thrombocytopenia	1 (2.9%)	1 (2.6%)	2 (2.8%)
Peripheral neuropathy	2 (5.9%)	2 (5.3%)	4 (5.5%)
Diarrhea	3 (8.8%)	1 (2.6%)	4 (5.5%)
Skin rash	1 (2.9%)	0 (0%)	1 (1.4%)
Fatigue	0 (0%)	1 (2.6%)	1 (1.4%)

tecans or oxaliplatin (FOLFOX, FOLFIRI, XELOX, XELIRI). As compared to their younger counterparts, elderly patients were more likely to receive single-agent chemotherapy (13.1% vs. 0%, $p < 0.001$). The mean number of chemotherapy sessions for patients treated with either FOLFOX or FOLFIRI was 6.2 for the elderly and 8.3 for the non-elderly ($p = 0.142$), while the corresponding values for the patients who received either XELOX or XELIRI were 5.1 for the elderly and 5 for the non-elderly ($p = 0.831$).

Mean dose intensity (DI) for oxaliplatin was significantly lower in the elderly population compared to non-elderly patients (32.47 mg/m²/week vs. 46.66 mg/m²/week, respectively; $p = 0.008$). Consequently, relative dose intensity (RDI) for oxaliplatin was 42.8% for the elderly and 78.4% for the non-elderly patients ($p = 0.012$). Mean DI for irinotecan was 62.81 mg/m²/week for the elderly and 69.62 mg/m²/week for the non-elderly patients ($p = 0.165$). Corresponding RDIs for irinotecan were 52.8% and 62.7%, respectively ($p = 0.170$) (Table 2). As for molecular targeted agents included in the chemotherapy regimens (cetuximab, panitumumab, bevacizumab), the small number of patients treated with these agents in our cohort did not allow safe conclusions to be drawn regarding their comparative use in the two age groups.

RESULTS

Treatment delivery and adherence

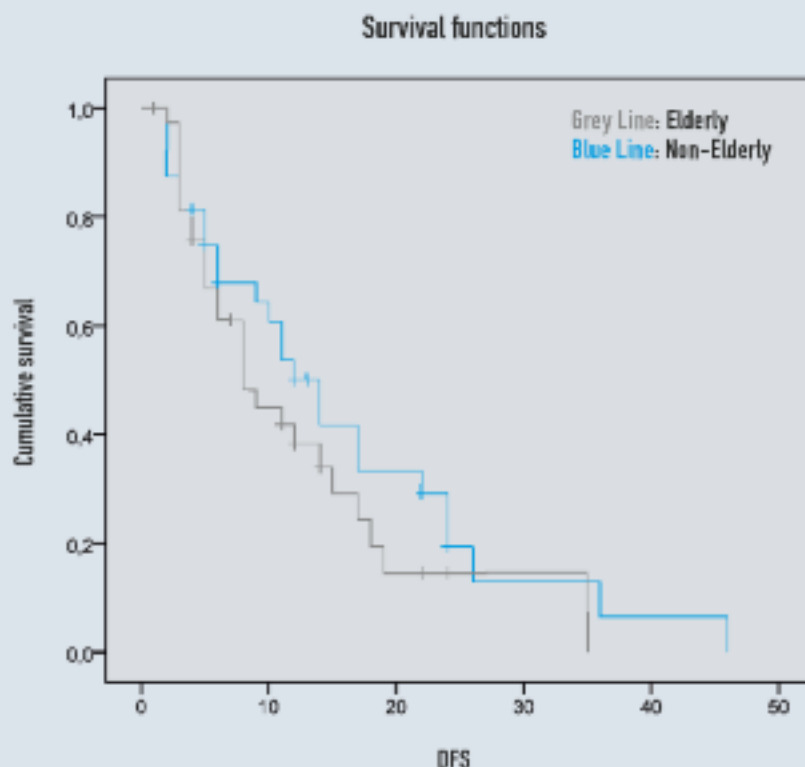
Among 94 patients who met the inclusion criteria, full data were available for 72 patients (76.6%). Using the cut-off of 70 years, 38 (52.8%) patients were assigned to the elderly and 34 (47.2%) to the non-elderly group of patients. Median age of the whole cohort was 72.0 years (range 34–88 years). There were no significant differences regarding basic clinicopathological variables between the two groups (Table 1). Only five patients (6.9%) received monotherapy with either 5-fluorouracil or capecitabine while the rest (93.1%) received various combination regimens implementing either irino-

Treatment tolerance and toxicity

The most frequent non-hematological grade 3–4 toxicities according to the NCI-CTC version 5.0 (available at: www.nci.gov/ctc5) were diarrhea (5.5%); peripheral neuropathy (5.4%); skin rash (1.4%); and fatigue (1.4%). Four patients discontinued chemotherapy due to unacceptable toxicity (two with diarrhea grade 4; one with diarrhea grade 4 and fatigue grade 3; and one with diarrhea grade 3 and rash grade 3). Regarding hematological toxicities, neutropenia grade 3–4 was reported in 4 patients (5.6%) and thrombocytopenia grade 3–4 in 2 patients (2.8%). Severe anemia (grade 3) was noted in one non-elderly patient (2.9%), requiring blood transfusions (Table 3). There were no

Figure 1A.

Kaplan-Meier curves of cumulative disease-free survival according to age group.



significant differences in terms of overall and severe (grade 3-4) hematological and non-hematological toxicity between the two groups.

Efficacy

Overall objective response rate (ORR), including complete response (CR), partial response (PR) and stable disease (SD) according to the RECIST criteria (available at www.recist.ncbi.com) in the whole study population was 63.8%. Among the responders, 22 were elderly (57.9% of the elderly population) and 24 non-elderly (70.5 of the non-elderly population). There were no significant differences in ORR between the two study groups (data not shown).

Median PFS for the whole study population was 11 months (95% CI: 8.84-13.16 months). As compared to their younger counterparts, elderly patients experienced shorter PFS, albeit not significantly (median: 9.3 vs. 12.8 months, $p=0.09$). Kaplan Meier curves for DFS are depicted in Figure 1A.

Median OS for the whole study population was 24.9 months (95% CI: 18.4-30.9 months). The corresponding values were 24.7 months (95% CI: 16.3-33.1 months) for the elderly patient cohort and 25.0 months (95% CI: 16.0-34.1 months) for the

non-elderly patient cohort ($p=0.208$). Kaplan Meier curves for OS are depicted in Figure 1B.

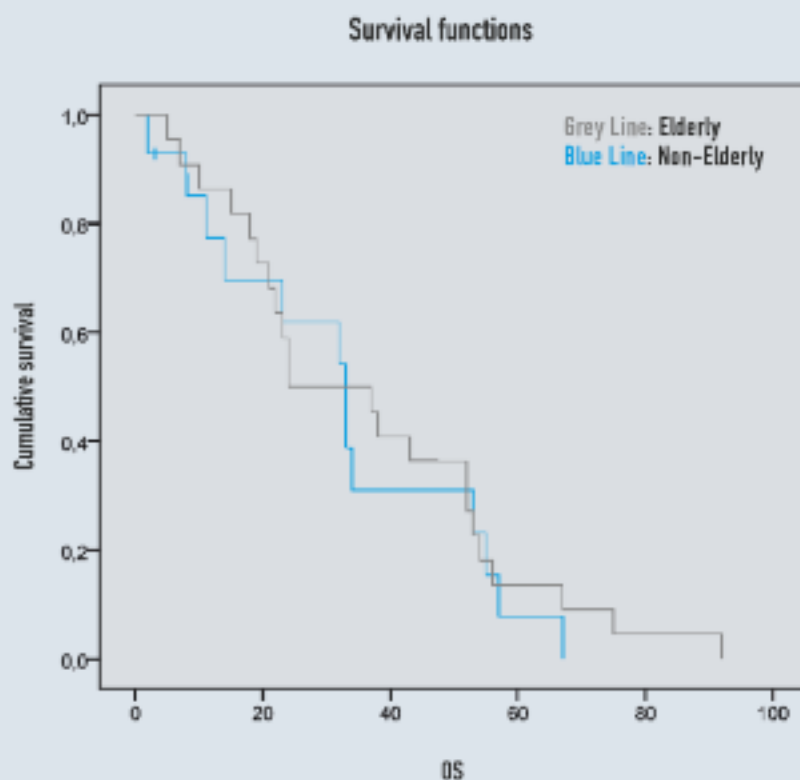
DISCUSSION

More than half (52.8%) of the patients in our cohort belonged to the elderly group (age at study entry more than 70 years); Given the fact that in most clinical trials in advanced colorectal cancer, elderly patients are under-represented -constituting approximately 25-35% of the whole study population [15, 17]- our cohort provides a suitable field for the comparison of the two age categories. We found that, compared to their younger counterparts, elderly patients were more likely to receive single-agent chemotherapy with either 5-fluorouracil or capecitabine, a fact that might have compromised treatment efficacy and subsequent therapeutic outcome. Regarding treatment duration, there was a trend for shorter treatment among elderly patients who were treated with the FOLFOX and FOLFIRI regimens, although this difference did not reach statistical significance, which may also have impacted therapeutic outcome.

Of note, dosing and frequency of oxaliplatin administration were significantly lower in the elderly group of patients, resulting in suboptimal intensity and duration of treatment

Figure 1B.

Kaplan-Meier curves of cumulative overall survival according to age group.



with this agent in the same age group; This may be attributed to the recognized toxicities of oxaliplatin and mainly sensory peripheral neuropathy, which is a main concern, especially in elderly patients with a history of diabetic neuropathy. The fact that such a difference was not observed for irinotecan suggests a better tolerance of irinotecan, as compared to oxaliplatin, in elderly patients with advanced colorectal cancer.

In the present work, the criterion used for dichotomizing the study population was strictly chronological (cut-off at 70 years of age). The elderly patient population, however, is highly heterogeneous, with respect to the general performance status of the patient, the presence of comorbidities and complicate biological factors. It has been suggested that 'fit' elderly patients may be offered the same treatment as that used in younger patients. On the contrary, less intensive or no chemotherapy should be preferred for more 'frail patients' [15]. In either case, individual functional reserve and life expectancy (regardless of cancer's prognosis), which could affect treatment decisions, might best be evaluated in older patients by a comprehensive geriatric assessment. This takes into account various sides of functionality and health, including mental status, emotional status/depression,

activities of daily living (ADLs), instrumental ADLs, home environment, social support, comorbidities, nutrition and polypharmacy [7, 18].

Despite the lower intensity and duration of chemotherapy in the elderly patient population, the number of patients that responded to first-line chemotherapy was similar in the two groups of patients (57.9% vs. 63.8% for the elderly and non-elderly, respectively), suggesting that elderly patients may also derive substantial clinical benefit from chemotherapy and should therefore not be *a priori* excluded from intensive chemotherapy protocols applied to the non-elderly population. Of note, a pooled analysis [15] of 22 European clinical trials, including 629 patients with advanced colorectal cancer with an age of ≥ 70 years at diagnosis, showed that efficacy of chemotherapy, in terms of response rate and overall survival, did not differ significantly in elderly and non-elderly patients. The absence of negative influence of age on chemotherapy efficacy was in accordance with reports from smaller cohorts in both first line and adjuvant setting [19-24]. Moreover, retrospective series and subset analyses [12] show that 'fit' older patients derive the same benefit from optimum multimodality strategies as their younger counterparts with no significant difference in toxicity. FOCUS2, an

open-label, prospective, randomized study [25], was designed to investigate reduced-dose chemotherapy options and to seek objective predictors of outcome in 'frail' patients with metastatic colorectal cancer. This study showed that, using an appropriate design, 'frail' elderly patients can participate in a randomized controlled trial. A combination including oxaliplatin was preferable to single-agent fluoropyrimidines, whereas capecitabine did not improve quality of life compared to fluorouracil [25].

No significant differences in severe (grade 3-4) hematological and non-hematological toxicities were noticed between elderly and non-elderly patients. Although this may be, at least in part, attributed to the lower intensity and duration of chemotherapy in the elderly patients, one may postulate that no life-threatening toxicities appear when intense chemotherapy protocols for metastatic colorectal cancer are applied in the elderly patient population.

