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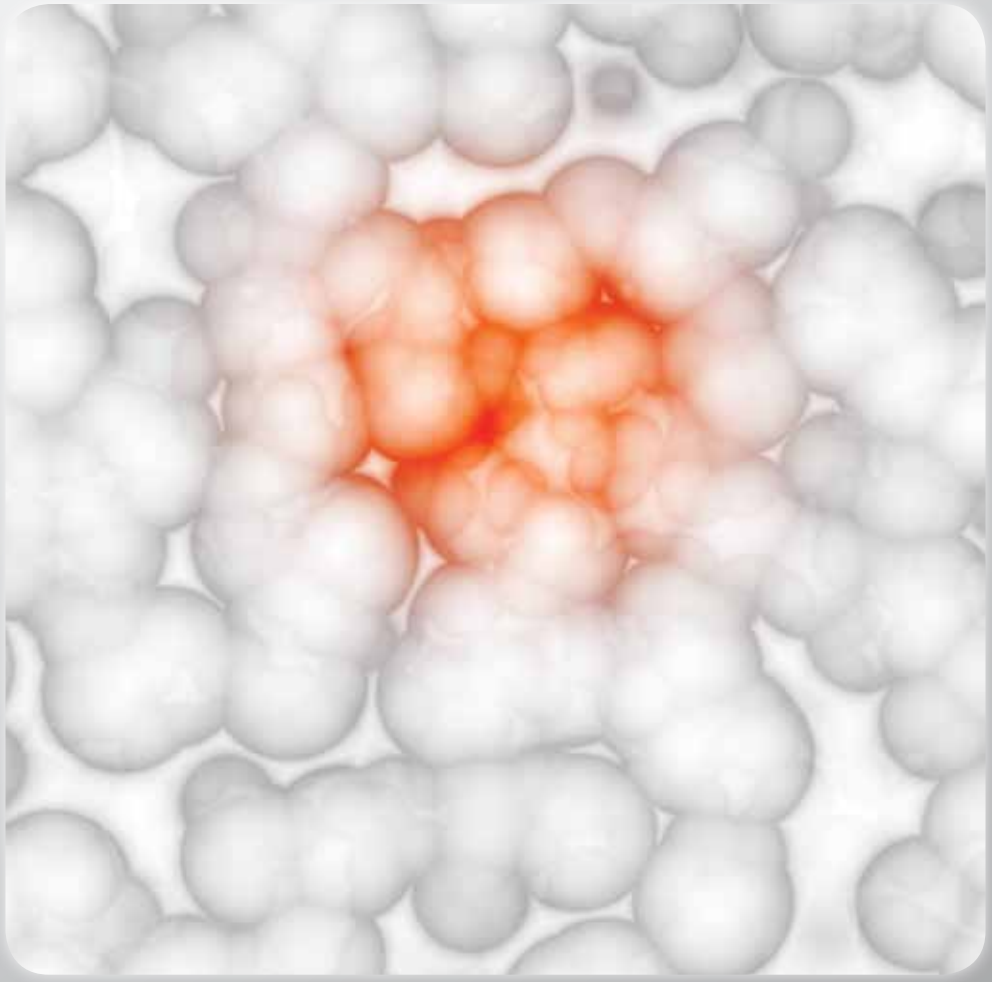

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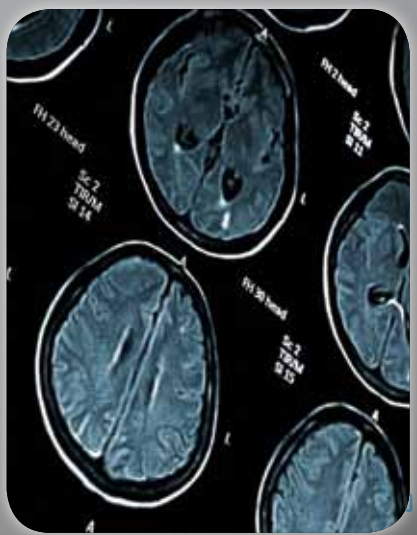

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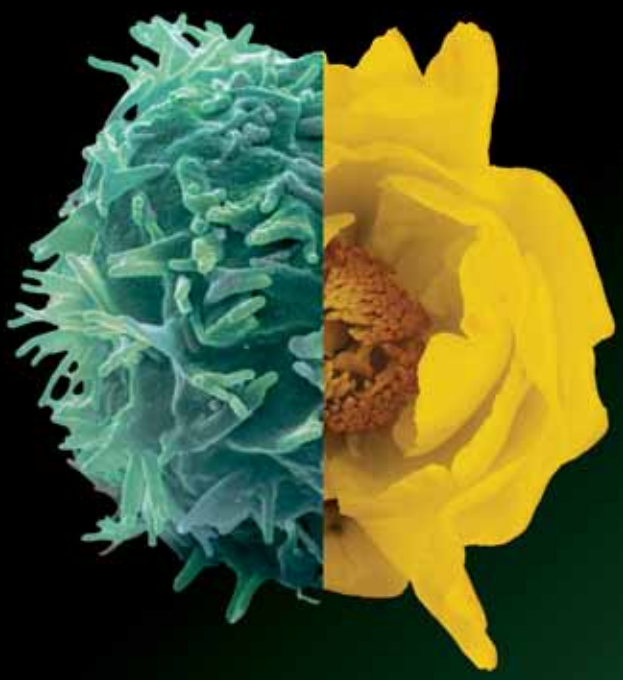
Νέα Ένδειξη
Θεραπεία πρώτης γραμμής



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Αναστέλλοντας τους υποδοχείς εσωτερικά δίνει ελπίδα για ζωή εξωτερικά

ΠΟΙΟΤΙΚΗ ΚΑΙ ΠΟΣΟΤΙΚΗ ΣΥΝΘΕΣΗ: Κάθε επικαλυμμένο με λεπτό υμένιο δισκίο περιέχει μονοϋδρική λαπατινίμπη ditosylate, που ισοδυναμεί με 250 mg λαπατινίμπης. ΘΕΡΑΠΕΥΤΙΚΕΣ ΕΝΔΕΙΞΕΙΣ: Το Tyverb, σε συνδυασμό με καπεσιταβίνη, ενδείκνυται για τη θεραπεία ασθενών με προχωρημένο ή μεταστατικό καρκίνο του μαστού, των οποίων οι όγκοι υπερεκφράζουν το ErbB2 (HER2). Οι ασθενείς πρέπει να έχουν προϊούσα νόσο κατόπιν προηγούμενης θεραπείας που περιελάμβανε ανθρακυκλίνες και taξάνες και θεραπεία με τραστουζουμάμπη στη μεταστατική φάση. σε συνδυασμό με ένα αναστολέα αρωματάσης για μετεμμηνοπαυσιακές γυναίκες με μεταστατική νόσο θετική σε ορμονικό υποδοχέα, οι οποίες επί του παρόντος δεν προορίζονται για χημειοθεραπεία. Οι ασθενείς στη μελέτη έγκρισης δεν είχαν προηγουμένως λάβει τραστουζουμάμπη ή ένα αναστολέα αρωματάσης (βλέπε παράγραφο 5.1). **ΑΝΤΕΝΔΕΙΞΕΙΣ:** Υπερευαισθησία στη δραστική ουσία ή σε κάποιο από τα έκδοχα. Παρακαλείστε να ανατρέξετε στις συνταγογραφικές πληροφορίες της καπεσιταβίνης για σχετικές αντενδείξεις και για πληροφορίες ασφάλειας όταν χορηγείται λαπατινίμπη σε συνδυασμό με καπεσιταβίνη. Ειδικές προειδοποιήσεις και προφυλάξεις κατά τη χρήση: Η λαπατινίμπη έχει σχετιστεί με αναφορές για μείωση του κλάσματος εξώθησης αριστερής κοιλίας (LVEF) (βλέπε παράγραφο 4.8). Εφιστάται προσοχή όταν πρόκειται να χορηγηθεί λαπατινίμπη σε ασθενείς με νόσους που θα μπορούσαν να προκαλέσουν εξασθένηση της λειτουργίας της αριστερής κοιλίας. Το LVEF πρέπει να αξιολογείται σε όλες τις ασθενείς πριν από την έναρξη της θεραπείας με λαπατινίμπη προκειμένου να διασφαλιστεί ότι το αρχικό LVEF της ασθενούς βρίσκεται εντός των φυσιολογικών ορίων του ιδρύματος. Η αξιολόγηση του LVEF πρέπει να συνεχίζεται κατά τη διάρκεια της θεραπείας με λαπατινίμπη προκειμένου να διασφαλίζεται ότι το LVEF δεν μειώνεται σε μη αποδεκτό επίπεδο. Η λαπατινίμπη έχει σχετιστεί με αναφορές πνευμονικής τοξικότητας περιλαμβανομένης της διάμεσης πνευμονοπάθειας και της πνευμονίτιδας. Οι ασθενείς πρέπει να παρακολουθούνται για τυχόν συμπτώματα πνευμονικής τοξικότητας. Με τη χρήση λαπατινίμπης έχει εμφανισθεί ηπατοτοξικότητα και σε σπάνιες περιπτώσεις μπορεί να είναι θανατηφόρα. Η ηπατική λειτουργία (τρανσαμινάσες, χολερυθρίνη και αλκαλική φωσφατάση) θα πρέπει να παρακολουθείται πριν την έναρξη της θεραπείας και στη συνέχεια κάθε μήνα, ή όπως ενδείκνυται κλινικά. Η δοσολογία της λαπατινίμπης θα πρέπει να διακόπτεται εάν οι μεταβολές της ηπατικής λειτουργίας είναι σοβαρές και δεν πρέπει να επαναχορηγείται στους ασθενείς. Συνιστάται προσοχή εάν η λαπατινίμπη συνταγογραφείται σε ασθενείς με μέτρια ή σοβαρή ηπατική δυσλειτουργία. Συνιστάται προσοχή εάν η λαπατινίμπη συνταγογραφείται σε ασθενείς με σοβαρή νεφρική δυσλειτουργία. Κατά τη διάρκεια της θεραπείας με λαπατινίμπη έχουν αναφερθεί περιστατικά διάρροιας, συμπεριλαμβανομένης της σοβαρής διάρροιας. Η προληπτική αντιμετώπιση της διάρροιας με αντιδιαρροϊκά φάρμακα είναι σημαντική. Για τα σοβαρά περιστατικά διάρροιας μπορεί να απαιτηθεί η χορήγηση από του στόματος ή ενδοφλεβίως ηλεκτρολυτών και υγρών, καθώς και η προσωρινή ή η οριστική διακοπή της θεραπείας με λαπατινίμπη. Η παράλληλη θεραπεία με επαγωγείς του CYP3A4 πρέπει να αποφεύγεται λόγω του κινδύνου μειωμένης έκθεσης στη λαπατινίμπη. Η παράλληλη θεραπεία με ισχυρούς αναστολείς του CYP3A4 πρέπει να αποφεύγεται λόγω του κινδύνου αυξημένης έκθεσης στη λαπατινίμπη. Η κατανάλωση χυμού γκρέπ φρουτ πρέπει να αποφεύγεται κατά τη διάρκεια της θεραπείας με λαπατινίμπη. Η συγχορήγηση λαπατινίμπης και φαρμακευτικών προϊόντων με περιορισμένο θεραπευτικό εύρος που είναι υποστρώματα του CYP3A4 ή CYP2C8 πρέπει να αποφεύγεται. Η ταυτόχρονη χορήγηση με ουσίες που αυξάνουν το γαστρικό pH πρέπει να αποφεύγεται, καθώς η διαλυτότητα και η απορρόφηση της λαπατινίμπης μπορεί να μειωθούν. Ανεπιθύμητες ενέργειες: Η ασφάλεια της λαπατινίμπης αξιολογήθηκε σε σχήμα μονοθεραπείας ή συνδυασμού με άλλες χημειοθεραπείες για διάφορους τύπους καρκίνου, περιλαμβανομένων ασθενών που έλαβαν λαπατινίμπη σε συνδυασμό με καπεσιταβίνη. Οι πλέον συχνές ανεπιθύμητες αντιδράσεις (>25%) κατά τη διάρκεια της θεραπείας με λαπατινίμπη συν καπεσιταβίνη ήταν από γαστρεντερικές (διάρροια, ναυτία και έμετος) ή δερματολογικές (παλαμο-πελματιαία ερυθροδυσαισθησία [PPE] και εξάνθημα). Η επίπτωση PPE ήταν παρόμοια στο σκέλος θεραπείας της λαπατινίμπης συν καπεσιταβίνη και στο σκέλος μονοθεραπείας με καπεσιταβίνη. Η διάρροια ήταν η συνηθέστερη ανεπιθύμητη αντίδραση που οδήγησε σε διακοπή της θεραπείας και η επίπτωσή της ήταν παρόμοια στις δύο ομάδες θεραπείας (λαπατινίμπη συν καπεσιταβίνη: 5%, καπεσιταβίνη: 3%). Για την ταξινόμηση των ανεπιθύμητων ενεργειών ανάλογα με τη συχνότητά τους, χρησιμοποιήθηκε η ακόλουθη συνθήκη: πολύ συχνές (1/10), συχνές (1/100 έως <1/10), όχι συχνές (1/1.000 έως <1/100), σπάνιες (1/10.000 έως <1/1.000) και πολύ σπάνιες (<1/10.000), μη γνωστές (δεν μπορούν να εκτιμηθούν με βάση τα διαθέσιμα δεδομένα). Εντός κάθε κατηγορίας συχνότητας εμφάνισης, οι ανεπιθύμητες ενέργειες παρατίθενται κατά φθίνουσα σειρά σοβαρότητας. Οι παρακάτω ανεπιθύμητες αντιδράσεις έχει αναφερθεί ότι σχετίζονται με τη λαπατινίμπη: Καρδιακές διαταραχές – Συχνές: Μειωμένο κλάσμα εξώθησης αριστερής κοιλίας, διαταραχές του αναπνευστικού συστήματος, του θώρακα και του μεσοθωρακίου. Όχι συχνές: Διάμεση πνευμονοπάθεια/πνευμονίτιδα. Διαταραχές του γαστρεντερικού συστήματος – Πολύ συχνές: Διάρροια, που μπορεί να προκαλέσει αφυδάτωση, ναυτία, έμετος. Διαταραχές του δέρματος και του υποδόριου ιστού – Πολύ συχνές: Εξάνθημα (συμπεριλαμβανομένης δερματίτιδας ομοιάζουσας με ακμή). Διαταραχές του μεταβολισμού και της θρέψης – Πολύ συχνές: Ανορεξία. Γενικές διαταραχές και καταστάσεις της οδού χορήγησης – Πολύ συχνές: Κόπωση. Διαταραχές του ήπατος και των χοληφόρων – Συχνές: Υπερχολερυθριναιμία, ηπατοτοξικότητα. Οι παρακάτω επιπρόσθετες ανεπιθύμητες αντιδράσεις έχει αναφερθεί ότι σχετίζονται με τη λαπατινίμπη σε συνδυασμό με καπεσιταβίνη με διαφορά συχνότητας μεγαλύτερη από 5% σε σύγκριση με τη μονοθεραπεία καπεσιταβίνης: Διαταραχές του γαστρεντερικού συστήματος – Πολύ συχνές: Δυσπεψία. Διαταραχές του δέρματος και του υποδόριου ιστού – Πολύ συχνές: Ξηροδερμία. Επιπλέον, οι παρακάτω ανεπιθύμητες αντιδράσεις αναφέρθηκε ότι σχετίζονται με τη λαπατινίμπη σε σχήμα συνδυασμού με καπεσιταβίνη, αλλά εμφανίστηκαν σε παρόμοια συχνότητα στο σκέλος μονοθεραπείας καπεσιταβίνης: Διαταραχές του νευρικού συστήματος – Συχνές: Κεφαλαλγία. Διαταραχές του γαστρεντερικού συστήματος – Πολύ συχνές: Στοματίτιδα, δυσκοιλιότητα, κοιλιακό άλγος. 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Μειώσεις του LVEF αναφέρθηκαν στο 2,5% των ασθενών που έλαβαν λαπατινίμπη σε συνδυασμό με καπεσιταβίνη, έναντι ποσοστού 1,0% στην ομάδα της μονοθεραπείας με καπεσιταβίνη. Διάρροια: Διάρροια εμφανίστηκε στο 65% περίπου των ασθενών που έλαβαν λαπατινίμπη σε συνδυασμό με καπεσιταβίνη. Τα περισσότερα περιστατικά διάρροιας ήταν βαθμού 1 ή 2 και δεν οδήγησαν σε διακοπή της θεραπείας με λαπατινίμπη. Η διάρροια ανταποκρίνεται καλά στην προληπτική αγωγή (βλέπε παράγραφο 4.4). Εξάνθημα: Εξάνθημα εμφανίστηκε στο 28% περίπου των ασθενών που έλαβαν λαπατινίμπη σε συνδυασμό με καπεσιταβίνη. Το εξάνθημα ήταν γενικά χαμηλού βαθμού και δεν οδήγησε σε διακοπή της θεραπείας με λαπατινίμπη.
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Hellenic Society of Medical Oncology
105, Alexandras Avenue,
GR-11475 – Athens, Greece
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Publication coordinator