In conclusion, our data suggests that elderly patients in good general health could and should be offered chemotherapy with the same regimens as those used in younger patients and should be included in the same clinical trials. Thus, elderly patients should not be left untreated or be undertreated because of the misperception that they will have greater toxic effects, will poorly tolerate chemotherapy and will not adhere to the treatment protocol. Elderly patients represent a substantial portion of the whole patient population with advanced colorectal cancer and should be offered equal therapeutic opportunities as their younger counterparts in order to derive substantial clinical benefit from available treatment options.

Conflict of interest statement

The authors declare no conflict of interest.

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A cost-effectiveness analysis of trastuzumab plus docetaxel vs. docetaxel alone for the treatment of HER2-positive metastatic breast cancer in the Greek healthcare setting

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ABSTRACT

Background: The purpose of this analysis was to investigate the cost-effectiveness of the addition of trastuzumab to docetaxel as a first-line treatment for women with HER2-positive metastatic breast cancer (MBC) in the Greek healthcare setting.

Patients & Methods: A 3-state Area Under the Curve model was constructed to simulate disease progression and overall quality-adjusted survival for patients receiving trastuzumab and docetaxel (T+D) or docetaxel alone (D) over a total period of 12 years. Data on treatment efficacy was derived from a randomized controlled trial comparing the outcomes of six cycles of docetaxel 100 mg/m² every 3 weeks, with or without trastuzumab 4 mg/kg loading dose followed by 2 mg/kg weekly until disease progression. Costs were estimated from a third-party payer perspective (2011 euros).

Results: Patients in the T+D arm had a mean incremental gain of 0.729 years (95% CI: 0.10, 1.36) in overall survival and 0.449 (95% CI: 0.14, 0.76) QALYs in quality-adjusted survival compared to those in the D-alone arm. Taking into account incremental costs, the analysis revealed that the Incremental Cost Effectiveness Ratios (ICERs) were €37,759 and €61,323 for every life-year or QALY, respectively, gained with trastuzumab. Probabilistic sensitivity analysis showed that the ICERs produced by T+D were favourable in 25.9% of the Monte Carlo simulations at the €50,000 and 47.5% at the €60,000 threshold.

Conclusions: The addition of trastuzumab to a first-line treatment of HER2-positive MBC with docetaxel represents an intervention that is likely to have a high probability of being cost-effective from a third-party payer perspective.

Key words: cost-effectiveness analysis; trastuzumab; docetaxel; metastatic breast cancer.

INTRODUCTION

Breast cancer is a major public health issue worldwide. It is the most common malignant cancer among women and has a poor prognosis following metastasis, representing the leading cause of cancer deaths [1]. The burden of disease associated with breast cancer also entails a significant economic burden imposed on patients, caregivers and health systems internationally [2]. It is estimated that the direct costs of treatment for patients with breast cancer in the US exceed \$4.2 billions annually [3], whereas the cost per patient falls within the range of US\$20,000 to US\$100,000 [4]. A notable proportion of the overall expenditure is attributed to the metastatic forms of the disease; according to calculations in Sweden, total per-patient costs of metastatic

breast cancer (MBC) amount to \$12,900–\$46,500 annually, depending on patient age and stage of the disease [5].

The introduction of targeted therapies has had a significant impact on breast cancer care, offering advanced treatment strategies and altering disease management, both in the adjuvant setting, as well as progressed stages of the disease. Among them, trastuzumab, a recombinant humanized anti-HER2 (human epidermal growth factor receptor 2) monoclonal antibody, that acts by inhibiting the growth of breast cancer cells that over-express cell surface receptor HER2. HER2 over-expression, which is present in 20%–25% of patients with MBC, is related to a high risk of relapse and low rates of survival [6].

Trastuzumab has repeatedly been shown to

be a clinically efficacious and cost-effective intervention for the treatment of early breast cancer. Younis *et al.*, in their 2008 review on the economic value of trastuzumab [7] report Incremental Cost-Effectiveness Ratios (ICERs) ranging from \$18,970 [8] to \$39,982 [9] per Quality-Adjusted Life Year (QALY) gained and \$23,706 [10] to \$29,060 [11] per life year gained with treatment (all values in 2007 US dollars). In the same context, Chan *et al.* [12] evaluated all published cost-effectiveness analyses (up to 2009) for trastuzumab used as an adjuvant treatment for HER2-positive early breast cancer. The authors reported a wide variation in ICERs that ranged from \$5,020/QALY [13] to \$134,610/QALY [14] for 1 year of therapy, with most studies (68.2% of those reviewed), however, demonstrating favourable cost-effectiveness values, i.e. below the \$50,000/QALY threshold.

However, much less evidence exists as to the cost-effectiveness of trastuzumab in the metastatic state of the disease. In this light, the purpose of the present study was to evaluate the addition of trastuzumab to a commonly used agent, docetaxel, for patients with MBC, from the perspective of the Greek healthcare system setting.

METHODS

In order to assess the cost-effectiveness of the aforementioned regimens, an Area Under the Curve (AUC) model for each strategy was constructed using MS Excel®. The AUC model estimates total costs, survival and quality-adjusted survival over time, by indicating the proportion of the cohort that is event-free at a given point in time. As presented in Figure 1, the constructed AUC model consists of three

mutually exclusive health states. Patients start at the "progression free survival" state (PFS), from where they can either proceed to the "progressed" disease state; die, as a result of the disease or general mortality; or remain there. Similarly, when a patient enters the "progressed" state, she can either remain there or die.

The model simulated the progress of patients, over a total period of twelve years, the point at which most patients were considered to no longer be alive. Transitions among health states were assumed to occur at monthly intervals.

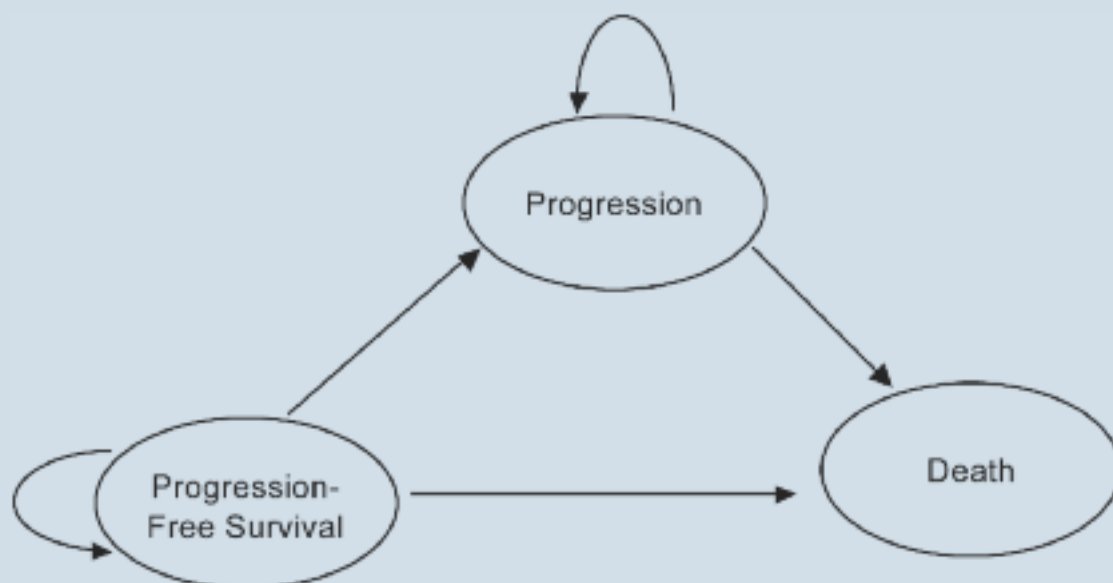
Baseline population and estimation of effectiveness

Effectiveness data, i.e. clinical course of patients for each treatment strategy, were derived from the study of Marty *et al.* [15], a randomized, phase II multicenter, multinational trial that compared first-line trastuzumab plus docetaxel versus docetaxel alone in patients with HER2-positive MBC. In the study, patients were randomly assigned to six cycles of docetaxel 100 mg/m² every 3 weeks, with or without trastuzumab 4 mg/kg loading dose followed by 2 mg/kg weekly until disease progression. Measures of efficacy in the trial included overall response rate, progression-free survival, and overall survival.

The baseline population of the analysis in question followed that of the clinical trial, i.e. patients had an average age of 53 years in both arms, median duration of primary disease (i.e. time from first diagnosis to diagnosis of metastasis) of 26.6 and 22.6 months and median duration of metastatic disease of 1.3 months and 1 month in the trastuzumab + docetaxel and the docetaxel alone arms, respectively [15].

Figure 1.

Overview of the AUC model.



Cost calculations

The analysis was performed from a third-party payer perspective, thus it considered only direct medical costs associated to treatment and patient follow-up. Major cost variables included the costs of supportive care for each disease state, the cost of pharmaceuticals (including costs of administration) and the costs of treatment-related adverse events. Unit costs were derived from the database of the Greek Social Insurance Institute (IKA), the main social security foundation, covering about 50% of the population. The unit costs are applicable for the rest of the social security foundations in Greece and are based on 2011 fees and prices. Drug costs were obtained from the latest price list published by the General Secretariat for Commerce of the Ministry of Development, Competitiveness, Infrastructure, Transport and Networks.

Health utilities

Currently there are no published utility values for the corresponding disease states in the model specifically for Greek patients. Thus, utilities for the PFS state and

progressed state were taken from the publication of Lloyd *et al.* [16].

Discounting

Discounting was deemed necessary, given that the outcomes in the model are projected beyond 1 year. In this light, outcomes were discounted at an annual 3.5% discount rate for the 12-year horizon of the analysis, a common approach in the Greek healthcare setting [17].

Sensitivity analyses

To address the uncertainty of model parameters and to evaluate result robustness, extensive probabilistic sensitivity analysis (PSA) was performed, during which random values according to a beta distribution were assigned to utilities and to a gamma distribution to costs [18]. Sensitivity analyses results for the incremental cost effectiveness ratios (ICERs) for trastuzumab and docetaxel relative to docetaxel alone were produced after 5000 iterations using 2nd order Monte Carlo simulation.

Table 1.

Base case scenario parameters.

Base case parameter	Value	Reference
<i>Patient demographics</i>		
Average age (years, both arms)	53.00	Marty <i>et al.</i> [15]
Median duration of primary disease (months): trastuzumab + docetaxel	26.6	Marty <i>et al.</i> [15]
Median duration of primary disease (months): docetaxel alone	22.6	Marty <i>et al.</i> [15]
Median duration of metastatic disease (months): trastuzumab + docetaxel	1.3	Marty <i>et al.</i> [15]
Median duration of metastatic disease (months): docetaxel alone	1.0	Marty <i>et al.</i> [15]
<i>Costs of pharmaceuticals</i>		
Cost of trastuzumab (€/mg)	3.28	GNF
Cost of docetaxel (€/mg)	5.95	GNF
<i>Monthly administration costs of pharmaceuticals</i>		
Trastuzumab + docetaxel arm	Trastuzumab (€)	252.5
	Docetaxel (€)	165.3
Docetaxel alone arm	Docetaxel (€)	185.60
		IKA
<i>Monthly supportive care costs (consultations and pain medication)</i>		
Progression-free survival (€)	69.77	IKA
Progressed state (€)	82.2	IKA
<i>Utilities</i>		
PFS health state	0.74	Lloyd <i>et al.</i> [16]
Progressed health state	0.44	Lloyd <i>et al.</i> [16]
Discount rate (Costs & Utilities)	0.035	

Table 2.

Base case scenario results.

	Trastuzumab + Docetaxel	Docetaxel Alone	Incremental
Mean life years gained	3.427	2.698	0.729
95% CI	(2.95 3.92)	(2.28 3.15)	(0.10 1.36)
Mean time in PFS (yrs)	1.613	1.184	0.429
95% CI	(1.30 1.97)	(0.93 1.47)	(0.06 0.82)
Mean time in progression (yrs)	1.814	1.514	0.300
95% CI	(1.24 2.41)	(1.01 2.03)	(-0.43 1.03)
Mean QALYs gained	1.992	1.542	0.449
95% CI	(1.75 2.25)	(1.33 1.77)	(0.14 0.76)
Mean QALYs in PFS	1.193	0.876	0.317
95% CI	(0.96 1.46)	(0.69 1.09)	(0.05 0.61)
Mean QALYs in progression	0.798	0.666	0.132
95% CI	(0.54 1.07)	(0.44 0.90)	(-0.19 0.45)
Mean total cost (€)	36,442.04	9,112.61	27,323.98
95% CI	(36,611.56, 41,172.56)	(8,184.99, 10,027.98)	(21,569.04, 33,699.93)
Cost per life year gained (€)			37,759.97
Cost per QALY gained (€)			61,323.33

RESULTS

Patients in the trastuzumab + docetaxel arm had a mean incremental gain of 0.729 years [95% CI: 0.10, 1.36] in overall survival, out of which 0.429 years [95% CI: 0.06, 0.82] (Table 2) were due to an increase in progression free survival and 0.3 [95% CI: -0.43, 1.03] due to extended time in the progressed state compared to patients in the docetaxel alone arm.

Adjusting for health-related quality of life, patients under trastuzumab + docetaxel were expected to gain 0.449 [95% CI: 0.14, 0.76] more QALYs than those in the docetaxel alone arm (1.992 vs. 1.542), mainly attributed to more time spent in the PFS state, which had a better quality of life prognosis.

Taking into account that patients in the trastuzumab + docetaxel arm had an average incremental cost of €27,323.98 [95% CI: 21,569.04, 33,699.93], the analysis revealed that the Incremental Cost Effectiveness Ratios (ICERs) were €37,759.97 and €61,323.33 for every life year or every QALY gained with trastuzumab, respectively.

Sensitivity analysis showed that the ICERs (cost/QALY) produced by trastuzumab and docetaxel vs. docetaxel alone were favourable at 25.9% of the Monte Carlo iterations at the €50,000 and 47.5% at the €60,000 threshold.

DISCUSSION

In the context of scarce resources against infinite needs in which healthcare systems are obliged to operate, informed decision-making, especially in the field of reimbursement

judgments by third-party payers, is necessary. Specifically in the case of MBC, one of the leading causes of morbidity and, at the same time, of a significant socioeconomic burden on people and societies, reimbursement decisions can have an important impact on human lives as well as on healthcare budgets.

In this light, we performed a cost-effectiveness analysis of the addition of trastuzumab to a commonly used strategy in patients with HER2-positive MBC, i.e. docetaxel, for patients in the Greek healthcare setting. For this purpose, we constructed an AUC model that estimates disease outcomes and corresponding costs for a 12-year horizon, according to efficacy data from published clinical trials and local economic data.

Analysis results indicated that the addition of trastuzumab to a first-line treatment of HER2-positive MBC with docetaxel represents an intervention with a high probability of being cost-effective from a third-party payer perspective. Currently, there are no explicit thresholds for health technology assessments in Greece. However, an implicit "rule of thumb" criterion could be obtained by taking into account reimbursement decisions for corresponding interventions in Europe, as well as the "x3 GDP" recommendation of the WHO [19] (the latter, however referring to the cost per DALY averted with a potential of being extended to per QALY decisions) [20]. This would place the threshold to a range of €50,000–60,000/QALY gained. In those terms, trastuzumab plus docetaxel for the treatment of HER2-positive MBC is an

Figure 2.
PSA Scatter plot.

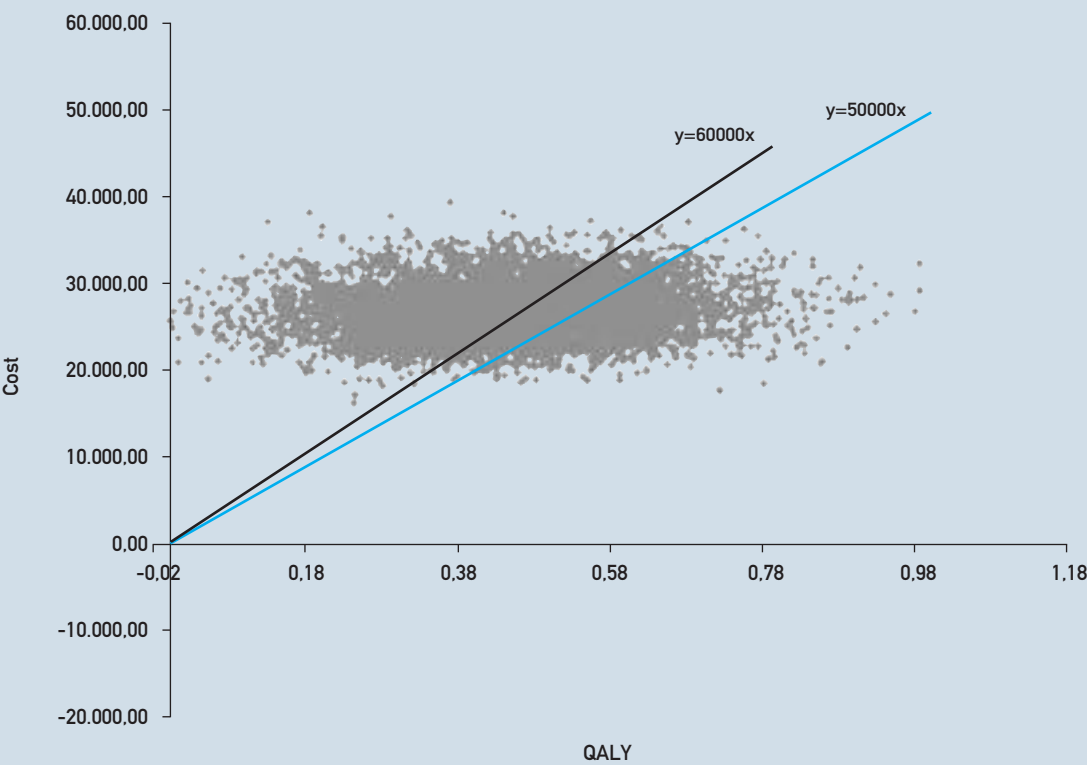
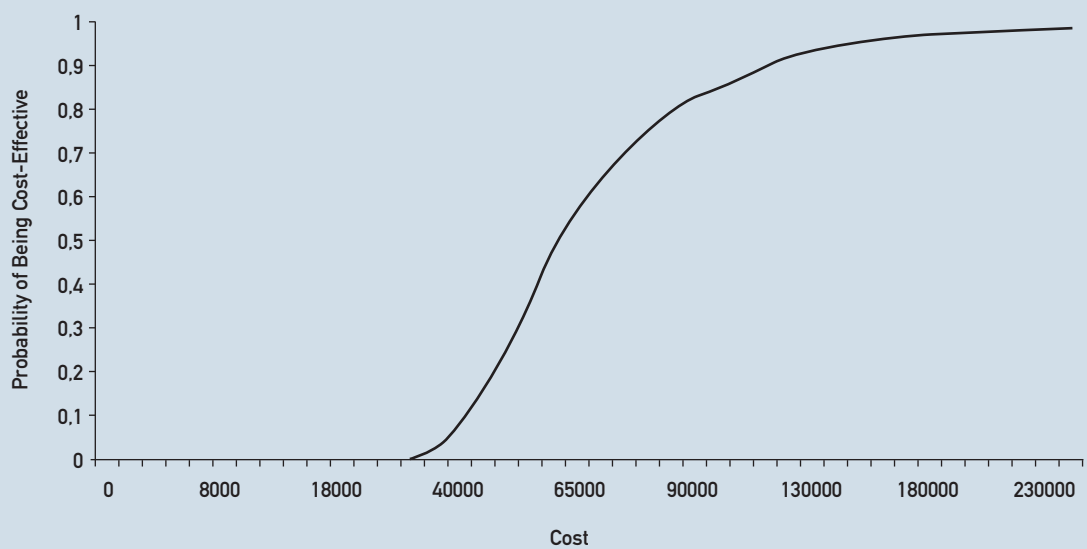


Figure 3.
Cost-effectiveness acceptability curve.



intervention that produced favourable ICERs at 25.9% of the iterations for a €50,000 and at 47.5% for a €60,000/QALY threshold.

To the best of our knowledge, the present analysis is the first to directly compare the costs and outcomes of trastuzumab plus docetaxel versus docetaxel alone in the treatment of MBC. In this context, the study outcomes cannot be benchmarked with corresponding evidence from other healthcare settings. However, the literature indicates that the addition of trastuzumab in standard chemotherapy for patients with MBC can be a cost-effective intervention, with ICERs being comparable to or more favourable than the ones presented by this analysis. Among these, the Matter-Walstra *et al.* [21] 2010 study, that reported an incremental cost-effectiveness ratio of €98,329/QALYs gained for the combination of trastuzumab with capecitabine in the Swiss healthcare setting; the Lindgren *et al.* [22] 2008 study that estimated an ICER of €53,880/QALY gained for HER2 testing and trastuzumab in combination with chemotherapy for patients in Sweden; and the analyses by Perez-Ellis *et al.* [23] and Poncet *et al.* [24] that demonstrated ICERs of €27,492 and €15,370 per life year gained for the French setting.

As with any study of its kind, the present analysis has several limitations that should be acknowledged. Firstly, data on progression, transition probabilities and overall survival is based on the study by Marty *et al.*, which considered patients in a different (multinational) healthcare setting. The Marty *et al.* cohort might not be fully representative for patients with MBC in Greece; the extent of this discrepancy, however, is

very difficult to quantify and include in the sensitivity analysis. Moreover, analysis perspective (third-party payer, i.e. the Greek Social Security Foundations) does not include other costs (indirect), the magnitude of which is analogous to disease severity. Should the societal perspective be adopted, there is evidence that the ICERs would probably be more favourable (lower). The present study concludes that the intervention under survey was followed by favourable incremental cost-effectiveness ratios, compared to other treatment strategies on cancer. However, the discussion on Social Security adopting such a policy will be complete, in economic terms, when accompanied by estimates of this intervention to insurance budgets, i.e. a budget impact analysis. This issue certainly constitutes an area of future research.

CONCLUSIONS

Economic evaluation is not a panacea or a solution for all health care policy issues, but merely a significant input in the decision-making process, the latter including a series of health-related and societal values. Analysis limitations notwithstanding, this data supports the current standard of care of a trastuzumab-docetaxel first-line regimen for patients with HER-positive MBC in Greece.

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The role of radiotherapy (RT) in the management of metastatic bone disease

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ABSTRACT

RT has been an established mode of treatment for metastatic bone disease for decades and has shown to be both effective and safe. It brings about significant pain relief, with large metaanalyses reporting equal effectiveness between single fraction (SF) and multi fraction (MF) RT. Overall pain response was reported to reach 59% and complete response 32%. The rates of re-irradiation after SF RT are significantly higher than after MF RT. Re-irradiation after recurrent pain is effective and well-tolerated, resulting in similar response rate as to that achieved with primary irradiation of a metastatic site. Additionally, no difference was shown in the rates of pathological fractures after SF or MF RT. Last but not least, in the event of a pathological fracture, RT is usually administered after surgical stabilization, whereas in cases of cord compression either SF or MF RT may be administered as soon as possible for patients who are not candidates for surgery.

Key words: bone metastases; radiotherapy; spinal cord compression; pathological fracture; re-irradiation; pain.

INTRODUCTION

In the event of malignancy, metastatic bone disease is not only common but also of particular clinical importance, since it may bring about serious complications such as pain, pathological fractures, spinal cord- or nerve root compression and hypercalcemia [1]. These complications can exacerbate patient quality of life or even be life-threatening [2]. Bone metastases are classified as osteoblastic, osteolytic or mixed-type based on their radiological appearance, with lytic bone lesions involving more pain and distress [3] and a higher risk of fracture.

Patient prognosis after the diagnosis of bone metastases mainly depends on the primary malignancy. The median survival of lung cancer patients is only a few months, whereas breast- and prostate cancer patients may live for several years [4-6]. The therapeutic management of bone metastases is important both for preventing detrimental complications such as pathological fractures and for palliation. In this article, we discuss the pathophysiology of bone metastases, their clinical picture and the role of RT in their management.

PATHOPHYSIOLOGY AND CLINICAL PICTURE OF BONE METASTASES

The pathophysiology of bone metastases is

rather complicated, involving numerous processes both at the primary and metastatic site. These processes involve the detachment of tumor cells from the primary tumor mass; circulation in the blood stream and migration; arrest at a distant (metastatic) site; invasion and infiltration in the neighboring normal tissues; and proliferation and formation of blood supply through neo-angiogenesis [7]. The formation of bone metastases is favored by several factors such as the high and slow blood flow in the bone marrow compartment [8]; tumor cell adhesive molecules that promote adhesion to stromal cells and bone matrix [9]; and the fertile soil of the osteomedullary compartment that enhances tumor cell homing [10].