Mindwork Business Solutions Ltd.
15, M. Botsari Street,
GR-14561 – Kifissia,
Athens, Greece
tel.: 0030 210 6231305
fax: 0030 210 6233809
e-mail:
info@forumclinicaloncology.org
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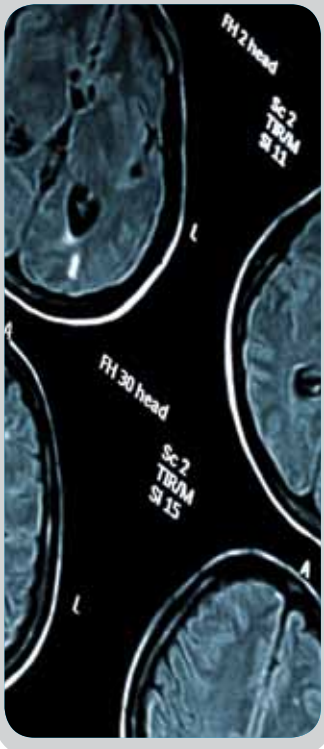

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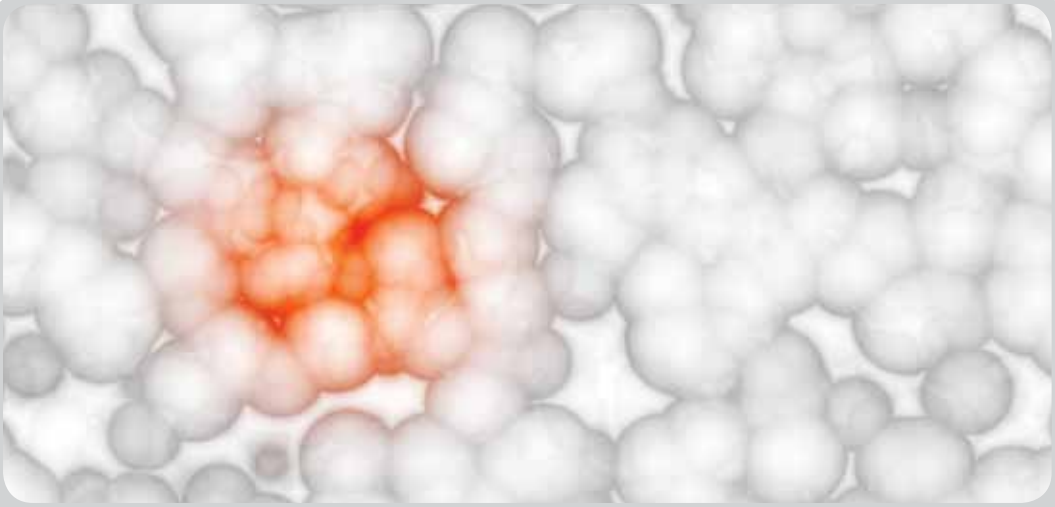

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The great leap forward

Editorial

Vassilios Barbounis

We would like to welcome you to the Forum of Clinical Oncology (FCO), the official scientific journal of the Hellenic Society of Medical Oncology!

In the Hellenic Society of Medical Oncology we share the view that there are many issues we deal with in our every day clinical and research practice that are common to our colleagues in other parts of the world and probably, a little bit more to those closer to us, in the Balkans and the Mediterranean basin. This view led us to dare the great leap forward: to broaden the scope of our Greek scientific journal for oncology, published in Greek for the last 10 years, and develop Forum of Clinical Oncology, a web-based open access journal in English.

FCO will serve as a forum for us all to communicate clinical and research achievements. We envision the journal to be the means, by which our efforts in the fight against cancer will become known to a wider audience, thus establishing our presence in the global setting. Undoubtedly there are many such journals, but we wish to put forth another respected publication, which will be accepted by the PubMed database in due course. Our endeavor is embraced by a large number of eminent foreign colleagues who participate in the International Editorial Board and will grant us direction and support.

One of the innovations of the journal is its online management from submission of an article to its publication. Online is more efficient: submitting, reviewing, proofreading, filing and indexing. However, the most important benefit of all is the easy universal access.

English has become the common language amongst scientists from around the globe. This is the reason why we chose English as the official language of the journal. Many Greek colleagues have already published work in English in distinguished journals or have studied or worked abroad. We believe that the language change will not be an impediment for our Greek colleagues to present their work in FCO, whereas on the other hand it will allow our colleagues from other countries to participate.

The Forum of Clinical Oncology publishes original and translational research articles relevant to diagnosis and treatment of cancer, state-of-the-art reviews, case reports, research articles, statements of opinion and comments, all related to clinical practice and basic research.

We share the view that there should be no barriers to knowledge and thus, we decided Forum of Clinical Oncology to be an open-access journal, i.e., any work submitted to the journal and accepted for publication shall be made immediately available to the scientific community and the general public, via the journal's website and printed version. Authors are requested to adjust accordingly the information regarding their work they wish to make public. It is the desire of the editorial team to make this journal an interactive educational tool to offer knowledge and it is addressed to scientists working in the field of oncology.

In the current issue, the articles presented relate to every day clinical practice: a multi-center phase II study, a review in cancer cachexia, an article for the new agent pazopanib that recently got approval for use in renal cell carcinoma (RCC) from the FDA and EMEA, as well as an article dedicated to the targeted treatment for older patients with advanced/metastatic non-small cell lung cancer. Finally, a case study, a case of fiber in an ovarian cyst in a patient under anti-angiogenesis treatment is also presented.

It is expected that despite our efforts to get everything right, our first steps will not be flawless. Nonetheless, we strongly believe that with your support and guidance we will become better. Please join us in our effort and submit your work to the FCO.

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Salvage Chemotherapy with Gemcitabine and Pegylated Liposomal Doxorubicin in Pretreated Patients with Ovarian Cancer: A Multicenter Phase II Study

Antonia Kalykaki, Pavlos Papakotoulas, Ioannis Boukovinas, Nikolaos Vardakis, Vasiliki Bozionelou, Ioannis Varthalitis, Athanasios Athanasiadis, Aris Polyzos, Anna Potamianou, Dimitris Mavroudis, Vassilis Georgoulias

Hellenic Oncology Research Group (HORG), 55 Lomvardou Street, 11470 Athens, Greece

Correspondence:
Vassilis Georgoulias,
Department of Medical Oncology,
University General Hospital of Heraklion,
P.O. Box 1352, 71110,
Heraklion, Crete, Greece.
e-mail: georgsec@med.ouc.gr

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ABSTRACT

Objective: To evaluate the safety and antitumor activity of gemcitabine and pegylated doxorubicin combination in pretreated ovarian cancer patients.

Patients and Methods: Pretreated patients (n=38; ≥3rd line: 45%; platinum/taxane-resistant/refractory disease: 42.1%) with locally advanced or metastatic ovarian cancer were enrolled. Gemcitabine (800 mg/m^2) was administered on day 1 and 8 and pegylated liposomal doxorubicin (30 mg/m^2) on day 1 every 21 days. Results: Four (10.5%) complete and 5 (13.2%) partial responses (overall response rate 23.7%; 95% CI 10.17%-37.2%) were observed; the objective response rate was 25% and 22.7% in patients with platinum-resistant/refractory and platinum-sensitive disease, respectively. The median duration of response was 4 months, the median time to tumor progression 6.8 months and the median survival 18.4 months. Grade 3-4 neutropenia (with one episode of febrile neutropenia) and grade 3 thrombocytopenia were observed in 12 (31.6%) and 4 (10.5%) patients, respectively. Grade 3-4 Palmar-Plantar Erythrodysesthesia (PPE) occurred in only one patient. There was no treatment-related death.

Conclusions: The combination of pegylated liposomal doxorubicin and gemcitabine is a well tolerated and active regimen in patients with pretreated ovarian cancer, regardless of its sensitivity to platinum compounds. The regimen merits further evaluation in patients with platinum-resistant/refractory disease.

Key words: Gemcitabine, pegylated liposomal doxorubicin, phase II study, ovarian cancer.

INTRODUCTION

Ovarian carcinoma is the leading cause of death in patients with gynecologic malignancies (1). The epithelial ovarian cancer is the most common histologic type. Most of the patients with ovarian cancer are diagnosed at an advanced stage of the disease resulting in an impaired survival as compared to patients who are diagnosed at earlier clinical stages. Cytoreductive surgery followed by chemotherapy is the treatment of choice for patients with advanced ovarian cancer. The standard chemotherapy for primary ovarian cancer is a regimen combining a platinum compound with paclitaxel (2). However, despite the excellent initial antitumor efficacy of these combinations, over three quarters of women will relapse and will die from the disease. Patients, who relapse within 6 months after this front-line paclitaxel/platinum chemotherapy, are considered to have platinum- and taxane-resistant disease. These patients have a poor prognosis and the aims of treatment efforts are palliation and the improvement of quality of life rather than cure.

The pegylated liposomal doxorubicin is a formulation of doxorubicin encapsulated in small, sterically stabilized liposomal vesicles. This liposomal encapsulation protects from formulation detection and destruction by the reticuloendothelial system, thus resulting in an increase of the agent's half-life. Additionally, liposomal encapsulation of doxorubicin reduces nonspecific delivery to normal tissues and avoids the high plasma levels responsible for toxicity, such as cardiotoxicity (3,4). These pharmacological activities, which improve the exposure

of tumors to higher drug levels of doxorubicin, have demonstrated that pegylated liposomal doxorubicin is an active drug against ovarian cancer in both the first- and second-line setting with an acceptable safety profile (4-9).

Gemcitabine (Gemzar) is an antimetabolite, which inhibits DNA chain synthesis by competing with deoxycytidine for DNA incorporation (10). In addition, gemcitabine has shown activity as salvage treatment in ovarian cancer (11-17). Doxorubicin and gemcitabine have different mechanisms of action and non-overlapping toxicity.

The combination of pegylated liposomal doxorubicin and gemcitabine has been evaluated in patients with advanced solid tumors showing that their combination may be both feasible and active (18-19). Since both drugs are active against ovarian cancer, a phase II trial was conducted by the Hellenic Oncology Research Group (HORG) in order to evaluate the efficacy and the impact on Quality of life (QoL) of their combination in patients with relapsed ovarian cancer.

MATERIALS AND METHODS

Patient Selection

Thirty-eight patients with histologically confirmed epithelial ovarian cancer were enrolled into this phase II study. Eligibility criteria included: age >18 years old, advanced ovarian cancer (stage III-IV), disease relapse after a taxane/platinum combination regimen, evaluable disease (by physical examination, imaging studies or tumor markers), a life expectancy of ≥6 months, a performance status (ECOG) of 0–2, an adequate bone marrow (absolute neutrophil count (ANC) ≥1500/dL, platelet count ≥100,000/dL), renal (creatinine level ≤1.5 mg/dL) and liver (bilirubin level ≤1.5 the institutional upper normal (UNL), and aspartate transaminase and alanine transaminase levels ≤2 times the UNL) function. In addition, patients had to have a left ventricular ejection fraction ≥50%. Patients with pregnancy or breastfeeding, a second primary tumor (except of non-melanoma skin tumors or cervix CIN I, II), or previous treatment with pegylated liposomal doxorubicin or gemcitabine, brain metastasis and active infection were excluded from the study. All patients gave written informed consent to participate in the study, which had been approved by the Ethics and Scientific Committees of the participating centers.

Study design

All patients had a baseline medical history, physical examination, complete blood cell count (CBC) with differential and platelet counts, a complete chemistry panel and measurement of tumor markers serum levels (CEA and CA 125). All patients had baseline computed tomography thorax and abdomen scans, an electrocardiogram and a Multiple Gated Acquisition Scan (MUGA). A CBC with differential and platelet count was repeated on a weekly basis, whereas a physical examination, CBC with differential and platelet count, chemistry panel and tumor markers, performance status, toxicity and medication assessment were recorded every 3 weeks. A Left Ventricular Ejection Fraction (LVEF) was determined by MUGA every 3 chemotherapy cycles.

Response to treatment was assessed by imaging studies and tumor marker measurements every 3 chemotherapy cycles. A complete response (CR) was defined as the disappearance of all measurable disease or normalization of tumor markers for a minimum of 4 weeks. A partial response (PR) was defined as a 50% or greater decrease in the sum of the product of all measured lesions the diameters, with the appearance of no new lesions, for at least 4 weeks. Stable disease (SD) was defined as a less than 50% decrease and a less than 25% increase in the sum of the diameter products with no new lesions. Progressive disease (PD) was defined as a 25% or greater increase in the total area of any bidimensionally measurable lesion compared with best response or as the appearance of any new lesion. Patients who received at least one cycle of chemotherapy were evaluable for toxicity which was assessed according to the National Cancer Institute Common Terminology Criteria of Adverse Events (version 3).

Treatment and dose modifications

Gemcitabine (Gemzar; Eli Lilly, Indianapolis, USA) was administered first at a dose of 800 mg/m^2 over a 30-minute intravenous (IV) infusion on days 1 and 8; pegylated liposomal doxorubicin (Caelyx; Schering Plough; USA) was administered next over a 60-minute IV infusion at a dose of 30 mg/m^2 on day 1. The treatment was repeated every 21 days. The primary prophylactic use of G-CSF was not allowed.

In case of grade 3 or 4 neutropenia or febrile neutropenia, subsequent cycles were administered with prophylactic use of Granulocyte-colony stimulating factor (G-CSF) (Filgrastim; 5 μg/kg/d from day 4-8 and 10-15); if grade 3 or 4 neutropenia or febrile neutropenia occurred, subsequent cycles were administered with a 25% dose reduction of both drugs. A similar dose reduction was required in patients with grade 3 or 4 thrombocytopenia as well as in patients presenting ≥ grade 3 non-hematologic toxicity. A 25% dose reduction of pegylated liposomal doxorubicin was also required in patients presenting a decrease of the LVEF ≥20% of the baseline.

Statistical analysis

The primary endpoint of the study was the objective response rate. The time to tumor progression (TTP) was measured from the time of treatment allocation to the date of disease progression was first noticed. Overall survival (OS) was calculated from the diagnosis

of the disease until death or the date of last follow-up. TTP and OS were calculated using the Kaplan-Meier method. Survival analysis data is shown as median and 95% confidence interval. Pearson's Exact test was used to compare statistical differences between patient subgroups. Statistical significance was defined as $p<0.05$.

Table 1.
Patient characteristics. Patients with platinum sensitive disease have better prognosis than patients with platinum resistant/refractory. See Efficacy section.

	n (= 38)	%
Age		
Median (min-max)	65.4 (39-75)	
Performance status		
0	18	47.4
1	16	42.1
2	4	10.5
Line of therapy		
2nd	21	55.3
≥3rd	17	44.7
Taxane/Platinum sensitivity		
Resistant/refractory	16	42.1
Sensitive	22	57.9
No. of Organs Involved		
0 (Ca-125)	4	10.5
1	13	34.2
2	11	28.9
≥3	10	26.4
Organs Involved		
Peritoneum	20	52.6
Lung	6	15.8
Pleura	5	13.2
Nodes	7	18.4
Liver	12	31.6
Ascites	9	23.7
Other	11	28.9
Time since prior chemotherapy		
<6 mo	16	42.1
≥6 mo	22	57.9

RESULTS

Patient Characteristics

Thirty-eight patients with ovarian cancer pretreated with paclitaxel and cisplatin or carboplatin were enrolled into the study; all patients were evaluable for response and toxicity. Patient characteristics are listed in Table 1. The median age was 65.5 years, 89.5% of patients had a PS of 0-1 and 78.9% had International Federation of Gynecology and Obstetrics (FIGO) stage IV disease and 44.7% of patients had received at least two prior lines of chemotherapy. Almost 50% of patients relapsed within 6 months [median 6.0 mo (range, 0.5-32.5)] from the prior treatment. The overall response rate (CR and PR) to previous front-line treatment was 52.6%.

Compliance with the treatment

A total of 158 chemotherapy cycles were administered, with a median of 5 cycles/patient (range, 1 to 8 cycles). The median duration of cycles was 22.5 days (range, 21-31 days). The median delivered dose was 82.9% (442 mg/m^2/week) and 90% (9 mg/m^2/week) of the protocol planned dose for gemcitabine and pegylated liposomal doxorubicin, respectively. Forty-two (26.6%) chemotherapy cycles were delayed because of hematologic (n=14; 8.9%), non-hematologic (n=5; 3.2%) or other reasons, unrelated to the disease or treatment (n=23; 14.6%). A dose reduction was required in 29 (18.4%) cycles, because of hematologic (n=8 cycles; 27.6%), non-hematologic (n=12 cycles; 41.4%), both hematologic and non-hematologic (n=1 cycle; 3.4%) toxicity, as well as for other reasons unrelated to the treatment (n=8; 27.6%).

Efficacy

All patients were evaluable for response. In an intention-to-treat (ITT) analysis, four (10.5%) and five (13.2%) patients presented a CR and PR respectively (ORR: 23.7% 95% C.I: 10.17%-37.20%); 10 (26.3%) patients presented SD and 19 (50%) PD. The objective response rate (CR+PR) was 28.6% in patients who received the PLD/GEM combination as 2nd line and 17.6% in patients who received the regimen as >2nd line treatment (p=0.431). In addition, the objective response rate was 25% and 22.7% in patients enrolled in the study <6 months and ≥6 months from the prior treatment (Table 2). The median duration of response was 3 months (range, 2.0-15.5). After a median follow-up period of 7.2 months (range, 0.5-27), the median TTP was 4.7 months (range, 0.5-19.2). The median TTP for patients with platinum/taxane-refractory/resistant and sensitive disease was 1.6 months and 5.6 months respectively (p=0.008; Figure 1). The median OS was 18.4 months (range, 0.5-27.0). The 1-year survival rate was 59.1%. Similarly, the median OS for patients with platinum/taxane-refractory/resistant and sensitive disease was 2.1 months and 13.4 months respectively (p=0.003; Figure 2).

Table 2.
Response according to time since prior chemotherapy.

Time since prior chemotherapy	Response to 2nd line chemotherapy			
	Complete Response (CR)	Partial Response (PR)	Stable Disease (SD)	Progression Disease (PD)
<6 months (n=16)	3 (18.8%)	1 (6.2%)	1 (6.2%)	11 (68.8%)
≥6 months (n=22)	1 (4.5%)	4 (18.2%)	7 (31.8%)	10 (45.5%)

Toxicity

All patients were evaluable for toxicity. In general, the regimen toxicity profile was manageable (Table 3). Grade 4 neutropenia occurred in four patients (10.5%), febrile neutropenia and grade 3 PPE in one patient each (2.6%). The most common adverse events of any grade, was anemia which was observed in 34 (89.5%) patients; grade 2-3 thrombocytopenia occurred in seven (18.4%) patients, grade 3 mucositis in four (10.5%) and grade 1-2 PPE in seven (18.4%) patients. Treatment was discontinued in two patients because of grade 3 hypersensitivity reactions against the pegylated liposomal doxorubicin. G-CSF administration was required in 58 (36.7%) cycles. There was no patient who presented a more than 10% decrease of the baseline LVEF. Finally, there was no treatment-related death.