Once bone metastasis develops, the normal continuous process of bone remodeling is disrupted, and the balance between osteoblasts and osteoclasts is lost [11]. As a result, a signal cascade leads to increased osteolytic activity and bone destruction; release of several growth factors from the bone matrix; and the stimulation of tumor cell growth and release of cytokines [12]. Bone loss and lysis may bring about pathological fractures whereas the release of calcium from the bone matrix may result in malignant hypercalcemia. Other potential complications of metastatic bone

disease include impaired mobility, spinal cord- or nerve root compression, bone marrow infiltration and bone pain [13-15]. The exact pathophysiology of pain is not understood; several causes, such as tumor induced bone lysis; growth factors and cytokine production; and periosteum or nerve stretching or infiltration [16] have been suggested.

RADIOTHERAPY MODE OF ACTION

The exact mechanism of action through which RT causes metastatic bone pain relief remains uncertain. The doses used for bone metastases irradiation are less than radical. However, they bring about a high level of tumor cell kill even in relatively resistant tumors. This results in shrinkage of the tumor bulk that enables osteoblastic repair and reossification of the damaged bone [9]. Even though this process undoubtedly occurs, it does not explain the rapid pain response (within 24-48 hrs) after systemic irradiation in up to 25% of irradiated patients [19]. Moreover, it has been shown that RT causes suppression in the level of urinary resorption markers, with the level of decrease correlating with response to treatment [20]. This supports the hypothesis that RT may create an analgesic affect through a suppression of osteoclastic activity.

EFFECTIVENESS OF RT FOR THE PALLIATION OF PAINFUL BONE METASTASES

RT has been an established mode of treatment of metastatic bone disease for many decades, offering a considerable analgesic effect and reduction in complication rates [21-23]. In various trials for bone metastases performed up to now, different response criteria have been employed to assess pain response. In order to achieve better comparisons between different clinical trials, a recent international consensus panel developed definitions of pain response after irradiation [24, 25]. These criteria take into account changes in bone pain score (which is measured by using the visual analogue scale) and alterations of analgesic medication, which is measured using oral morphine requirements. Additionally, the consensus included eligibility criteria, radiation techniques, follow-up parameters, timing of evaluations, re-irradiation and statistical analysis.

Different radiation schemes have been used to assess pain response after RT. These trials showed that SF RT is equal to MF RT in terms of pain relief [4, 27-41] (Table 1). This was confirmed by 3 different meta-analyses [21-23]. The first meta-analysis, by WU JS *et al.*, which included eight randomized studies and 3260 patients, compared SF RT with 1X8Gy to an MF RT regimen such as 5X4Gy and 10X3Gy. After intention to treat analysis, it was seen that complete pain response was 33% after SF RT and 32% after MR RT ($p=0.05$). After treatment per protocol analysis the corresponding values were 39% and 50%, respectively ($p=0.06$). The overall response rates were 62% after SF and 59% after MF RT ($p=0.04$) (intention to treat analysis). The

corresponding values in the per-protocol treatment analysis was 73% for each treatment mode ($p=0.9$) [21].

Similar results were published in the meta-analyses by Sze WM *et al.*, which included 12 randomized trials and a total of 3621 patients [22]. The rate of complete pain response was 34% after SF RT and 32% after MF RT ($p>0.05$). Overall pain response rates were reported at 60% and 59%, respectively ($p>0.5$) [22]. The most recently published meta-analysis is one by Chow E *et al.*, which included 5000 patients from 16 randomized trials [23]. In this trial, the overall response rates (intention to treat analysis) were 58% after SF RT and 59% after MF RT ($p=0.6$). Complete pain response was reported in 25% and 24% of patients, respectively ($p=0.51$) [23].

RE-IRRADIATION OF BONE METASTASES DUE TO RECURRENT PAIN

Overall, six trials compared SF to MF RT for re-irradiation of recurrent bone pain in irradiated bone metastases (Table 1). In four of these trials, the re-irradiation rate was significantly higher after SF RT, as compared to MF RT [31-33, 35-37]. Comparable results were reported in the 3 meta-analyses discussed earlier. Even though Wu *et al.* did not present pooled data, MF RT was reported to be superior to SF RT in terms of re-irradiation rates [21]. In the meta-analyses presented by Sze *et al.*, the re-irradiation rates after SF RT were 22%, as compared to 7% for MF RT ($p<0.05$) [22]. In the most recent and larger meta-analyses, the corresponding rates were 22% after SF RT and 8% after MF RT ($p<0.0001$) [23]. It should be noted that re-irradiation after SF RT is safer and more effective and that acute toxicity after re-irradiation does not exceed grade II.

Similar response rates were reported after re-irradiation of painful bone metastases [42]. Complete pain responses were reported to reach 31% and overall responses ranged between 74-87% [43, 44]. Re-irradiation should be performed with caution since radiation toxicity should be avoided, taking into account and not exceeding the tolerance doses of neighboring organs at risk. If primary RT was MF and involved an equivalent effective dose close to the radiation tolerance dose of neighboring normal tissues, highly conformal techniques should be applied to spare healthy tissues and minimize potential toxicity. Irradiation of the vertebral column and skull base is of particular concern, as it may lead to radiation myelopathy. RT techniques that allow high procession treatments include stereotactic body RT; radio-surgery using either linear accelerator, gamma knife or CyberKnife®; dynamic arc RT; and Intensity Modulated RT (IMRT) [42].

PATHOLOGICAL FRACTURES AFTER RT

Pathological fractures may complicate irradiated bone metastases after RT. As shown in Table 1, overall five trials have investigated pathological fracture rates after RT. In four of these trials, no significant difference between SF and MF RT

Table 1.

Randomized trials on bone metastases.

Study	No of patients	Overall pain response	Complete pain relief	Rate of re-irradiation	Rate of pathological fractures
Gaze 1997 [29]	265				
1X10Gy		84%	39%	Not reported	Not reported
5X4,5Gy		89% (p>0.05)	42% (p>0.05)		Not reported
Nielsen 1998 [30]	241				
1X8Gy		62%	Not reported	21%	5%
5X4Gy		71% (p>0.05)	Not reported	12% (p>0.05)	5% (p>0.05)
BPTWP 1999 [31]	761				
1X8Gy		72%	52%	23%	2%
5X4Gy		68% (p>0.05)	51% (p>0.05)	10% (p<0.001)	<1% (p=0.2)
Steenland 1999 [32]	1171				
1X8Gy		72%	37%	25%	4%
6X4Gy		69% (p=0.24)	33% (p>0.05)	7% (p<0.001)	2% (p<0.05)
Roos 2005 [33]	272				
1X8Gy		53%	26%	29%	4%
5X4Gy		61% (p=0.18)	27% (p=0.89)	24% (p=0.41)	4% (p>0.05)
Koswig 1999 [34]	107				
1X8Gy		79%	31%	Not reported	Not reported
10X3Gy		82% (p>0.05)	33% (p>0.05)	Not reported	Not reported
Hartsell 2005 [35]	888				
1X8Gy		65%	15%	18%	5%
10X3Gy		66% (p=0.6)	18% (p>0.05)	9% (p<0.001)	4% (p>0.05)
Amouzegar 2008 [36]	70				
1X8Gy		78%	11%	Not reported	Not reported
10X3Gy		65% (p>0.05)	37% (p<0.05)	Not reported	Not reported
Foro Arnalot 2008 [37]	160				
1X8Gy		75%	15%	28%	Not reported
10X3Gy		86% (p>0.05)	13% (p>0.05)	2% (p=0.001)	Not reported
Tong 1982 [38]	613				
5X3Gy		85%	49%	Not reported	5%
5X4Gy		83%	56%	Not reported	7%
5X5Gy		78%	49%	Not reported	9%
10X3Gy		87% (p=0.16)	57% (p=0.26)	Not reported	8% (p>0.05)
Okawa 1988 [39]	80				
5X4,5Gy		75%	40%	Not reported	Not reported
10X2Gy		78%	37%	Not reported	Not reported
15X2Gy		76% (p>0.05)	41% (p>0.05)	Not reported	Not reported
Rasmusson 1995 [40]	217				
3X5Gy		69%	Not reported	Not reported	Not reported
10X3Gy		66% (p>0.05)	Not reported	Not reported	Not reported
Niewald 1996 [41]	100				
5X4Gy		77%	33%	2%	8%
15X2Gy		86% (p>0.05)	31% (p>0.05)	2% (p>0.05)	12% (p>0.05)

was demonstrated [30, 31, 33, 35]. In the fifth study by Steenland E *et al.*, significantly more pathological fractures were observed after SF RT, as compared to MF RT [32]. The results of the 3 meta-analyses are inconclusive. The study by Wu *et al.* did not investigate this endpoint [21], whereas in the study by Sze *et al.*, the pathological fracture rate after SF RT was reported to be 3% versus 1.6% for MF RT ($p < 0.05$) [22]. In contrast to the above, Chow *et al.* reported no difference in pathological fracture rates between the two therapeutic schemes [23]. Therefore, it is not clear whether SF RT results in a higher rate of pathological fractures or not.

PAIN FLARE DURING RT FOR BONE METASTASES

An intermittent exacerbation of bone pain may be experienced during RT. The exacerbation of pain is considered significant if the pain score increases by at least two points (visual analogue scale) without an alteration of analgesic intake, or if the analgesic intake increases by 25% with no reduction in pain [45]. If a pain relief is experienced with a pain score reduction or a decrease in analgesic consumption to or below initial values, diagnosis of pain flare is established [45-47]. If no spontaneous pain improvement is seen, then the increase in pain is considered as treatment failure. Pain flare occurs in 14-44% of patients and can be considerably reduced by prophylactic use of dexamethasone [45-47]. In a study by Chow E *et al.*, the rate of pain flare after prophylactic administration of 8 mg of dexamethasone prior to the onset of RT was limited to 3% [46].

COMPLICATED BONE METASTASES

Complicated bone metastases are metastases associated with pathological fractures or spinal cord compression. Such complications are detrimental for patient quality of life and should be managed with no delay. In the case of pathological fractures, surgical management is preferred whenever possible. After surgical stabilization, post-operative RT should be administered in order to deal with any residual tumor and avoid slacking or dislocation of any prosthetic/osteosynthetic material [42]. It is well-known that RT results in the reossification of bone metastases. However, this procedure requires several months and remineralization is faster after long-course RT [34]. It may therefore be advisable to treat patients with a poor prognosis/survival with SF or short course RT and patients with a good prognosis with MF RT. Spinal cord compression is a medical emergency that calls

for urgent evaluation and treatment since neurological recovery is probable only if compression is managed within 24-48 hours from the onset of neurological symptoms [48]. Patients are generally treated with either de-compressive surgery or RT or a combination of both. Surgery is usually preferred for younger patients with a good performance status, a single site of cord compression and spinal instability [49]. Ambulation prior to treatment is the most important factor for response to therapy [50]. In the study by Hill *et al.*, 96% of patients who were ambulant prior to therapy maintained their ability to walk after treatment, whereas only 45% of those who were unable to walk before treatment regained ambulation [50]. The median survival of ambulatory patients is 7 months and only 1.5 months for non-ambulatory patients [51].

SF and MF RT have shown to be equally effective for the management of metastatic spinal cord compression [52]. Overall response rate (improvement or stabilization) was reported to be about 85%. However, recurrences are more common after SF and short-course MF RT, as compared to long-course MF RT [52]. This was evident in both prospective and retrospective studies [53, 54]. It is therefore recommended to administer long-course MF RT to patients with a good prognosis/survival and reserve short-course SF RT for patients with an unfavorable prognosis/survival.

CONCLUSION

RT is an established mode of treatment for metastatic bone disease that is both effective and safe. It leads to considerable pain relief, with large meta-analyses reporting equal effectiveness between SF and MF RT. The re-irradiation rates after SF RT are significantly higher than after MF RT. Re-irradiation of metastatic skeletal disease is effective and well-tolerated, resulting in similar response rates as to those achieved with primary irradiation of a metastatic site. Additionally, no difference has been reported in the rates of pathological fractures after SF or MF RT in the most recent and larger meta-analyses, by Chow E *et al.* [22]. Last but not least, in the event of pathological fractures, RT is usually administered after surgical stabilization, whereas for cord compression either SF or MF RT may be administered as soon as possible for patients who are not candidates for surgery.

Conflict of interest statement

The authors declare no conflict of interest.

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Bisphosphonates: Future perspectives and anti-tumor activity in malignant diseases

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ABSTRACT

Bone metastases secondary to advanced cancer represent a major clinical problem. Complications of bone metastases include pain, pathological fractures, and spinal cord compression, which lead to significant impairment of patients' quality of life. Treating skeletal metastases from solid tumors involves a multidisciplinary approach aimed primarily at palliating symptoms. Palliative therapies include radiation to bone, surgery, analgesics, and, over the past decade, bisphosphonate administration which has been used in the treatment of hypercalcemia, as well as in reducing the skeletal-related complications of bone metastases. Recent *in vitro* and *in vivo* evidence suggests that bisphosphonates may also exert direct anti-tumor activity by inducing apoptosis, inhibiting angiogenesis and invasive potential of tumor cells and indirectly reducing tumor growth via immunomodulatory effects. In this review, we summarize the existing evidence for this anti-tumor effect of bisphosphonates in various tumor types.

Key words: bisphosphonates; anti-tumor activity; breast cancer; lung cancer; multiple myeloma.

INTRODUCTION

Bone metastases are a major source of morbidity for patients with solid tumors and can lead to diminished mobility and performance status, thereby contributing to quality of life deterioration [1]. In addition, they are the most common cause of potentially debilitating pain reported by patients with advanced cancer, since they are associated with a loss of bone structural integrity, thus increasing the risk of pathologic fractures, which usually require surgical intervention. Furthermore, pathologic fractures have been associated with increased mortality in patients with bone metastases from solid tumors [2].

The incidence of skeletal-related events (SREs) is becoming a greater concern in cancer patients, as their lives are extended by new advances in anti-neoplastic treatment. Recent studies suggest that more than half of all patients with bone metastasis from solid tumors experience at least one SRE during their lifetime, and approximately 25% of patients experience at least two SREs [3, 4]. In addition, SREs are associated with increases in healthcare costs. An economic analysis in the United States reported that the cost of treating patients who had experienced an SRE was approximately \$12,000 per lung cancer patient in 2002

[4]. Similarly, economic analyses in Europe in 2009 revealed SRE-related treatment costs ranging between €4,400-7,200 beyond the standard costs of anticancer therapies for patients with bone metastases [5].

Therefore, bone metastases continue to represent a substantial clinical and health-economic problem.

CANCER-BONE INTERACTIONS

Bone undergoes constant remodeling regulated by the osteoblasts and osteoclasts [6]. Cancer metastasis to the bones involves a complex cascade of events that disrupts bone homeostasis and potentially stimulates cancer cell proliferation [6, 7]. In addition, bone marrow may provide a sanctuary site for disseminated cancer cells (or micrometastases), allowing them to remain quiescent yet viable over prolonged periods of time [8].

In the bone marrow niche, cell-cell contacts through integrins and exposure to cytokines collectively promote drug resistance and inhibit proapoptotic signaling [8]. As a consequence, cancer cells in the bone marrow can evade anticancer therapy and survive without proliferating until they encounter conditions that promote development of overt metastases.

Table 1.
Mechanisms of bone destruction by the tumor.

- Tumor cells release growth factors and cytokines (PTHrP, IL-6, IL-8, PGE₂, TNF-α, CSF-1)
- Osteoclasts are stimulated for bone resorption
- Peptides (BMP, PDGF, FGFs, IGFs, TGF-β) are released by bone resorption
- Tumor cell proliferation is stimulated
- Vicious cycle is repeated and perpetuated

Table 2.
Effects of bisphosphonates on bones.

- Decrease activity of osteoclasts
- Reduced release of peptides (BMP, PDGF, FGFs, IGFs, TGF-β)
- Slowed tumor cell growth
- Reduced production of PTHrP, IL-6, IL-8, PGE₂, TNF-α, CSF-1
- Decreased bone resorption

Table 3.
Anti-tumor activities of zoledronic acid.

- Inhibition of angiogenesis
- Inhibition of invasion and adhesion
- Induction of tumor cell apoptosis
- Inhibition of tumor cell proliferation
- Synergistic antitumor activity with cytotoxic drugs

ses. In Paget’s “seed and soil” hypothesis, the bone micro-environment serves as a fertile “soil” in which cancer cell “seeds” may grow [9]. After circulating tumor cells lodge in the bone, they are stimulated by growth factors that are released into the bone microenvironment from the matrix by osteoclast activity. Many tumor cells also secrete factors that increase osteoclast-mediated osteolysis, resulting in further release of growth factors from the bone matrix. Some tumors secrete factors that stimulate osteoblasts, increasing their production of new bone matrix. Osteolytic and osteoblastic lesions release growth factors that can stimulate tumor growth and are associated with bone health deterioration, leading to a vicious cycle of tumor growth and bone destruction [10] (Table 1).

BISPHOSPHONATES: GENERATIONS AND MECHANISM OF ACTION

Multiple generations of bisphosphonates have been developed, each with different potency for inhibiting bone resorption. Non-nitrogen containing bisphosphonates (e.g. clodronate) function as weak-affinity competitors for phosphorylation reactions, thereby inhibiting osteoclast activity. Early generation nitrogen-containing bisphosphonates (e.g. pamidronate, alendronate and ibandronate) are high-affinity inhibitors of farnesyl diphosphate synthase, a key enzyme in the mevalonate pathway of protein prenylation [6]. Recent generation, high-potency bisphosphonates (e.g. risedronate and zoledronic acid) can also affect other steps in bone metabolism including inhibition of osteoclast maturation and recruitment to sites of bone remodeling and induction of apoptosis in osteoclasts (Table 2). Of the new generation agents that are approved for clinical use, zoledronic acid (ZOMETA; Novartis Pharmaceuticals Corporation) contains two nitrogen atoms in an imidazole ring, and has the highest activity for the cellular target enzyme [11]. Zoledronic acid has demonstrated clinical utility in managing malignant bone disease from a variety of solid tumors and multiple myeloma, and has received international regulatory approval for use in these clinical settings [12, 13, 14].

In addition to the established benefits of bisphosphonate therapy, there is a strong rationale from preclinical data and recent clinical data to support the hypothesis that bisphosphonates may reduce the risk of developing metastases within or even outside the bones.

In clinical trials of the first generation oral bisphosphonate clodronate, there was a significant reduction in metastasis to bone among patients with high-risk non-metastatic breast cancer who were treated with daily clodronate compared with placebo, but the results were inconsistent [15-18]. Nonetheless, the more active new generation bisphosphonates may provide additional benefits [19]. Indeed, in pre-clinical assays and model systems, it has been shown that recent generation bisphosphonates can inhibit multiple steps necessary for bone metastasis and exert anticancer effects *in vitro*.

TRANSLATIONAL EVIDENCE FOR THE ANTICANCER ACTIVITY OF BISPHOSPHONATES

a. Inhibiting new blood vessel formation: Bisphosphonates can inhibit angiogenesis by tumor cells -an important step in tumor progression [20-22]. Systemic zoledronic acid treatment inhibited basic fibroblast factor (bFGF)-induced angiogenesis in a mouse model system [21] and led to reductions in circulating levels of angiogenic factors in the pilot trials of zoledronic acid in the clinic [22-24].

b. Inhibiting invasion and attachment: Zoledronic acid has been shown to reduce migration and invasion in human breast cancer cell lines and thus impede the formation of visceral and bone metastases in a mouse model system [25]. Relevant concentrations of zoledronic acid also reduced the motility of a variety of human cancer cell lines and have been reported to block migration of highly motile NSCLC cell lines *in vitro* [26, 27].

c. Inhibiting tumor proliferation in the bone microenvironment: Bisphosphonate treatment can lower the levels of growth factors such as transforming growth factor beta (TGF- β); insulin-like growth factors (IGFs); and fibroblast growth factors (FGFs) which are normally released from the bone matrix, thus rendering the bone microenvironment less conducive to the development of metastatic foci [28].

d. Immunomodulatory effects: In approximately one third of patients, flu-like symptoms occur after receiving intravenous bisphosphonates, which has been termed as the acute-phase reaction [29]. Several studies suggest that bisphosphonates may indeed affect circulating lymphocytes and antigen-presenting cells [30-34]. Bisphosphonates have been shown to activate the $\gamma\delta$ T cells and this may result in anticancer activity contributing to the treatment benefits. It was also shown in preclinical models that treatment of human cancer cell lines with nitrogen-containing bisphosphonates caused $\gamma\delta$ T cells to initiate a cytotoxic activity resulting in lysis of the cancer cells [35, 36].

e. Direct anticancer effects: There is some preclinical data to support that bisphosphonates can inhibit the proliferation and induce apoptosis in a broad range of human cancer cell lines [37, 38]. The mechanisms and pathways behind these effects are currently unknown and it has been proposed that multiple factors may be implicated [11, 39-40]. Also, bisphosphonates have been shown to alter the course of disease progression in mouse model systems of human cancers, including breast and prostate cancer [41-44]. In addition, preclinical studies suggest that bisphosphonates may potentiate the cytotoxic effects of chemotherapy [45]. Zoledronic acid has been shown to display a dose and sequence specific synergy with doxorubicin in preclinical models of breast and prostate cancer [46-49] (Table 3).

CLINICAL RESULTS FOR PREVENTING BONE METASTASES AND IMPROVING SURVIVAL

Clinical evidence from breast cancer

A large amount of efficacy data has emerged over the past years from randomized phase III trials investigating the anticancer potential of bisphosphonates, especially in the breast cancer setting.

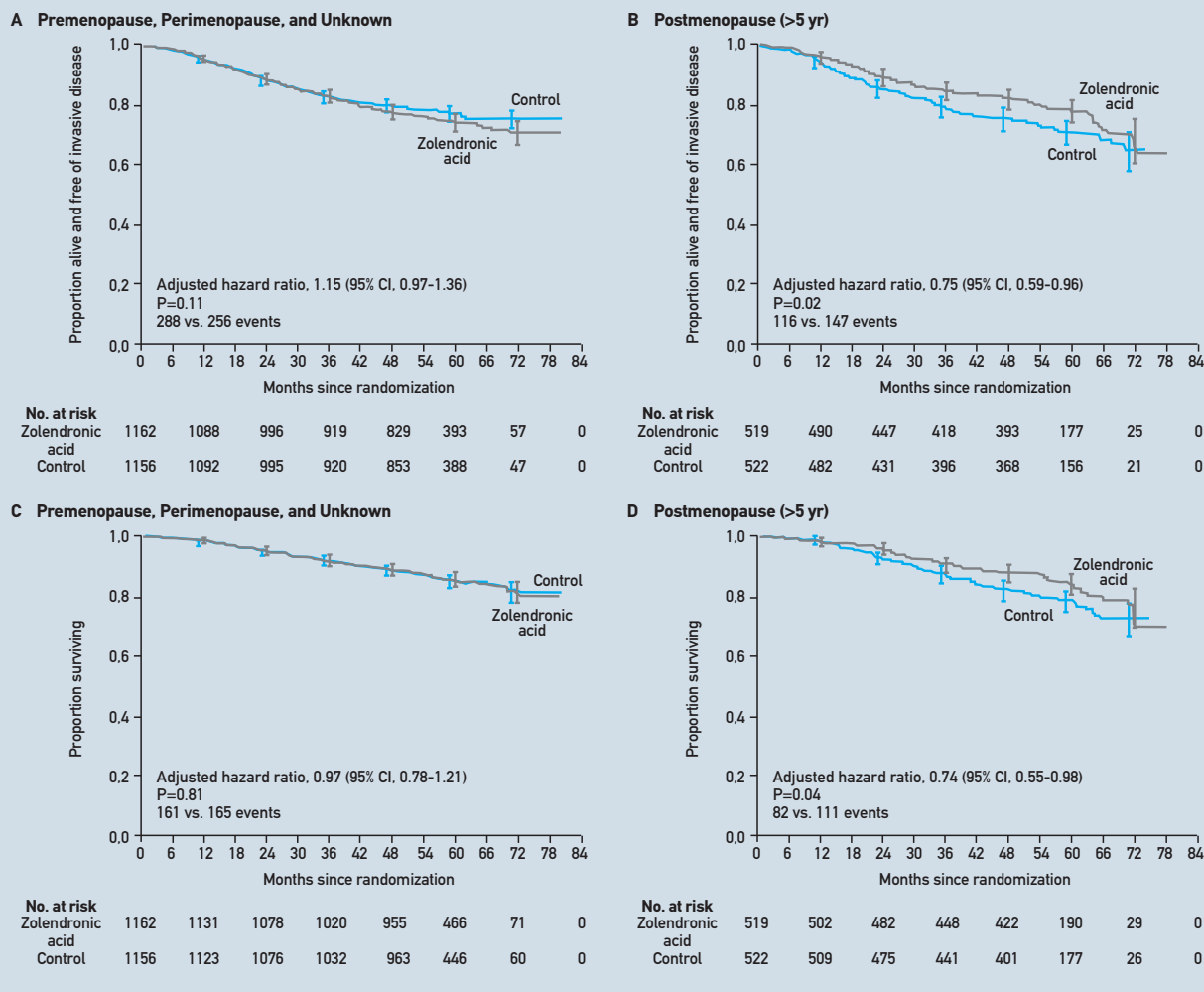
ABCSG-12 was a randomized open-label phase III, four arm trial comparing tamoxifen (20 mg/day p.o.) and goserelin (3.6 mg every 28 days sc) with or without zoledronic acid (ZOMETA; 4 mg IV every 6 months) versus anastrozole (1 mg/day p.o.) and goserelin with or without zoledronic acid for three years in premenopausal women with endocrine responsive breast cancer. Adding zoledronic acid twice yearly to adjuvant endocrine therapy, significantly improved disease-free survival (DFS) and reduced disease recurrence within and outside the bones [50]. Longer follow-up of the ABCSG-12 trial confirmed the durability of the DFS benefit, and showed a strong trend toward improved overall survival (OS) [50-51].