DISCUSSION

Current study results indicate that the combination of PLD/GEM is an active and well-tolerated regimen for the treatment of patients with recurrent or resistant/refractory epithelial ovarian cancer. Indeed, an overall response rate of 23.7% was achieved with this chemotherapy regimen irrespectively of the tumor's sensitivity to platinum compounds and paclitaxel (Table 2). However, both the TTP and the overall survival were significantly higher in patients with platinum/taxane-sensitive disease than in patients with platinum/taxane- resistant/refractory disease. Previous studies have clearly indicated that both PLD and gemcitabine are active agents for the treatment of recurrent epithelial ovarian cancer (4,5,7,11-17). In phase II trials, an objective response rate of 14-27% has been reported with single agent PLD in patients with

Figure 1.
Kaplan-Meier curves of time to tumor progression (TTP) in patients with platinum-sensitive and refractory/resistant disease.

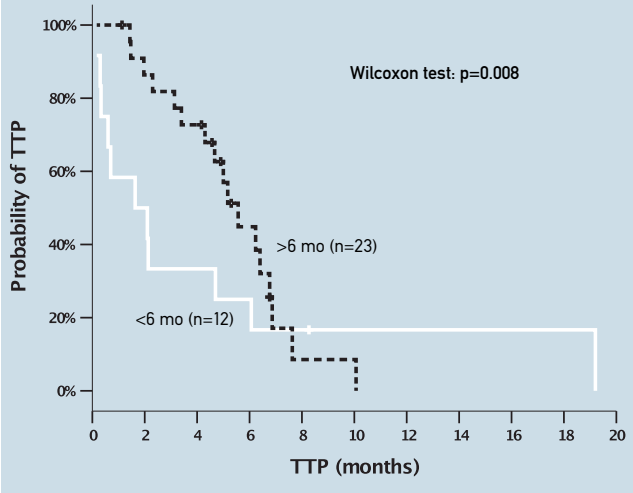

Figure 2.
Kaplan-Meier curves of overall survival (OS) in patients with platinum-sensitive and refractory/resistant disease.

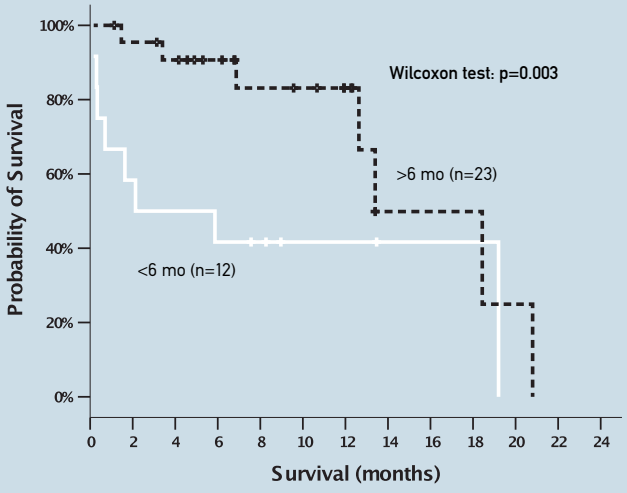

Table 3.
Adverse events possibly or probably related to study treatment.

	GrI		GrII		GrIII		GrIV	
	n	%	n	%	N	%	n	%
Neutropenia	7	18.4	8	21.1	8	21.1	4	10.5
Anemia	13	34.2	17	44.7	4	10.5	-	-
Thrombocytopenia	11	28.9	3	7.9	4	10.5	-	-
Nausea/Vomiting	5	13.2	7	18.4	2	5.3	-	-
Asthenia	5	13.2	7	18.4	-	-	-	-
Constipation	4	10.5	3	7.9	-	-	-	-
Stomatitis	2	5.3	4	10.5	4	10.5	-	-
Neurotoxicity	2	5.3	-	-	1	2.6	-	-
Allergy	2	5.3	1	2.6	1	2.6	-	-
Diarrhea	1	2.6	2	5.3	-	-	-	-
Febrile neutropenia	-	-	-	-	-	-	1	2.6
Edema	-	-	-	-	-	-	-	-
Infection	-							
Fever in absence of infection	-							
PPE	4		3		1			

recurrent disease (4,5,7). In patients with disease non-responsive to platinum or paclitaxel, PLD resulted in a 17-26% response rate with a median PFS of 5-6 months (4,5). Similarly, single agent gemcitabine resulted in a 14-19% overall response rate with a median TTP of 2.8-5 months (11-17). In these studies patients had platinum-resistant disease and the majority also had prior exposure to paclitaxel. The comparison of gemcitabine and PLD in two randomized phase III trials failed to demonstrate any significant difference in terms of response rate, time to tumor progression and overall survival between the two drugs in patients with platinum-resistant ovarian cancer (20,21).

In the current study, the combination of PLD/GEM demonstrated an objective response rate of 25% with a median TTP of 1.6 months in patients with platinum/taxane-resistant/refractory disease. These results are in agreement with previous phase II studies which have demonstrated that the combination of these two drugs is an active regimen in patients with platinum-resistant or refractory ovarian tumors. Indeed, Ferrandina et al. (22) reported that the PLD/GEM combination resulted in an impressive response rate of 34% in patients with recurrent disease. The subgroup analysis demonstrated that patients with platinum-sensitive disease achieved a response rate of 53.7% with a duration of response of 22 weeks and a Progression-Free Survival (PFS) of 35 weeks; conversely, in patients with platinum-resistant disease the observed response rate was 21.6% with a PFS of 20 weeks. In another phase II study in patients with platinum-resistant/refractory disease, the PLD/GEM regimen resulted in an overall response rate of 33%; it should be noted that in this particular study, 77% of the patients had received only one prior chemotherapy regimen (23). Similarly, Scarlos et al. (24) reported a 22% overall response rate and a median TTP of 2.7 months in patients with platinum- and/or taxane-resistant/refractory disease.

The development of resistance to platinum compounds is a well known negative prognostic factor for the clinical outcome of patients with ovarian cancer. In the current study, despite the encouraging response rate observed with the pegylated liposomal doxorubicin plus gemcitabine combination, both the median TTP and the overall survival were significantly shorter in patients with platinum-resistant/refractory tumors than in patients with platinum-sensitive tumors. The enrollment in the study of almost 50% of the patients for whom the study

treatment was ≥3rd-line of treatment may also account for this poor outcome of patients with platinum-resistant/refractory disease.

The PLD/gemcitabine combination showed a favorable toxicity profile. Myelosupression was the main adverse event with anemia of any grade to be the most common toxicity; however, there was no need for blood transfusions. Other relatively frequent toxicity was grade 1-2 PPE which was manageable with PLD dose reductions as has already been reported by other investigators (22-24). It is also interesting to note that the regimen was not associated with clinically relevant cardiotoxicity.

In conclusion, the results of the present study indicate that the pegylated liposomal doxorubicin in combination with gemcitabine is an active and well-tolerated regimen for the treatment of patients with platinum-sensitive and platinum-resistant/refractory epithelial ovarian cancer. This regimen merits to be further evaluated in association with agents targeting the angiogenesis which seems to be significantly involved in the progression of ovarian cancer.

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The Insulin-like Growth Factor 1 Receptor: Biochemical and Preclinical Evidence Supporting its Role as a Target for Cancer Treatment

Giannis Mountzios

Departments of Medical Oncology and Translational Research, 251 General Airforce Hospital, Athens, Greece

Correspondence:
Giannis Mountzios,
Departments of Medical Oncology and Translational Research,
251 General Airforce Hospital,
Athens, Greece,
e-mail: gmountzios@med.uoa.gr

Abstract: The insulin growth factor (IGF) network of ligands, cell-surface receptors and IGF-binding proteins plays important roles at multiple levels, including the cellular, organ and organism levels. The IGF system mediates growth, differentiation and developmental processes and is also involved in various metabolic activities. Dysregulation of IGF expression and activity is linked to diverse pathologies, ranging from growth deficits to cancer development. IGF axis targeting emerged in recent years as a valid therapeutic approach. Specific IGF-1 receptor (IGF-1R) targeting in particular, has yielded the most promising experimental and clinical results so far, thus attracting scientific interest . This review provides the fundamental framework of the IGF-1R role in cancer biology and explores the functional interactions between the IGF signaling pathways and various genes implicated in carcinogenesis. In addition, we review a number of specific malignancies in which the IGF system is involved and summarize recent data on preclinical studies employing IGF-1R-targeting modalities.

Key words: Insulin growth factor-1 receptor, cancer treatment, preclinical data.

BIOCHEMICAL PROPERTIES

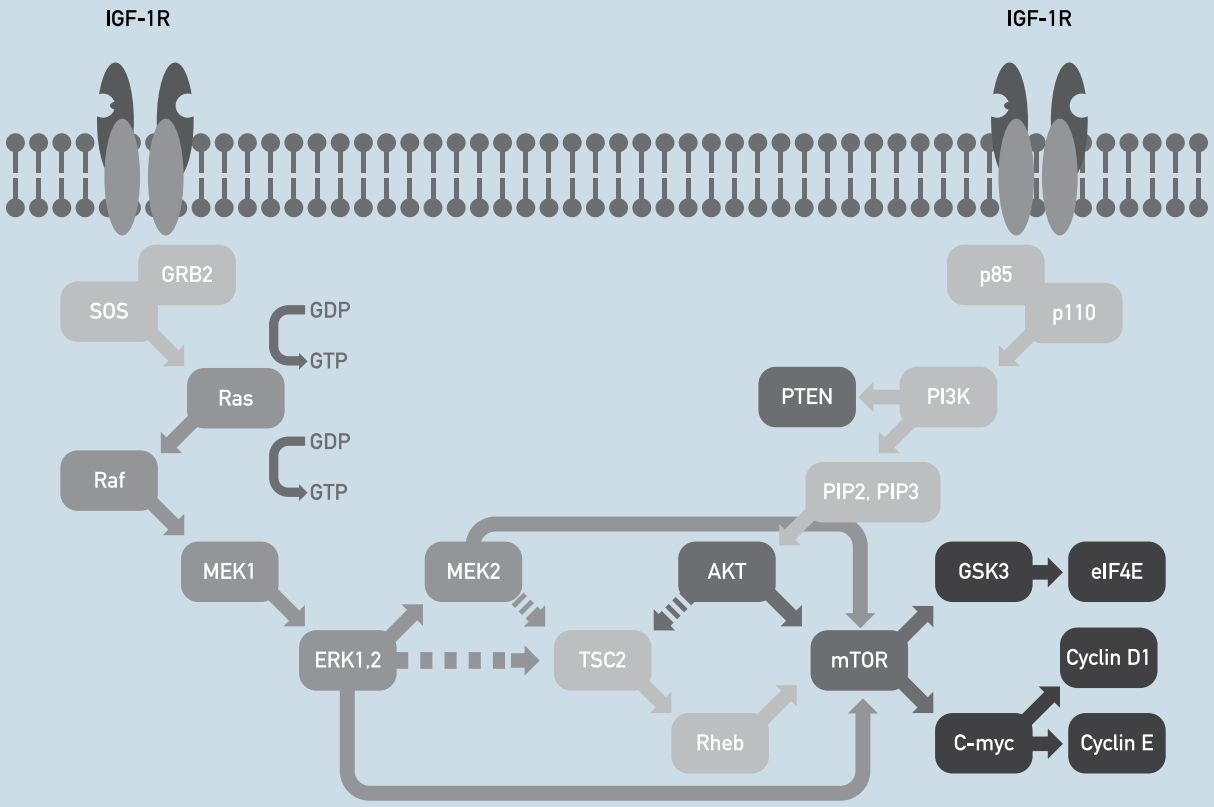
The insulin-like growth factor 1 receptor (IGF-1R), which belongs to the tyrosine kinase receptor family, is a transmembrane tyrosine kinase consisting of 2 a- and 2 b-subunits (1). The extracellular a-subunits are required for ligand binding, while the transmembrane b-subunits contain the tyrosine kinase catalytic site and the ATP-binding site (2). Two ligands, IGF-1 and IGF-2 bind to IGF-1R (3). The local bioavailability of ligands is subject to complex physiological regulation and is probably abnormally high in many human disorders, including cancer (2). IGF-binding proteins (IGFBPs) (3) and IGFBP proteases play key roles in regulating ligand bioavailability. IGFBPs prolong the half-life of IGFs, which may lead to subsequent increase in IGF-1R activation. On the other hand, these proteins have affinity for IGFs comparable to IGF-1R and there is competition between IGFBPs and IGF-1R for available ligands in tissue microenvironment (3). This provides a basis for the inhibitory role of IGFBPs on IGF-1 signaling. There is also evidence that certain IGFBPs have direct, IGF-independent, growth-regulatory action: The IGF-2R binds IGF-2 but has no tyrosine kinase domain and appears to act as an indirect suppressor of proliferation by reducing the amount of IGF-2 available for binding to IGF-1R. Certain IGFBP proteases (often produced by neoplastic cells) that cleave IGFBPs can release free ligand and thereby increase IGF-1R activation. Following ligand binding to IGF-1R, its tyrosine kinase (TK) activity stimulates signaling through intracellular networks that regulate cell proliferation and survival.

BIOCHEMICAL PATHWAYS ACTIVATED BY IGF-1R

Binding of IGF-1 and IGF-2 to IGF-1R causes its auto-phosphorylation and leads to activation of multiple signaling pathways. There are 4 insulin receptor substrate (IRS) proteins in mammalian cells, but IRS-1 and IRS-2 are the most prominent in transmitting signals from either the IGF-1R or the insulin receptor (IR). At least two major different signal transduction

Figure 1.

Binding of extracellular ligands to IGF-1R cell-surface receptors activates RAS and this initiates RAF activation. This leads to activation of the dual-specificity protein kinases MEK1 and MEK2 (MAPK and ERK kinase) and subsequently the MAPK/ERK proteins ERK1 and ERK2. Depending on the cellular context, this pathway mediates diverse biological functions such as cell growth, survival and differentiation predominantly through the regulation of transcription, metabolism and cytoskeletal rearrangements. The binding of the growth factor (IGF-1) to its TK receptor (IGF-1R) also results in the recruitment and activation of the PI3K to the plasma membrane receptor, which in turn phosphorylates the phosphoinositides, increasing the local concentration of PIP3 and PIP2 at the plasma membrane. The PI3K activity is counteracted in the cell by PTEN, a lipid 3- phosphatase which is the second most common sporadically mutated tumor suppressor. This increase in lipid second messengers recruits and activates the PDK and AKT protein kinases at the plasma membrane where AKT is then fully activated by phosphorylation of ser-473 and thr-308. Through the phosphorylation of a diverse set of substrates, AKT regulates four intersecting biological processes: cell survival, cell-cycle progression, cell growth and cell metabolism. The AKT substrates that mediate some of these biological processes have been identified. AKT controls cell-cycle progression through several substrates. AKT can phosphorylate and inhibit Glycogen synthase kinase-3 (GSK-3) which phosphorylates several cell-cycle regulators such as c-Myc, cyclin D1 and cyclin E and controls a number of critical cell-cycle events. AKT may also enhance the functions of some transcription factors by inactivating GSK-3.



pathways have been identified for IGF-1R. One activates Ras, Raf, and mitogen-activated protein kinase (MAPK)/ extracellular signal regulated kinase (ERK), the main mitogen transduction pathway, while a distinct pathway is responsible for anti-apoptotic signal transduction, involving the phosphatidylinositide- 3-kinase (PI3K) – AKT axis (Figure 1). AKT controls cell survival through its inactivation of the BAD pro-apoptotic protein and the subsequent activation of the IκB kinase (IKK)–NFκB (nuclear factor-κB) pathway. In addition to that, the activated AKT protein moves to the cell nucleus where it phosphorylates the FOXO family of "forkhead" transcription factors which is a set of highly conserved substrates of AKT; This activation results in their translocation from the nucleus to the cytoplasm and induces a change in the "forkhead" transcriptional activity (4).

PI3K and AKT are also implicated in the activation of the mammalian target of rapamycin (mTOR) protein kinase pathway which, in turn, is implicated in a variety of cellular processes (4). Activation of the mTOR pathway by AKT is mediated by the inactivation of two tumor suppressor

genes: TSC2 or tuberin, and its obligate binding partner, hamartin (TSC1), which are mutated in a familial tumor syndrome called tuberous sclerosis complex (TSC). Of particular interest is the fact that AKT and mTOR can mediate activation of the HIF-1α (hypoxia-inducible factor-1α) transcription factor which is crucial for neovascularization and subsequent tumor growth (5); Finally, AKT increases the expression of the GLUT1 glucose transporter and glycolytic enzymes, ultimately leading to increased glucose uptake which allows the hypermetabolic state of most tumors (6).

Stimulation of the PI3K-AKT- mTOR pathway by IGF-1R also causes an mTOR-dependent loss in IRS-1 expression leading to feedback downregulation of signaling through the same pathway. The mTOR inhibition induces IRS-1 expression and abrogates feedback inhibition of the pathway, resulting in AKT activation in cancer cell lines and in patients treated with the mTOR inhibitors, such as rapamycin, CCI-779 (7) or RAD001 (8). Rapamycin enhances basal AKT activity, AKT phosphorylation, and PI3K activity in multiple myeloma cells and prolongs activation of AKT induced by exogenous IGF-1 (7). Rapamycin also prevents serine phosphorylation of IRS-1, enhances IRS-1 association with IGF-1 receptors, and prevents IRS-1 degradation (7); This feedback inhibition could paradoxically reduce the antitumor effects of mTOR inhibitors by enhancing IGF-1 signaling. IGF-1R inhibition could therefore prevent rapamycin-induced AKT activation and may sensitize tumor cells to mTOR inhibition. In contrast, IGF-1 antagonizes the antiproliferative effects of rapamycin in serum-free medium (8). This information suggests that feedback downregulation of receptor tyrosine kinase signaling is a frequent event in tumor cells with constitutive mTOR activation. Hence, reversal of this feedback loop by rapamycin may attenuate therapeutic effects, while combination therapy with an IGF-1R inhibitor that ablates mTOR function and prevents AKT activation may result in improved antitumor activity.

EVIDENCE FOR IGF-1R INVOLVEMENT IN CANCER

Tumor type and IGF-1R expression

The IGF-1R has been implicated in promoting oncogenic transformation, growth, and survival of cancer cells. Several studies, both experimental and clinical, have demonstrated that IGF-1R is overexpressed in tumor samples compared to the corresponding normal tissues,

Table 1.
IGF-1R expression, IGF serum levels and IGF gene polymorphism in tumors in relation to cancer risk or prognosis.

Tumor type	IGF-1R expression	IGF serum level or gene polymorphism
Prostate cancer	expression in most prostate cancer cell lines, overexpression in PC-3 and DU-45 cells	high circulating IGF-1 levels, 19-CA-repeat allele associated with worse survival
Breast cancer	higher in estrogen-dependent cell lines, presence of IGF-1R in biopsy specimens	circulating levels of IGF, IGFBP and 19-CA-repeat allele associated with high risk the same for A-202 C polymorphism in the IGFBP 3
Colorectal cancer	presence on HCT 116 and CoLo-205, and human colon cancer specimens	a high IGF-I/IGFBP-3 ratio correlates with high risk, same for CA ≤17 repeat allele
Lung cancer	expression common in SCLC and NSCLC	IGF stimulate growth in SCLC and NSCLC cell lines, A-202C polymorphic variation of IGFBP-3 associated with high risk
Gastric cancer	Overexpression in primary tumor correlated with increased lymph node metastasis	NR
Pancreatic cancer	overexpression	NR
Bladder cancer	expression	NR
Sarcoma	expression	IGF-2R expression
Adrenal neoplasia	overexpression in pheochromocytomas	NR
CNS	gliomas meningiomas express receptor	NR

IGF: Insulin growth factor; IGFR: Insulin growth factor receptor; IGFBP: Insulin growth factor receptor binding protein, NSCLC: Non small-cell lung cancer, SCLC: Small-cell lung cancer, CNS: Central nervous system; NR: Not reported.

especially in cases of prostate cancer (9-13) (Table 1). Findings based on prostate cancer studies raised the possibility that tumor cell dependency on IGF-1R may be stage-specific. The multi-step transformation of the prostate epithelium is initially IGF-1R dependent: IGF-1 has been shown to stimulate the proliferation of human prostate epithelial cells in culture and to be necessary for normal growth and development of the rat and mouse prostate (11). IGF-1R mRNA appears to be abundantly expressed in most prostate cancer cell lines, including PC-3 and DU-45 (11).

The concentration of IGF-1R is higher in estrogen-dependent breast cell lines than in estrogen-independent cell ones. There is a positive correlation between the estrogen, progesterone, and prolactin receptors and IGF-1R expression (14). IGF-1R expression, however, is ubiquitous and its activation has been demonstrated to be a potent stimulus for growth. IGF-1R overexpression is observed in 43.8% of tumors in primary breast cancer patients, although IGF-1R overexpression was not found to correlate with prognosis or with other clinicopathologic parameters (14).

IGF-1R is overexpressed in 62% of primary tumor site or lymph node metastasis of gastric cancer when compared with adjacent tumor-free gastric mucosa. IGF-1R overexpression in primary tumor correlates with increased lymph node metastasis (15). IGF-1R is also expressed on the human colon cancer cell lines HCT116 and CoLo-205, and a high IGF-1/IGFBP-3 ratio may increase the risk of colon cancer development (16).

IGF receptor expression is also common in lung cancer. Presence of IGF-1R mRNA has been found in almost all cell lines and mostly primary lung adenocarcinomas (11). IGF-1 is a potent mitogen, stimulating cancer cell growth 1.6- to 4.2-fold in a panel of small cell lung cancer (SCLC) cell lines and 1.1- to 2.7-fold in a panel of non-small cell lung cancer (NSCLC) cell lines such as NCI-H1299 (11).

Significant overexpression of the IGF-1R in human pheochromocytomas suggests IGF system involvement in the pathogenesis of adrenal neoplasia (17). Gastrointestinal neuroendocrine tumors (NET) frequently express IGFs and IGF-1R and apoptosis or cell cycle arrest may be induced by the IGF-1R-TK inhibitor, NVP-AEW541, in NET cells (17). The inhibition of the IGF/IGFR system appears to be a promising novel approach for future treatment strategies of NET disease (18).

Circulating level of IGFs

Circulating levels of IGF-1 are associated with an increased risk for developing prostate, breast, colorectal and lung cancer (Table 1). Men with high levels of serum IGF-1 are at increased risk of developing clinically evident prostate cancer (19). Circulating levels of IGF-1 and IGFBP-3 may predict the risk of developing advanced-stage prostate cancer (20). Men in the highest quartile of IGF-1 level have a five-fold increased risk of advanced-stage prostate cancer than men in the lowest quartile (20). Elevated IGF-1 levels are also associated with sporadic colorectal cancer (CRC) risk in hereditary non-polyposis colorectal cancer (HNPCC) (11). Finally, women in the highest quartile of circulating levels of IGF and IGFBP have more than twice the risk of developing breast cancer than those in the lowest, although this effect is only apparent at young ages (27).

Genetic polymorphisms and IGF expression

The presence of millions of genetic variations (polymorphisms) in the human genome may provide extensive biological variations that affect cancer physiology, treatment outcome and prognosis. Polymorphisms of genes encoding growth factors may be good candidates for a possible determinant of treatment outcome and prognosis.

A known genetic cytosine–adenine (CA) repeat polymorphism in the promoter region of the human IGF-1 gene may be associated with circulating IGF-1 levels. The 19-CA-repeat allele is more frequent in prostate cancer patients than controls and males homozygous for the 19-allele have a significantly increased risk for prostate cancer (21). The presence of more than 19 repeats of IGF-1 is associated with a worse cancer-specific survival and was found to be an independent risk factor for death along with well-established clinical parameters (22). The number of IGF-1 (CA) repeats may be a novel predictor in prostate cancer patients with bone metastasis (23).