The ZO-FAST trial evaluated the efficacy and safety of zoledronic acid in preventing aromatase inhibitors-associated bone loss in postmenopausal women with early breast cancer who were receiving adjuvant letrozole therapy. A total of 602 postmenopausal women with hormone receptor-positive early breast cancer starting adjuvant letrozole were randomized to upfront versus delayed zoledronic acid. The delayed group received zoledronic acid when either the post-baseline bone density T-score decreased to below -2 or a clinical fracture occurred. This trial also confirmed the reduction in disease recurrence within and outside the bones with upfront versus delayed administration of zoledronic acid [52].

In another study, adding zoledronic acid to neoadjuvant chemotherapy also reduced the residual invasive tumor size, improved the rate of pathological complete response, and reduced the need for mastectomies in women with high-risk breast cancer [53]. Furthermore, in an open-label phase III study (AZURE trial), 3360 patients with early stage breast cancer were randomly assigned to receive standard adjuvant systemic therapy either with or without zoledronic acid. The zoledronic acid was administered every 3 to 4 weeks for 6 doses and then every 3 to 6 months to complete 5 years of treatment. The primary endpoint of the study was disease-free survival. After a median follow-up of 59 months, overall there was no significant between-group difference in the primary endpoint, with a rate of disease-free survival of 77% in each group. However, in a subgroup analysis limited to postmenopausal women, the addition of zoledronic acid conferred a significant benefit in both DFS and OS. Despite these promising results for postmenopausal women, the findings of the AZURE study do not support the routine use of zoledronic acid in the adjuvant management of breast cancer [54] (Figure 1). There are a number of ongoing studies investigating the anti-neoplastic

Figure 1.

Results of the AZURE trial on DFS (A, B) and OS (C, D) in premenopausal (A, C) and postmenopausal (B, D) women with early breast cancer.



effect of bisphosphonates in breast cancer which may help to clarify their clinical utility [55]. In a recent meta-analysis that was presented by Valachis *et al.* in the last ECCO congress, 8,469 patients from twelve randomized trials were included. The use of zoledronic acid in the adjuvant treatment of early breast cancer resulted in a significant improvement of OS in 6,414 patients from 5 studies (HR=0.82; $p=0.009$) but regarding DFS, no significant difference was found [56].

Clinical evidence from other cancer types

i) Lung cancer

There is an expanding database of preclinical evidence that bisphosphonates, especially zoledronic acid, can inhibit the proliferation and induce apoptosis in cell lines derived from both small-cell and non-small-cell human lung cancer [57, 58].

In a recent study, 144 patients with lung cancer and bone metastases were treated with chemotherapy plus zoledronic acid if they had bone pain or with chemotherapy alone in case of asymptomatic bone disease. Median survival was significantly longer in patients receiving zoledronic acid (578 days vs. 384 days; $p<0.001$) [59]. Similar results were also obtained for time to disease progression (265 days vs. 150 days, $p<0.001$) [59]. Moreover, the study supported a greater benefit with longer treatment since the number of cycles of zoledronic acid positively correlated with time to disease progression [59]. In another report zoledronic acid was associated with a 39% reduction in the risk of death and a 61% reduction in the risk of disease progression ($p<0.001$ for both), as well as two-fold higher rate of tumor response at the primary site and a 38% lower rate of progressive disease in the skeleton compared with chemotherapy alone [60].

However, after the results of a phase II study which showed

no additional benefits in disease progression and survival by adding zoledronic acid to docetaxel and carboplatin regimen in patients with stages IIIB and IV NSCLC without bone metastases, it would appear that the potential anticancer benefits from zoledronic acid in the lung cancer setting may depend on the presence of skeletal disease [61].

A number of clinical trials studying the anticancer effect of zoledronic acid in lung cancer are underway and their results are expected to answer this question.

ii) Urinary bladder cancer

It has been estimated that 12-35% of patients with bladder cancer develop bone metastases during the course of the disease [62]. In a study of patients with bone metastases from bladder cancer, zoledronic acid treatment not only prevented SREs, but also significantly improved OS [63].

iii) Other solid tumors

Mystakidou *et al.* reported that monthly zoledronic acid delayed the onset of bone metastases in patients with advanced solid tumors who had no evidence of skeletal disease at the time of randomization [64].

iv) Multiple myeloma

By blocking growth factor release from the bone matrix, bisphosphonates can indirectly impede myeloma growth [65]. The antimyeloma effect was independent of the effect of zoledronic acid on the bone, but dependent on inhibition of protein prenylation, a mechanism of action not shared by non-nitrogen-containing bisphosphonates such as clodronic acid (clodronate) [66].

Although differences in overall survival with bisphosphonates were not significant in the total population of patients of large randomized controlled trials in multiple myeloma, bisphosphonates seemed to improve overall survival in subsets of patients in some phase III studies [67-70]. For example, in the UK Medical Research Council (MRC) trial in patients with bone lesions from multiple myeloma ($n=535$), overall survival was similar between clodronic acid and placebo in the whole population, but clodronic acid significantly improved overall survival over placebo in the subset of patients who had no fractures before study entry [69].

Despite strong consensus that bisphosphonate therapy should be given to symptomatic patients with multiple myeloma, no optimal regimen has emerged [71, 72].

Recently, in an ongoing trial in patients with multiple myeloma, zoledronic acid not only prevented SREs but also improved overall survival [73].

SIDE-EFFECTS OF BISPHOSPHONATES

The use of amino-bisphosphonates in the management of cancer-related bone involvement and hypercalcemia remains a cornerstone in malignant disease management. However, being aware of short- and long-term side-effects is still crucial.

Patients receiving bisphosphonates may develop osteone-

crosis of the jaw, with an estimated incidence of 1.5% for patients treated for 4 to 12 months, and 7.7% for treatments lasting between 37 and 48 months [74]. The etiology of osteonecrosis of the jaw has not yet been defined; therefore, the strategy for its prevention or treatment remains empirical. It is advised for patients receiving dental evaluation and preventive dental treatments before starting treatment with bisphosphonates. During bisphosphonate treatment, undergoing invasive dental procedures is not recommended. Osteonecrosis of the jaw is managed conservatively with prolonged use of antibiotics and mouth care.

Effective inhibition of osteoclast activity can result in hypocalcemia and hypophosphatemia. However, most patients do not become hypocalcemic because of compensatory mechanisms, most importantly, increased secretion of parathyroid hormone.

Patients are at a higher risk of electrolyte imbalance if they have renal insufficiency or decreased compensatory mechanisms (e.g. prior parathyroidectomy, low vitamin D levels, hypomagnesemic hypoparathyroidism, renal failure) [75-76].

Renal impairment has also been observed with zoledronic acid. Patients treated with zoledronic acid develop rises in creatinine often without proteinuria. However, with long-term treatment, patients may develop albuminuria that improves upon discontinuation of the drug [77]. For patients receiving IV bisphosphonates, renal toxicity may be minimized by observing recommended infusion times, optimizing hydration prior to bisphosphonate administration and avoiding concurrent nephrotoxic medications. The US FDA-approved package insert for zoledronic acid recommends a lower initial dose of zoledronic acid (ranging from 3 to 3.5 mg) in patients with preexisting renal impairment ($\text{CrCl} < 60 \text{ mL/min}$ but $\geq 30 \text{ mL/min}$).

In about 15 to 30 percent of patients, IV zoledronic acid and pamidronate cause transient fever and an influenza-like syndrome in patients naive to these drugs. The syndrome is typical of an acute phase response characterized by fever, chills, bone pain, headache, myalgias, and arthralgias and is related to transiently increased cytokine production. These symptoms are usually mild and self-limiting, and most often do not occur with subsequent dosing of these drugs. This syndrome may be treated with acetaminophen or NSAIDs [78-79].

CONCLUSIONS

Survival prospects after metastases to the bones vary greatly depending on tumor type and sites of involvement. Mean survival ranges from a low of six months for those with lung carcinoma, to several years for those with bone metastases from prostate, thyroid or breast carcinoma. With prolongation of survival in such diseases due to the development of more effective therapies, the main challenge is to improve the quality of the patient's remaining life. Over the past years, bisphosphonates have been used successfully

in the treatment of hypercalcemia and the reduction of skeletal-related complications of bone metastases.

Recent *in vitro* and *in vivo* evidence suggests that zoledronic acid may also have direct anti-tumor activity. The increasing understanding of the molecular mechanisms through which bisphosphonates act on tumor and endothelial cells led to the design of clinical trials intended to investigate whether the anti-tumor activity of bisphosphonates could be realized in the clinical setting. Based on these studies, bisphosphonates appear to exert anti-tumor activity within a broad range

of tumors and may be used for the treatment of cancer types that are likely to metastasize to the bones.

Therefore, it is likely that multiple factors, as already mentioned, may contribute to bisphosphonate efficacy, and their clinical utility may expand into earlier disease stages for several solid tumor types in the future.

Disclosure

Dr. D. Mavroudis has received honoraria for meet the expert meetings from Novartis.

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Low-grade cribriform cystadenocarcinoma of the parotid gland

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ABSTRACT

Low-grade cribriform cystadenocarcinoma (LGCCC) is a very rare tumor of the parotid gland with favorable prognosis. This is a case report of a 77-year-old male patient, who presented with a painless mass in the right preauricular area. Computed tomography revealed a 3x2cm inhomogeneous mass in the right parotid gland with moderate inhomogeneous enhancement and areas of low density (cysts) after intravenous contrast administration. Fine needle aspiration (FNA) cytology was consistent with benign salivary gland neoplasm suggesting an adenolymphoma. A few months later the patient underwent a right superficial parotidectomy. The final diagnosis was LGCCC. The patient did not receive any adjuvant treatment.

Key words: low-grade cribriform cystadenocarcinoma; parotid gland; salivary glands.

INTRODUCTION

Most patients with a parotid gland tumor present with a painless mass or swelling in the preauricular area. Differential diagnosis includes salivary cysts; salivary gland stones; hemangioma; lymphoepithelial cysts; chronic sclerosing sialadenitis; lymphadenopathy from infectious disease; inflammation of the parotid gland; lymphoma; metastases from other primary tumors; and primary malignant disease. Salivary gland tumors vary considerably in their histological patterns and behavior. Table 1 lists the benign and malignant tumors of the salivary glands according to the 2005 WHO histological classification [1].