Women with 19-CA-repeat allele homozygote and high IGF-1 levels have a much higher risk of breast cancer (24). The polymorphisms in the IGF-1 and IGFBP-3 genes are associated with an increased risk of breast cancer in familial cases carrying the variant alleles (25,26).

The risk of colorectal cancer may be associated with having an IGF-1 genotype other than homozygous for 19 repeats and with the GG IGFBP-3 genotype. IGF-1 and IGFBP-3 genotypes are significant modifiers of the relationship between risk factors (body mass index, postmenopausal hormone use and physical activity) and colorectal cancer in multivariate analysis (28). Patients carrying a shorter IGF1 CA-repeat lengths polymorphism (≤17 repeat) have higher colorectal cancer risk in hereditary non-polyposis colorectal cancer (HNPCRC) syndrome (29).

A-202C polymorphic variation of IGFBP-3 gene constitutes an independent risk factor for NSCLC. The risk for developing NSCLC was found to be significantly associated with the AA genotype (30).

Finally, IGF polymorphisms are also associated with osteogenic sarcoma and this is the first evidence for a possible pathogenetic role of IGF in oncogenesis of mesenchymatous tissues (31).

INTERACTIONS BETWEEN IGF-1R AND OTHER TYROSINE KINASE RECEPTORS

IGF-1R signaling interferes with numerous other growth factors or receptors such as epidermal growth factor receptor (EGFR) and vascular endothelial growth factor (VEGF). Increased IGF-1 serum levels have been shown to stimulate VEGF secretion and induce VEGF promoter activation (32). As mentioned above, IGF-1 stimulates PI3K/Akt and Erk/MAPK pathways, each contributing to HIF-1α expression, which is an important mediator of VEGF secretion (33). Functional inhibition of IGF-1R signaling has been shown to upregulate VEGF-C mRNA levels (34).

IGF-1R and EGFR are often co-expressed in pancreatic cancer cell lines and their expression patterns through the cell have been shown to correlate with tumor grade and prognosis (35). Membrane-dominant EGFR and cytoplasm-dominant IGF-1R are more frequent in lower-grade tumors and are associated with favorable prognosis in primary invasive ductal pancreatic carcinomas, whereas cytoplasm-dominant EGFR and membrane-dominant IGF-1R are more frequent in higher-grade tumors and usually associated with poor prognosis (36).

IGF-1R AND RESISTANCE TO TARGETED THERAPIES

Signaling via IGF-1R has been associated with resistance to anti-EGFR and HER-2-based therapies in preclinical studies. Primary resistance to anti-EGFR therapy with either monoclonal antibodies or tyrosine kinase inhibitors (TKI) has been observed in preclinical models of EGFR-expressing tumors such as lung cancer and glioblastoma (37). IGF-1R mediates resistance to anti-EGFR therapy in primary human glioblastoma cells through continued activation of PI3K-AKT signaling (37). Interestingly, co-targeting IGF-1R with EGFR greatly enhances both spontaneous and radiation-induced apoptosis in a glioblastoma model (38).

In lung cancer, the recent identification of a novel mutation of the EGFR gene in the TK domain (T790M), rendering cells resistant to the EGFR TKIs erlotinib and gefitinib strongly suggests that tumor cells remain dependent on an active EGFR pathway for their proliferation (39).The addition of an anti-IGF-1R strategy to EGFR targeting treatment may be more effective than a single-agent approach (40) and dual EGFR/IGFR targeting compounds are currently in development. Tyrphostin AG1024 (an inhibitor of IGF-1R) is being tested with gefitinib in MDA468, MDA231, SK-BR-3, and MCF-7 breast cancer lines, which express similar levels of IGF-1R but varying levels of EGFR (40). Gefitinib and AG1024 when used in combination revealed an additive-to-synergistic effect on cell growth inhibition. Overexpression of IGF-1R in SK-BR-3 cells is sufficient to cause a marked enhancement in gefitinib resistance. IGF-1R signaling reduces the anti-proliferative effects of gefitinib in several breast cancer cell lines (40). Similar findings of an involvement of IGF-1R in EGFR resistance mechanism where also reported in pancreatic and prostate cancer cell lines (41,42).

Co-targeting HER2 and IGF-1R improved the efficacy of therapies directed against HER2/erbB2. In two cell lines (MCF7 and BT474) IGF-1R antagonists potentiated the effect of HER2 and estrogen receptor (ER) antagonists. While these agents produce a moderate rate of apoptosis when used separately, their combination induces a dramatic increase in apoptosis (43). Trastuzumab inhibited the growth of MCF-7/HER2-18 cells, which express both HER2 and IGF-1R, only when IGF-1R signaling was minimized (44). In SKBR3 cells, which also express HER2, but to a much lesser extent IGF-1R, trastuzumab reduced proliferation index by 42% regardless of IGF-1 concentration. When the SKBR3 cells were genetically altered to over-express IGF-1R and cultured with IGF-1, trastuzumab has no effect on proliferation. However, the addition of IGFBP-3, which decreased IGF-1R signaling, restored trastuzumab-induced growth inhibition (45). A strong synergistic interaction has been found in combining trastuzumab and reduction of IGF-1R signaling by expression of dominant-negative IGF-1R in HER2 – overexpressing MCF7her18 breast cancer cells and this resulted in a potentiation of growth inhibition in transfected cancer cells (46). Taken altogether, these results suggest that targeting IGF-1R signaling may prevent or delay development of resistance to trastuzumab (44). Simultaneous co-targeting of TK receptors may be therapeutically useful and provides a specific rationale for combining IGF-1R and HER2 targeting strategies (45).

Signaling transduction through IGF-1R may exhibit a cross-talk with other molecular mediators, including the stem-cell factor (SCF) – c-KIT system of ligand and receptor respectively (47). It has been recently reported that Bcr-Abl expressing cells harboring imatinib (an SCF-KIT loop inhibitor) resistance due to Bcr-Abl gene amplification are sensitive to AG1024 (48). Whether this effect is a direct consequence of IGF-1R or due to an "off target effect" of AG1024, remains to be determined. Several lines of evidence demonstrated that IGF-1R targeting inhibitors are effective against leukemia, multiple myeloma, and lymphoma models (49-52). IGF-1R blockade by ADW742, a small molecule specific for this receptor, alone and in combination with imatinib on Ewing tumor cell lines has been studied (53). Addition of imatinib to ADW742 synergistically augmented these effects and is especially effective in inhibiting AKT/mTOR phosphorylation and reducing VEGF expression in cell lines having high IGF-1R activation levels. Combination of ADW742 with imatinib induces a significant reduction of tumor cell growth, mainly by the increase in apoptosis with a pattern depending on IGF-1R activation levels (53).

PRECLINICAL DATA ON IGF-1R INHIBITION

A variety of approaches, including dominant negative mutants, kinase defective mutants, antisense oligonucleotides, IGF-

binding proteins, soluble forms of the receptor, antagonistic and/or neutralizing antibodies or small molecule kinase inhibitors have been used to inhibit IGF-1R signaling. Reducing the levels of the ligands (IGF-1 and IGF-2) has given promising results in mice which express only IGF-1 in adult life. However, in adult humans, IGF-1 and IGF-2 are both expressed and, theoretically, both of them would have to be targeted. Antisense strategies are the first to be used successfully in vitro and in vivo. Antagonistic antibodies and TK inhibitors represent the most probable clinically viable options (54).

Humanized monoclonal antibodies such as: EM164 (55, 56), (AVE1642) (57), IMC-A12 (41) and CP-751, CP- 871, h7C10 (58), have been successful in inducing apoptosis in cancer cells and their usefulness is further supported by the observation that antibodies to the IGF-1R, like antisense strategies, downregulate the receptor. The feasibility of inhibiting IGF-1R function with a specific antibody was first demonstrated using a mouse monoclonal antibody (α-IR-3) directed against the α-subunit of IGF-1R (54). This antibody inhibits the binding of IGF-1 to its receptor, thereby preventing downstream signaling, tumor cell proliferation in vitro and tumor growth in vivo. Numerous groups have recently described the identification and characterization of antagonistic and/or neutralizing humanized antibodies targeting the extracellular domain of IGF-1R. Although generated by applying different strategies, such potential biopharmaceuticals have been shown to bind specifically to IGF-1R, thereby preventing the activation of IGF-1R-mediated signaling (54).

Parallel to the efforts directed at blocking the physical interaction between IGF-1R and its growth factors, drug

Table 2.
Specific IGF1R targeting compounds in preclinical or early clinical development.

Compounds	Type of targeting	Sponsor	Phase of development
CP-751, 871 (Figitumumab)	antibody	Pfizer	Phase III in NSCLC: CP-751 + erlotinib vs erlotinib (interrupted in interim analysis) Phase II in SCLC Phase II in breast cancer
		Saint-Luc- Université Catholique de Louvain	Phase II in SCCHN (lack of efficacy)
EM164 (AVE1642)	antibody	ImmunoGen/Sanofi-Aventis	Phase II in breast cancer (active, but not currently recruiting)
IMC-A12 (Cixutumumab)	antibody	ImClone LLC	Phase II in SCCHN Phase II in various sarcomas Phase II in prostate cancer Phase II in colorectal cancer Phase II in NET Phase II in HCC
		National Cancer Institute	Phase II in thymic carcinomas Phase II in NSCLC
		Southwest Oncology Group	Phase I/II in pancreatic cancer
h7C10	antibody	Pierre Fabre and Merck	Preclinical
INSM18	TK inhibitor	Insmed	Phase I
PPP	TK inhibitor	Karolinska Institute	Preclinical-Phase I
NVP-ADW742, NVP-AEW541	TK inhibitor	Novartis Pharma	Preclinical
BMS-536924, BMS-554417	TK inhibitor	Bristol-Myers Squibb	Preclinical

NSCLC: Non small-cell lung cancer; SCLC: Small-cell lung cancer; SCCHN: Squamous-cell carcinoma of the head and neck; NET: Neuroendocrine tumors; HCC: Hepatocellular carcinoma.

discovery activities have also aimed at modulating IGF-1R TK activity by targeting its intracellular kinase domain. The identification of specific low-molecular mass inhibitors of IGF-1R kinase activity has proven to be a major challenge for medicinal chemistry. In theory, a specific inhibitor of IGF-1R TK activity would be the best solution. The problem is that this type of inhibitor will have to distinguish the TK domain of the IGF-1R from the one of the insulin receptor. The two domains are highly homologous, but there are small differences that could be exploited. These kinase inhibitors could be divided into two groups: ATP antagonists such as: NVP-ADW742 (49), NVP-AEW541 (59) and BMS-536924 (60), BMS-554417 (61) and Non-ATP antagonists such as: picropodophyllin (PPP) (51), AG538 (62) and INSM18.

PPP is a cyclolignan derivative developed at the Karolinska Institute and is a selective inhibitor of IGF-1R kinase activity (51). PPP potently inhibits IGF-1R autophosphorylation (IC50 of 0.04 μM) and is selective against a panel of other receptor TKs, without interfering with insulin receptor activity (63-65). PPP did not compete with ATP but interfered with phosphorylation in the kinase domain activation loop . PPP reduces phosphorylated Akt, induces apoptosis and tumor regression in xenografted mice. IGF-1Rs of PPP-treated cells are undergoing rapid downregulation. This downregulation may be important for the strong apoptotic effect of this compound. PPP treatment of IGF-1R overexpressing cells results in the preferential inhibition of the PI3K/PKB pathway (63-65).

A summary of preclinical and early clinical data on compounds targeting IGF-1R are presented in Table 2.

QUESTIONS AND PERSPECTIVES

Recent success in the development of small-molecule TK inhibitors and blocking antibodies against the IGF-1R poses challenges to translational scientists seeking to design clinical trials. Small-molecule kinase inhibitors have potential advantages including convenient oral administration but it is difficult to predict a priori to what extent these agents will be specific for IGF-1R during long term in vivo use, where tissue concentrations might vary. Moreover, as there are hardly examples of genetic alterations of this pathway in human tumors, it is unclear how patients should be selected for treatment using this approach. Is activation of the receptor in a tumor likely to predict responsiveness? What effects may the inhibitors have on IGF-1R in normal tissues and even on the insulin receptor (66)? While several small molecules have a much lower affinity for the IGF-1R than the insulin receptor, the relative affinities in patients and on different tissues remain unknown. It is hoped that intermittent therapy with these or similar agents may have minimal effects, perhaps only on tissues that demonstrate a high level of cellular turnover such as the bone marrow and gastrointestinal tract. These side effects may therefore be similar to those seen with chemotherapy and may be limited in extent and duration; clinical trials will be required to establish this. Regarding the insulin receptor, intermittent therapy may provoke insulin resistance and diabetes to an extent that would be limited and easily treatable.

Finally, because of its strong antiapoptotic activity, downregulation of the IGF-1R could be used in combination with other anticancer therapies that induce apoptosis in cancer cells. Blockade of the IGF- 1R might be a valid option as an adjunct therapy for cancer patients. It may reduce side-effects by lowering the doses of chemotherapeutic agents, and perhaps render chemotherapy more effective. Whether the agent used is a humanized antibody, small peptide inhibitor, or small molecule, it is becoming clear that the IGF system plays a critical role in the development and treatment of cancer. Last but not least, sequence of co- administration in the case of IGF-1R targeting drugs and chemotherapy seems to be critical.

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Targeted Treatment for Older Patients with Advanced/Metastatic Non-Small Cell Lung Cancer

Athanasios G. Pallis, Lambros Vamvakas, Vassilis Georgoulias

Department of Medical Oncology, University General Hospital of Heraklion, Crete, Greece

Correspondence:
Athanasios G. Pallis,
Department of Medical Oncology,
University General Hospital of Heraklion,
P.O. Box: 1352, Heraklion 71110,
Crete, Greece
e-mail: georgsec@med.uoc.gr

Abstract: Non-small cell lung cancer (NSCLC) is a common health issue in the older population. Chemotherapy remains the cornerstone of treatment and prolongs survival with a positive impact on quality of life. However, it seems that chemotherapy has reached a plateau of activity in the treatment of NSCLC. Recently, the addition of bevacizumab or cetuximab to chemotherapy doublets has improved the outcome in selected patients with advanced NSCLC. Furthermore, erlotinib and gefitinib represent alternative therapies for second-line treatment. However, there is paucity of large, well conducted prospective trials of these targeted agents in older patients. The purpose of the current review is to present the currently available evidence regarding the role of targeted agents in the treatment of NSCLC in older patients.

Key words: Older, age, NSCLC, targeted therapies, erlotinib, gefitinib, cetuximab, bevacizumab.

INTRODUCTION

Lung cancer represents the most common type of cancer in terms of incidence and cancer-related mortality (1). Non-Small Cell Lung Cancer (NSCLC) accounts for approximately 80% of lung cancer cases (1).

As the global population ages, the incidence of lung cancer diagnosed in older patients is rising. Approximately 50% of newly diagnosed NSCLC cases occur in patients older than 65 years and 30-40% of cases are diagnosed in patients older than 70 years (2); the Surveillance, Epidemiology, and End Results (SEER) registry indicates that the median age at diagnosis in NSCLC is 69 years (3). Thus, it is clear that NSCLC represents a significant health problem in the older population. For older NSCLC patients, prospective, randomized phase III clinical trials have clearly demonstrated that single-agent chemotherapy offers a survival benefit, compared with best supportive care (4). Regarding combination therapy, published results are conflicting and it is not clear whether combination therapy offers benefits compared with monotherapy (5;6).

Although chemotherapy represents the backbone of treatment of advanced/metastatic NSCLC and chemotherapy doublets are considered the "standard" first-line treatment for the general NSCLC population (7), it should be noted that chemotherapy resulted in a statistically significant but modest survival benefit for most lung cancer patients; moreover, it is clear that chemotherapy has reached a plateau of activity in the treatment of NSCLC (8).

Advances in our understanding of molecular biology of cancer and mechanisms of tumorigenesis, have led to the development of novel "targeted therapies". Several of these "targeted agents" have been integrated into clinical practice for NSCLC patients. Recently, a phase III trial reported a significant prolongation of overall survival (OS) beyond the benchmark of 12 months with the addition of bevacizumab to a chemotherapy doublet in a selected NSCLC population (9). A similar European trial reported significant prolongation of Progression Free Survival (PFS) with the addition of bevacizumab to chemotherapy (10). Furthermore, the addition of cetuximab, an anti-Epidermal Growth Factor Receptor (EGFR) monoclonal antibody, to cisplatin/vinorelbine doublet resulted in a significant prolongation of OS (11). Finally, erlotinib significantly prolongs survival and improves quality of life in patients with one or two primary lines of treatment (12), while gefitinib has recently demonstrated similar efficacy to docetaxel as second-line treatment (13). However, although "targeted agents" are

routinely used in the treatment of advanced/metastatic NSCLC, their role in the treatment of older patients has not yet been thoroughly studied. The purpose of this review is to present current data regarding the role of "targeted agents" in the treatment of older patients with advanced/metastatic NSCLC.

ANTI-EGFR TREATMENT

Tyrosine Kinase Inhibitors

Erlotinib, offers a survival benefit compared to best supportive care according to a phase III trial for patients with advanced NSCLC after 1st and 2nd line failure (12). Jackman et al reported the results of a phase II trial with erlotinib as first-line treatment in 80 elderly (≥70 years of age) NSCLC patients (14). The response rate was 10% while 41% of patients had stable disease. Median Time to Tumor Progression (TTP) was 3.5 months and median OS 10.9 months. The 1- and 2-year survival rates were 46% and 19%, respectively. The most common toxicities were acneiform rash (79%) and diarrhea (69%). Four patients developed interstitial lung disease of grade 3 or higher, with one treatment-related death. An age-specific subgroup analysis of the global, open-label TRUST erlotinib study, which evaluated erlotinib in more than 6,000 patients, was reported during the previous ASCO meeting (15). Interim analysis data concerning 451 elderly (>70 years) patients who received erlotinib as first-line treatment revealed an objective response rate of 9% (1% complete response and 8% partial response), and a Progression-Free Survival (PFS) of 16.4 weeks (15). Table 1 summarizes several small prospective or retrospective studies which evaluated erlotinib or gefitinib in the first- (16;17) or second- (18) line treatment in elderly patients with advanced NSCLC.

Two randomized, phase II trials compared vinorelbine with either gefitinib (19) or erlotinib (20) as first-line treatment in older patients with NSCLC. Both trials failed to demonstrate any difference between vinorelbine and EGFR tyrosine kinase inhibitor in terms of response rate, TTP, and OS. These trials are presented in Table 2.

In the gefitinib trial reported by Crino et al (19) overall Quality of Life (QoL) improvement rates, as assessed by the total FACT-L scores, were higher with gefitinib than with vinorelbine (24.3% vs 10.9%). Furthermore, there were fewer treatment-related grade 3 to 5 adverse events with gefitinib (12.8%) than with vinorelbine (41.7%). An unexpected observation in that trial was that EGFR FISH-positive patients benefited more from vinorelbine than from gefitinib (19).

A randomized, phase III trial, conducted by the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) (BR.21 study), randomly assigned patients after failure of first- or second-line chemotherapy to erlotinib or placebo in a 2:1 ratio. Treatment with erlotinib resulted in a significant survival benefit over placebo (12). In the original cohort, 163 (22% of the original cohort; 112 on erlotinib, 51 on placebo) patients ≥70 years old were enrolled (21). Reponse rate and PFS were similar between younger and older patients. Additionally, there was no significant difference in terms of OS (erlotinib arm: 6.4 versus 7.6 months for younger and older patients, respectively; p-value=0.85; placebo arm: 4.7 versus 5.0 months for younger and older patients, respectively; p-value =0.22). Treatment effect was also similar between younger and older patients, with the latter deriving the same benefit from erlotinib treatment as their younger counterparts. However, it should be noted that older patients experienced significantly more ≥ grade III toxicities (35% for elderly patients versus 18% for younger patients; p<0.001).

On the basis of these studies, tyrosine kinase inhibitors are a reasonable treatment option for older patients with advanced NSCLC in the salvage setting. The presence of EGFR gene mutations in the tumor has turned out to be a significant predictor of efficacy with these agents (22). Validation of these markers in prospective studies will further optimize the use of erlotinib in all patients including the older subgroup.

Monoclonal antibodies

Gridelli et al evaluated in a randomized phase II trial the optimal way of combining gemcitabine and cetuximab (either concurrently, or sequentially) in elderly patients with NSCLC (23). No significant differences in terms of efficacy were observed between the two arms (1-year survival rate: 41.4% and 31%, respectively). However, the sequential approach was not recommended for further study because of low compliance while, according to the authors, the concurrent approach was not proposed for further development due to inconsistency of survival outcomes.

ANTI-ANGIOGENIC THERAPIES

Monoclonal antibodies

Bevacizumab is a recombinant, humanized, monoclonal antibody against VEGF, and is the most extensively studied anti-angiogenic agent in the treatment of NSCLC. A pivotal phase III trial, ECOG 4599, demonstrated a significant prolongation of median survival by two months for the combination of bevacizumab and paclitaxel/carboplatin followed by bevacizumab until disease progression. A similar European phase III trial (AVAiL study), evaluated the combination of cisplatin/gemcitabine plus bevacizumab (bevacizumab was administered at two different doses: 7.5 mg/kg and 15 mg/kg) followed by bevacizumab maintenance compared to the same chemotherapy regimen plus placebo. Although time-to-progression was significantly longer for either dose of the drug, the study failed to demonstrate any survival benefit (10).

An age-specific subgroup analysis of the ECOG 4599 study was reported by Ramalingan et al (24). This study enrolled

224 (26% of the whole cohort) patients with advanced/metastatic NSCLC aged ≥70 years. A Cox model analysis showed that treatment effects were not different for young and elderly patients (p=0.34) and that age was not a negative prognostic factor for survival. Among older patients, in the bevacizumab arm, there was a trend towards higher response rate (29% versus 17%; p=0.067) and higher PFS (5.9 versus 4.9 months; p=0.063). However, the addition of bevacizumab to paclitaxel/carboplatin doublet in the elderly population did not result in a significant prolongation of median OS (11.3 versus 12.1 months; p=0.4). On the other hand, it should be underlined that this subgroup analysis did not yield survival differences. Significantly, more ≥grade III toxicities were observed in older patients with the addition of bevacizumab, compared to the paclitaxel/carboplatin doublet. Seven treatment-related deaths were observed among elderly patients treated with the three-drug combination compared with only two deaths in the chemotherapy monotherapy arm. Furthermore, older patients who received bevacizumab suffered more ≥ grade III toxicities compared to their younger counterparts (24).

A similar age-specific retrospective analysis was reported for the AVAiL study (25). Efficacy data were available for 304 patients aged ≥65 years and for 739 younger patients. The response rate in older patients was 40%, 29% and 30% in the bevacizumab 7.5 mg/kg arm, 15 mg/kg arm and placebo arm, respectively. Progression-free-survival was significantly higher for older patients in the 7.5 mg/kg arm compared with the placebo arm (p=0.023), while there was no difference for the 15 mg/kg arm (p=0.25). Survival was similar in all treatment arms regardless of age. Safety data were available for 284 elderly and 702 young patients. There were no safety signals of concern in older patients. Grade ≥3 toxicities occurred in 84%, 80% and 80% of older pts treated with bevacizumab 7.5 mg/kg, 15 mg/kg and placebo respectively. No episodes of severe hemoptysis were observed in older patients, but in the bevacizumab 7.5 mg/kg and placebo arms, older subjects were more likely to have other clinical problems related to bleeding compared to younger patients. The incidence of hypertension and febrile neutropenia were similar in young and older patients treated with bevacizumab. The incidence of treatment-related deaths did not differ between the two age groups in both the bevacizumab and the placebo arms.

SAIL was an open-label, single-arm trial of first-line treatment consisting of bevacizumab in combination with standard chemotherapy in 2000 patients with NSCLC. An interim analysis to assess safety in older patients (≥65 years) was presented during the last meeting of the European Society of Medical Oncology (ESMO) (26). Three hundred sixty-one older patients and 955 young patients were evaluable for safety. There were six treatment-related deaths in the older population group and 11 in the younger patients group, while 28.3% of patients ≥65 years of age experienced a serious adverse event compared with 22.6% pts <65 years. There was no difference in the incidence of thromboembolic events between the two age groups.