LGCCC is an infrequent tumor of the salivary glands with a favorable prognosis that is recognized as a variant of cystadenocarcinoma by the 2005 World Health Organization classification [1, 2]. In medical literature there have been reported cases describing these tumors with various terms like "low-grade cribriform cystadenocarcinoma", "low-grade salivary duct carcinoma", "intraductal carcinoma" and "carcinoma in situ" [3]. This tumor mainly arises from the parotid gland and does not metastasize to the lymph nodes. Preoperative computed tomography and magnetic resonance imaging usually reveal a well-defined polycystic mass without evidence of invasion of the surrounding tissues. These tumors have a very good prognosis after radical surgical excision. In this report, we pre-

sent the case of a LGCCC of the parotid gland, the first reported in Cyprus.

CASE PRESENTATION

We report the case of a 77-year-old Cypriot male who noticed a painless mass in the right preauricular area. He mentioned the excision of a lump in the same region five years ago, diagnosed as adenolymphoma. Adenolymphoma is a benign glandular tumor usually arising in the parotid gland and composed of two rows of eosinophilic epithelial cells with a lymphoid stroma, also called "papillary cystadenoma lymphomatosum" and "Warthin's tumor". Preoperative fine needle aspiration biopsy, performed in February 2011, showed some lymphocytes, a few macrophages and aggregation of normal epithelial cells exhibiting some signs of oxyphilic changes. The appearance was consistent with benign salivary gland neoplasm with evidence more suggestive of adenolymphoma. A computed tomography revealed a 3x2cm multicystic tumor in the right parotid gland with moderate inhomogeneous enhancement and areas of low density after intravenous contrast administration (Figures 1 and 2). A few months later the patient underwent a right superficial parotidectomy with facial nerve preservation. Microscopically, the neoplasm was composed of widely dilated cystic structures lined by epithelial cells, which were flat in some areas

Figure 1.
Pre-contrast axial CT scan shows an inhomogeneous 3x2cm mass in the right parotid gland (arrow).

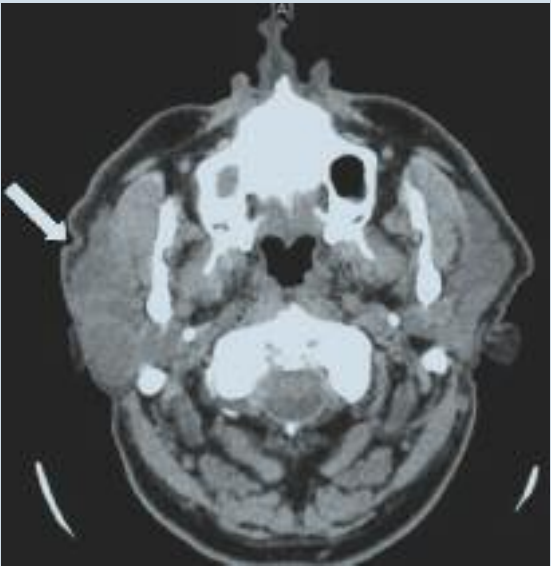


Figure 2.
After intravenous contrast administration, the mass presents moderate inhomogeneous enhancement with areas of low density (cystic).

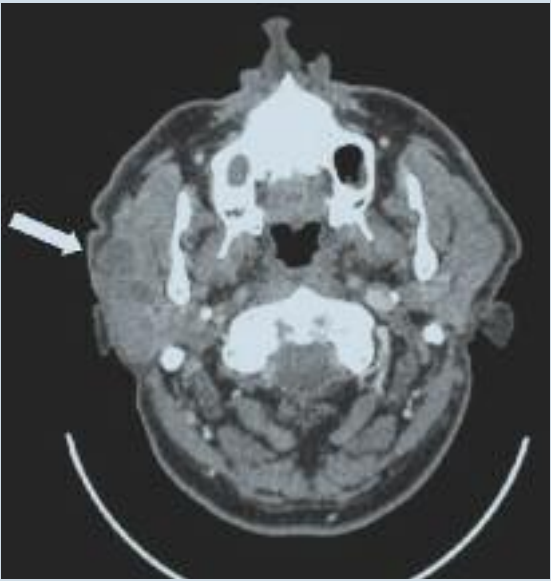


Table 1.
WHO histological classification of tumors of the salivary glands.

Malignant epithelial tumors	Benign epithelial tumors
Acinic cell carcinoma	Pleomorphic adenoma
Mucoepidermoid carcinoma	Myoepithelioma
Adenoid cystic carcinoma	Basal cell adenoma
Polymorphous low-grade adenocarcinoma	Warthin's tumor
Epithelial-myoepithelial carcinoma	Oncocytoma
Clear cell carcinoma, not otherwise specified	Canalicular adenoma
Basal cell adenocarcinoma	Sebaceous adenoma
Sebaceous carcinoma	Lymphadenoma
Sebaceous lymphadenocarcinoma	Sebaceous
Cystadenocarcinoma	Non-sebaceous
Low-grade cribriform cystadenocarcinoma	Ductal papillomas
Mucinous adenocarcinoma	Inverted ductal papilloma
Oncocytic carcinoma	Intraductal papilloma
Salivary duct carcinoma	Sialadenoma papilliferum
Adenocarcinoma, not otherwise specified	Cystadenoma
Myoepithelial carcinoma	Soft tissue tumors
Carcinoma ex pleomorphic adenoma	Hemangioma
Carcinosarcoma	Hematolymphoid tumors
Metastasizing pleomorphic adenoma	Hodgkin lymphoma
Squamous cell carcinoma	Diffuse large B-cell lymphoma
Small cell carcinoma	Extranodal marginal zone B-cell lymphoma
Large cell carcinoma	
Lymphoepithelial carcinoma	
Sialoblastoma	

and showed a proliferative cribriform pattern in several areas. The neoplastic cells were flat cuboidal, had abundant eosinophilic cytoplasm and vesicular nuclei with prominent nucleoli and a moderate degree of pleomorphism. Scattered mitotic figures were present. Some of the cystic lesions had evidence of peripheral invasion associated with desmoplasia. The final diagnosis was LGCCC of the parotid gland. In view of the rarity of the tumor we asked for a review of the histopathology specimen, which confirmed our diagnosis. The patient has no facial nerve paralysis after the superficial parotidectomy and did not receive any adjuvant treatment. He remains under observation.

DISCUSSION

LGCCC is a very rare tumor of the salivary glands and it was first reported by Delgado *et al.* in 1996 [1, 4, 5]. The World Health Organization recommended the name LGCCC to prescribe this variant of salivary duct carcinomas [2]. These tumors usually arise from the parotid gland. The incidence of LGCCC of the parotid gland is estimated to be less than 1%.

Most patients with LGCCC are elderly and present with a painless mass or swelling of the preauricular area. Neurological signs or symptoms, such as facial nerve paralysis,

are absent. It concerns a slowly growing tumor which does not metastasize to the regional lymph nodes. Computed tomography or magnetic resonance imaging of the parotid gland are necessary for the assessment of these lesions and mainly reveal a multicystic mass with well-defined margins. Radical surgical excision with total parotidectomy is the cornerstone treatment for LGCCC.

Conflict of interest statement

The authors declare no conflict of interest

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Erratum

In the Letter to the Editor entitled: "On the role of clinical practice guidelines in oncology", written by Dr Evangelia Razis and published in the June 2012 issue (FCO 2012 Jun; Vol. 3, Issue 2, p. 66), first column, fourth row, it reads "developments" whereas the correct word is "development".



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Παράρτημα 2: Αναπόσπαστες ενέργειες σε ασθενείς με πρόωγο έμφραγμα που έλαβαν YERVOY 3 mg/kg (n = 767)*	
Δυσμειώσεις και παρασυστώσεις	
Όχι συχνές	σηψαιμία ^a , οπτική καταπληξία ^a , μηνιγγίτιδα, γαστρεντερίτιδα, εκκολπωματίτιδα, ουρολοίμωξη, λοίμωξη του ανώτερου αναπνευστικού συστήματος, λοίμωξη του κατώτερου αναπνευστικού συστήματος
Συχνές	πόνος από όγκο
Όχι συχνές	παρανεοπλασματικό σύνδρομο
Διαταραχές του αιμοποιητικού και του λεμφικού συστήματος	
Συχνές	αναιμία, λειμφοπενία
Όχι συχνές	αιμολυτική αναιμία ^a , θρομβοπενία, ηωσινοφιλία, ουδετεροπενία
Διαταραχές του ανοσοποιητικού συστήματος	
Όχι συχνές	υπερευαισθησία
Διαταραχές του ενδοκρινικού συστήματος	
Συχνές	υποθυροειδισμός (συμπεριλαμβάνεται η υποφωσφίτιδα) ^a , υποθυρεοειδισμός ^a
Όχι συχνές	επινεφριδιακή ανεπάρκεια ^a , υπερθυρεοειδισμός ^a , υπογοναδιασμός
Διαταραχές του μεταβολισμού και της θρέψης	
Πολύ συχνές	μειωμένη όρεξη
Συχνές	αφυδάτωση, υποκαλιμία
Όχι συχνές	υπονατρίαιμία, αλκαλώση, υποφωσφοραμία, σύνδρομο λύσης όγκου
Ψυχιατρικές διαταραχές	
Συχνές	συγκυτική κατάσταση
Όχι συχνές	μεταβολές της νοσητικής κατάστασης, κατάθλιψη, μειωμένη γενετική ορμή
Διαταραχές του νευρικού συστήματος	
Συχνές	περιφερική αισθητική νευροπάθεια, ζάλη, κεφαλαλγία, λήθαργος
Όχι συχνές	σύνδρομο Guillain-Barré ^a , συγκοπή, κρανική νευροπάθεια, εγκεφαλικό οίδημα, περιφερική νευροπάθεια, στασία, τρόμος, μυοκλονός, δυσαρθρία
Οφθαλμικές διαταραχές	
Όχι συχνές	θαμπή όραση, πόνος του οφθαλμού
Συχνές	ραγοειδίτιδα, αμφογραφία του υαλοειδούς σώματος, ιρίτιδα ^a , μειωμένη οπτική οξύτητα, αίσθημα ξένου σώματος στους οφθαλμούς, επιπεφυκίτιδα
Καρδιακές διαταραχές	
Όχι συχνές	αρρυθμία, κοιλιακή μαρμαρυγή
Αγγειακές διαταραχές	
Συχνές	ύπταση, έξαψη
Όχι συχνές	αγγειίτιδα, αγγειοπάθεια ^a , περιφερική ισχαιμία, ορθοστατική υπόταση
Διαταραχές του αναπνευστικού συστήματος, του θώρακα και του μεσοθωρακίου	
Συχνές	δύσπνοια, βήχας
Όχι συχνές	αναπνευστική ανεπάρκεια, σύνδρομο σέξις αναπνευστικής δυσχέρειας ^a , δύσπνοια πνεύμονα, πνευμονικό οίδημα, πνευμονίτιδα, αλλεργική ρινίτιδα
Διαταραχές του γαστρεντερικού	
Πολύ συχνές	διάρροια ^a , έμετος, ναυτία
Συχνές	γαστρεντερική αμφογραφία, καλιτίδα ^a , δυσκοιλιότητα, γαστροεσφαγική παλινδρόμηση, κοιλιακό άλγος
Όχι συχνές	διάτρηξη του γαστρεντερικού σωλήνα ^a , διάτρηξη του παχέος εντέρου ^a , διάτρηξη του εντέρου ^a , περιτονίτιδα ^a , παγκρεατίτιδα, εντεροκολίτιδα, γαστρο-έλκος, έλκος του παχέος εντέρου, οισοφαγίτιδα, ειλεός ^a
Διαταραχές του ήπατος και του χοληφόρου	
Συχνές	μη φυσιολογική ηπατική λειτουργία
Όχι συχνές	ηπατική ανεπάρκεια ^a , ηπατίτιδα, ηπατομεγαλία, ίκτερος
Διαταραχές του δέρματος και του υποδόριου ιστού	
Πολύ συχνές	εξάνθημα ^a , κνησμός ^a
Συχνές	δερματίτιδα, ερύθημα, λεύκη, κνίδωση, αλωπεκία, κυνερνική ιδρώτης, έλκρωση
Όχι συχνές	τοξική επιδερμική νεκρόλυση ^a , λευκοκυτταροαπλαστική αγγειίτιδα, αποβολή του δέρματος
Διαταραχές του μυοσκελετικού συστήματος και του συνδετικού ιστού	
Συχνές	αρθραλγία, μυαλγία, μυοσκελετικός πόνος, μυϊκή σπασμοί
Όχι συχνές	ρευματική πολυμυαλγία, αρθρίτιδα
Διαταραχές των νεφρών και των ουροφόρων οδών	
Όχι συχνές	νεφρική ανεπάρκεια ^a , σπειροματωσηφρίτιδα ^a , νεφρική σωληνιαρική 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 ^a , σχετιζόμενη με την έγχυση αντίδραση
Παράπλευρες εξετάσεις	
Συχνές	αυξημένη αμινοτρανσφεράση της αλανίνης ^a , αυξημένη ασπαρτική αμινοτρανσφεράση ^a , αυξημένη χολερυθρίνη αίματος, μειωμένο οσματικό βάρος
Όχι συχνές	μη φυσιολογικές δοκιμασίες ηπατικής λειτουργίας, αυξημένη κρεατινίνη αίματος, αυξημένη θυρεοειδοτρόπος ορμόνη αίματος, μειωμένη κορτιζόλη αίματος, μειωμένη κορτικοτροπίνη αίματος, αυξημένη λιπάζη ^a , αυξημένη αμυλάση αίματος ^a , μειωμένη τεστοστερόνη αίματος

α) Οι συστάσεις βασίζονται σε αντικειμενικά στοιχεία από 9 κλινικές δοκιμές που εξέτασαν το TENVY 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.


Αναφορικά με προσαρμογές μεταξύ εκτός των συμπεριλαμβανόμενων κλινικών ομάδων στο μελέτημα.

Προσέτινες ανεπιθύμητες ενέργειες που δεν αναφέρονται στον Πίνακα 2 έχουν αναφερθεί σε ασθενείς που έλαβαν άλλες δόσεις (είτε < ή > 3 mg/kg) YERYOY σε κλινικές δοκιμές μελανώματος. Αυτά οι πρόσθετες ανεπιθύμητες παρουσιάζονται όπως εξής:

• αντιστόμια < 1%: μηνιγγισμός, μακροδόχμος, καρδιοαναπνευστική, απότονη φρίση, πολυμορφικό ερύθημα, αυθαιγόνο νεύρωμα, σπασμωδικά αμείβοτα, μολυσμένα βράδια, απότονη θρομβοκυτταρική ανοπησία, υπερουρελαική, δευτερευόντως ανεπάρκεια του φλοιού των επινεφριών, υποαρθροελαϊκή, θυρεοειδίτις, εποχιοδερμία, βλεφαρίτιδα, οίδημα του ωχρόθυμου, ακληρίτιδα, τροφαντική αρτηρίτιδα, νευρίτιση Raynaud, πικρίαση, σύνδρομο χρονοπολυαρθροελαϊκής ευρυδοστασιακής ψύξης, αιματορραγία, πρωτεϊνωσία, μειωμένη θυρεοειδοειδική ορμονία αίματος, μειωμένη θυροξίνη, λευκοπενία και πυλοκυτταραιμία.

Παραγωγή επιλεγμένων ανεπιθύμητων ενεργειών: Με εξέταση της περιπτώσεως στις οποίες εμφανίστηκε, τα δεδομένα για τις παρακάτω επιλεγμένες ανεπιθύμητες ενέργειες βασίζονται σε ασθενείς που έλαβαν μονοθεραπεία με YERYOY 3 mg/kg (n = 131) ή YERYOY 3 mg/kg σε συνδυασμό με gp100 (n = 380) με μέση ηλικία 39,7 ετών, 67% ήταν άνδρες και 33% γυναίκες.

Οι καταγεγραμμένες γράμμες για την αντιμετώπιση αυτών των ανεπιθύμητων ενεργειών περιγράφονται στην παράγραφο 4.4. Γαστρεντερικές ανησυχίες που συνδέονται με το ανοσοποιητικό. Το YERYOY γίνεται με σοβαρές γαστρεντερικές ανησυχίες που συνδέονται με το ανοσοποιητικό. Η βακτηριακή περικαρδιά λόγω διάτρησης του γαστρεντερικού σωλήνα είναι ανεπιθύμητη σε < 1% των ασθενών που έλαβαν YERYOY 3 mg/kg σε συνδυασμό με gp100. Στην ομάδα με μονοθεραπεία με YERYOY 3 mg/kg, ανεπιθύμητη διάρροια και κοιλιακό σπασμωδικό βαρύτητας στο 27% και το 8% αντίστοιχα. Η αντιστόμια σοβαρή (Βαθμότητα 3 ή 4) διάρροια και σοβαρή (Βαθμότητα 3 ή 4) κοιλίτις ήταν 5% για τα κατέβα. Ο διάμετρο χρόνος έως την εκδήλωση σοβαρών ή βαθύνουσας (Βαθμότητα 3 έως 5) γαστρεντερικών αντιδράσεων που συνδέονται με το ανοσοποιητικό ήταν 8 εβδομάδες (ένρος 0,6 έως 13 εβδομάδες) από την αρχή της θεραπείας. Με καταγεγραμμένες γράμμες για την αντιμετώπιση σχετιζόμενες με το πρωτόκολλο η υποχώρηση παρουσιάστηκε στις περισσότερες περιπτώσεις (80%), με διάμετρο χρόνο από την εκδήλωση έως την υποχώρηση (μέσος όρος 6,6 εβδομάδες). Σε κλινικές δοκιμές η κοιλίτις που συνδέεται με το ανοσοποιητικό συστήματος με στοιχεία φλεγμονής του βλεννογνώμη, με ή χωρίς εξέλκωση και λεμφοκυτταρική και ουδετεροφιλική διήθηση. Ηπατοκυτταρική που συνδέεται με το ανοσοποιητικό. Το YERYOY γίνεται σε σοβαρή ηπατοκυτταρική που συνδέεται με το ανοσοποιητικό. Βαθύνουσας πρακτική ανεπάρκεια είναι ανεπιθύμητη σε < 1% των ασθενών που έλαβαν μονοθεραπεία με YERYOY 3 mg/kg. Ακλειρσία της AST και της ALT αποδοτικότητα βαρύτητας αναφέρθηκε στο 1% και το 2% των ασθενών αντίστοιχα. Δεν υπήρχαν αναφορές σε σοβαρή (Βαθμότητα 3 ή 4) αύξηση της AST ή της ALT. Ο χρόνος έως την εκδήλωση μετριας έως σοβαρής ή βαθύνουσας (Βαθμότητα 2 έως 5) ηπατοκυτταρικής που συνδέεται με το ανοσοποιητικό κυμαίνεται από 0,7 έως 3,9 εβδομάδες από την αρχή της θεραπείας. Με καταγεγραμμένες γράμμες για την αντιμετώπιση σχετιζόμενες με το πρωτόκολλο, ο χρόνος έως την υποχώρηση κυμαίνεται από 0,7 έως 2,9 εβδομάδες. Σε κλινικές δοκιμές, πρώτος ρίπος από ασθενείς που είχαν ηπατοκυτταρική σχετιζόμενη με το ανοσοποιητικό, εμφάνιση στοιχείων άμεσης φλεγμονής (ουδετεροφιλία, λεμφοκύτταρα και μακροφάγα). Δερματικές ανεπιθύμητες ανησυχίες που συνδέονται με το ανοσοποιητικό. Το YERYOY γίνεται με σοβαρές δερματικές ανεπιθύμητες ανησυχίες που μπορεί να συνδεθούν με το ανοσοποιητικό. Βαθύνουσας τοπική επιδεικτική κεράτιση είναι ανεπιθύμητη σε < 1% των ασθενών που έλαβαν YERYOY σε συνδυασμό με gp100 (Παράγραφος 5.1). Στην ομάδα με μονοθεραπεία με YERYOY 3 mg/kg, ανεπιθύμητη εκζέματα και κνησμώδη διασκορπισμού βαρύτητας, το καθένα στο 27% των ασθενών. Εκζέματα και κνησμώδη επαγόμενο από YERYOY ήταν κυρίως ήπια (Βαθμότητα 1 ή 2) και ανταποκρινόταν σε συμπτωματική θεραπεία. Ο διάμετρο χρόνος έως την εκδήλωση μετριας έως σοβαρών ή βαθύνουσας (Βαθμότητα 2 έως 5) δερματικών ανεπιθύμητων αντιδράσεων ήταν 3 εβδομάδες από την αρχή της θεραπείας (ένρος 0,9 έως 16 εβδομάδες). Με καταγεγραμμένες γράμμες για την αντιμετώπιση σχετιζόμενες με το πρωτόκολλο, υποχώρηση παρουσιάστηκε στις περισσότερες περιπτώσεις (87%), με διάμετρο χρόνο από την εκδήλωση έως την υποχώρηση 5,5 εβδομάδες (ένρος 0,6 έως 29 εβδομάδες). Νευρολογικές ανεπιθύμητες ανησυχίες που συνδέονται με το ανοσοποιητικό. Το YERYOY γίνεται σε σοβαρές νευρολογικές ανησυχίες που συνδέονται με το ανοσοποιητικό. Βαθύνουσας σύνδρομο Guillain-Barre είναι ανεπιθύμητη σε < 1% των ασθενών που έλαβαν YERYOY 3 mg/kg σε συνδυασμό με gp100. Σπασμωδικά αμείβοτα που συνδέονται με το ανοσοποιητικό. Στην ομάδα με μονοθεραπεία με YERYOY 3 mg/kg, υποπονοούμενος απολαβή βαρύτητας αναφέρθηκε στο 4% των ασθενών. Επιδεικτική ανεπάρκεια, υπερουρελαική και υποουρελαική απολαβή βαρύτητας αναφέρθηκε το καθένα στο 2% των ασθενών. Η αντιστόμια σοβαρή (Βαθμότητα 3 ή 4) υποπονοούμενος αναφέρθηκε στο 3% των ασθενών. Δεν υπήρχαν αναφορές σε σοβαρή ή πολύ σοβαρή (Βαθμότητα 3 ή 4) επινεφριολική ανεπάρκεια, υπερουρελαική ή υποουρελαική. Ο χρόνος έως την εκδήλωση μετριας έως πολύ σοβαρής (Βαθμότητα 2 έως 4) σχετιζόμενης με το ανοσοποιητικό ενδοκρανιακής κυμαίνεται και 7 έως περίπου 20 εβδομάδες από την αρχή της θεραπείας. Ενδοκρανιακή σχετιζόμενη με το ανοσοποιητικό που παρηγορηθεί σε κλινικές δοκιμές, ήταν γενικά ελαφρώς με θεραπεία υποκατάστασης ορμονών. Άλλες ανεπιθύμητες ανησυχίες που συνδέονται με το ανοσοποιητικό. Οι παρακάτω ανεπιθύμητες ανησυχίες που πιθανολογείται ότι συνδέονται με το ανοσοποιητικό, έχουν αναφερθεί σε < 2% των ασθενών που έλαβαν μονοθεραπεία με YERYOY 3 mg/kg: ροειδοπάθεια, πρωτονιοπάθεια, αύξησή λήψης και σπειραματονεφρίτιδα. Επιπροσθέτως, ρίπος, αμυγδαλίτις, αμειβοτόνιο, απώλεια ακοής, πολυμορφική ανεπάρκεια και πνευμονία έχουν αναφερθεί σε ασθενείς που έλαβαν YERYOY 3 mg/kg σε συνδυασμό με πεπτικό αμινοξύ gp100. YERYOY 5 mg/ml ποσό διάλυμα για παρασκευή διαλύματος προς έγχυση – Συσκευασία: 1 Φιάλιδο (ανάλογο) x 10 ml με ενδεικτική Νοσοκομειακή τιμή € 3.887,16, και ενδεικτική Χονδρική τιμή € 1.468,00. YERYOY 5 mg/ml ποσό διάλυμα για παρασκευή διαλύματος προς έγχυση – Συσκευασία: 1 Φιάλιδο (ανάλογο) x 40 ml με ενδεικτική Νοσοκομειακή τιμή € 15.548,65, και ενδεικτική Χονδρική 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 ενήλικους 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 T-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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^{*}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.

YERVOY™
(ipilimumab)
πυκνό διάλυμα για παρασκευή
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