Further evaluation of bevacizumab combined with different chemotherapy regimens (single agent or platinum-based doublets with modified doses and schedules) are warranted (27).

CONCLUSIONS

NSCLC represents a significant health problem in the elderly population and approximately 40% of new NSCLC cases occur in patients older than 70 years of age (2). Despite this high incidence, older patients are frequently under-represented in clinical trials (28) evaluating new cancer treatments. As a result, it is difficult to reach evidence-based clinical recommendations which apply to the treatment of the elderly. Inclusion of bevacizumab in first-line treatment in combination with cytotoxic agents demonstrated a survival prolongation beyond the historical benchmark of 12 months. Erlotinib significantly prolongs

Table 1.
Erlotinib or Gefitinib in the treatment of older NSCLC patients.

	Treatment	Line of treatment	n	ORR(%)	Median OS (mo)
Jackman et al. (14)	E	1st	80	10	10.9
Rajdev et al. (16)	E	1st	30	10	5.57
Merimsky et al. (15)	E	1st	451	9	16.4* weeks
Ebi et al. (17)	G	1st	49	25	10
Bearz et al. (18)	G	1st -2nd	22	41**	4.1

*Median progression free survival, **partial response and stable disease
ORR: overall response rate, OS: overall survival, E: erlotinib, G: gefitinib

Table 2.
Randomized, phase II trials comparing cytotoxic agents with anti-EGFR tyrosine kinase inhibitors.

	treatment	n	ORR (%)	TTP (mo)	p-value	OS (mo)	p-value
Crino et al. (19)	Gefitinib	97	3.1	2.7	0.310	5.9	NS
	Vinorelbine	99	5.1	2.9		8.0	
Chen et al. (20)	Erlotinib	37	21.6	4.4	0.607	NR	
	Vinorelbine	40	12.8	3.9			

NS: non-significant, NR: not reported

survival and improves quality of life in patients with one or two primary lines of treatment, while gefitinib has recently demonstrated similar efficacy to docetaxel as second-line treatment. Although these "targeted therapies" seem feasible in older NSCLC patients, it should be underscored that much of the data currently available derive from retrospective, age specific, subgroup analyses of clinical trials conducted in the general NSCLC population. However, these analyses may suffer from selection bias in favor of treatment, since only the fittest older patients would have been included in such trials. Results from clinical trials conducted in younger patients cannot always be extrapolated to the general older population. These patients have more comorbidities and tend to experience more treatment-related toxicities compared to their younger counterparts. Thus, prospective, elderly-specific clinical trials are mandatory in order to optimize the integration of "targeted agents" in the treatment of advanced/metastatic NSCLC in older patients and to provide evidence-based recommendations for the treatment of this specific population.

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PAZOPANIB: a second generation antiangiogenic multitargeted tyrosine kinase inhibitor

Niki Karaxaliou, Zenia Saridaki

Department of Medical Oncology, University General Hospital of Heraklion, Heraklion, Crete, Greece

Correspondence:
Zenia Saridaki
Department of Medical Oncology,
University General Hospital of Heraklion,
PO BOX 1352, 71 110,
Heraklion, Crete, Greece,
e-mail: georgsec@med.uoc.gr

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Abstract: Vascular endothelial growth factor (VEGF) is a key regulator of angiogenesis. Inhibition of the VEGF-signaling pathway has emerged as one of the most promising new approaches for cancer therapy. Pazopanib (Votrient: Glaxo Smith Kline, UK) is an orally bioavailable second generation multitargeted tyrosine kinase inhibitor targeting VEGFR-1, -2 and -3, PDGFR and c-kit tyrosine kinases. Pazopanib has shown clinical benefit in renal cell carcinoma (RCC). In a randomized, placebo controlled, multicenter international phase III study that evaluated pazopanib monotherapy in treatment-naïve and cytokine-pretreated patients with advanced RCC, it was shown that pazopanib was well tolerated and demonstrated a significant improvement in progression-free survival and response rate compared to placebo, and thus, received EMEA and FDA approval for clinical use. Besides RCC, pazopanib has been and is currently evaluated in a wide variety of tumors (such as breast cancer, non small cell lung cancer, hepatocellular carcinoma) showing encouraging results with a favorable and manageable tolerability profile. Results from several trials are awaited in order to define its use in our daily clinical practice in a variety of tumors besides RCC, giving us more options towards personalized, targeted therapy.

Key words: Pazopanib, renal cell cancer, VEGFR-, PDGFR-, c-kit inhibitors.

INTRODUCTION

Over the past 30 years, the angiogenic process and its role in cancer biology has been studied thoroughly providing significant information about cancer therapy. Tumors depend on blood vessels to obtain nutrients and oxygen for growth and for metastasis to other tissues (1). Vascular endothelial growth factor (VEGF) is a key regulator of angiogenesis which mediates numerous changes within the tumor vasculature, including endothelial cell proliferation, migration, and degradation of the extracellular matrix, allowing new cells to migrate out of the tumor's primary site. These angiogenic growth factors are secreted by tumor cells and then bind to specific receptors on endothelial or other cells involved in the angiogenic process (1,2,3).

VEGFR (vascular endothelial growth factor receptors) tyrosine kinases represent a principal subfamily of transmembrane proteins possessing extracellular ligand-binding domains and intracellular kinase domains. There are three forms of VEGFR tyrosine kinases; fms-like tyrosine kinase-1 (VEGFR-1), kinase insert domain-containing receptor tyrosine kinase (VEGFR-2) and FLT-4 (VEGFR-3) (2). These VEGFR kinases play a fundamental role in tumor angiogenesis and their recognition has led to the development of several agents targeting VEGF. Another subfamily of receptor tyrosine kinases are the platelet-derived growth factor receptor (PDGFR) tyrosine kinases, which include PDGFR, c-kit and fms-like tyrosine kinase (FLT-3) and are involved in pericyte and stromal proliferation and they contribute to tumor growth (4).

Inhibition of the VEGF-signaling pathway has emerged as one of the most promising new approaches for cancer therapy. It has been intensively evaluated in the last decade and 5 years ago a clear clinical benefit has been demonstrated. VEGF-targeted therapy has been shown to be efficacious as a single agent in renal cell (RCC) (3,5-6) and hepatocellular carcinoma (HCC) (7); moreover, anti-VEGF therapy combined with chemotherapy was associated with a clear and statistically significant clinical outcome compared with chemotherapy alone in patients with metastatic colorectal cancer (CRC) (8), non-small-cell lung cancer (NSCLC) (9) and breast cancer (BC) (10). Such an anti-angiogenic therapy affects numerous cell types within the tumor microenvironment

Table 1.
Inhibitory concentrations (kinase IC 50 in nanomoles) for pazopanib and other multitargeted tyrosine kinase inhibitors studied in RCC (13).

Drug	VEGFR1	VEGFR2	VEGFR3	PDGFRα	PDGFRβ	KIT	FLT3	RET	RAF
Pazopanib	10	30	47	71	84	74	>1000	>1000	NA
Sunitinib	10	10	10	5-10	10	13	1-10	100-200	NA
Sorafenib	NA	90	20	50-60	50-60	68	46	100-150	5-10
Axitinib	0.1	0.2	0.1-0.3	5	1.6	1.7	>1000	>1000	NA

(endothelial cells, haematopoietic progenitor cells, dendritic and tumor cells) and influences vascular function (flow and permeability), in addition to blocking further new blood vessel growth (1). The action of VEGF-targeted therapy might be dependent on tumor type; indeed, in RCC, the inactivation of the von Hippel-Lindau tumor suppressor gene is associated with the constitutive activation of hypoxia inducible factor-1α (HIF-1α) gene which, subsequently, leads to the transcription of multiple hypoxia-induced genes and induces the expression of VEGF and PDGF, two important elements for tumor growth and progression (2,11).

VEGF-targeted agents that have been developed include neutralizing antibodies to VEGF or VEGFRs, soluble VEGF receptor or receptor hybrids and tyrosine kinase inhibitors (TKIs) with selectivity for VEGFRs (1). Different agents, such as bevacizumab (a humanized monoclonal antibody that neutralizes VEGF) and multikinase inhibitors, such as sunitinib (Sutent, Pfizer, active against VEGFR-1,-2,-3, PDGFR, c-kit and FLT3) and sorafenib (Nexavar, Bayer/Onyx, active against VEGFR-2,-3, PDGFR, c-kit, FLT3 and RAF) have demonstrated improved overall survival (OS) and disease-free survival (DFS) in patients suffering from CRC, NSCLC, BC, RCC, HCC (1,3,5,7-10,12) and, thus they are currently approved (both by the FDA and EMEA) for clinical use.

Pazopanib (indazolylpyrimidine [5-({4-[2,3-dimethyl-2H-indazole-6-yl) methylamino] 2-pyrimidinyl} amino)-2methyl-benzenesulfonamide; Votrient: Glaxo Smith Kline, UK) is an orally bioavailable second generation multitargeted tyrosine kinase inhibitor (13) targeting VEGFR-1, -2 and -3, PDGFR and c-kit tyrosine kinases. Pazopanib has shown clinical benefit in a variety of tumors, including RCC (where it is FDA approved for clinical use) (14), NSCLC (15,16), soft tissue sarcomas (STS) (17), cervical (18) and breast cancer (19).

Pazopanib was found to be selective against a panel of kinases when compared with other clinically available multitargeted TKIs (Table 1) (13).

RENAL CELL CARCINOMA (RCC)

At presentation, almost up to 30% of patients with renal cell carcinoma have a poor prognosis since they present with locally advanced and practically inoperable disease, or with distant metastases. In addition, approximately 40% of patients treated for localized disease will eventually develop clinical recurrence (20). Although a large proportion of RCC patients require systemic therapy, the fact that RCCs have high levels of expression of the multi-drug resistance protein P-glycoprotein makes them resistant to most chemotherapy agents. A growing understanding of the underlying molecular biology of RCC has established the VEGF pathway as a relevant therapeutic target. To date, the VEGF and the mTOR signal transduction pathways have been utilized for the treatment of RCC (21).

Renal cancer research has evolved. Significant and long-awaited advances in the treatment of advanced RCC occurred over the past few years. Sunitinib, sorafenib, temsirolimus, bevacizumab/INF, everolimus and pazopanib have demonstrated major improvements in clinical benefit with manageable side effects (2,13,20).

Pazopanib was initially tested in *in vitro* studies, and subsequently, in several preclinical Phase I, II, and III studies, both as monotherapy and in combination with other agents, providing insight into its different properties and possible future uses (4,13). The first phase I study of oral pazopanib in patients with advanced-stage refractory solid tumors (NCT00060151) published by Hurwitz et al., (22) was designed to define the safety profile and the pharmacokinetics of the drug after single- and multiple-dose administration. In this phase I dose escalation study a steady state concentration of pazopanib of ≥40 μmol/l was targeted (13,22). Sixty-three (dose escalation, n=43; dose expansion, n=20) patients with solid tumors including RCC, STS, CRC, neuroendocrine tumors, BC and NSCLC were enrolled into sequential dose-escalating cohorts (50 mg three times weekly to 2,000 mg once daily and 300-400 mg twice daily). Escalation or de-escalation was based on toxicities observed in the preceding dose cohort. The

Table 2.
Primary Efficacy and Response Rates of a phase II randomized discontinuation trial of pazopanib in patients with metastatic clear-cell RCC (23,24).

	Response Rate n (%)	
	Independent Review	**Investigator assessment**
Responses (n=225)		
Complete Response	3 (1.3%)	2 (0.9%)
Partial Response	75 (33.3%)	74 (32.9%)
Stable Disease	101 (44.9%)	95 (42.2%)
Progressive Disease	24 (10.7%)	37 (16.4%)
Not Evaluable	22 (9.8%)	17 (7.6%)
Response Rate (CR+PR)		
Overall Population	78 (34.7%)	95%CI, (26.1%-41%)
(N=225)	76 (33.8%)	95% CI, (27.6%-40%)

mean plasma pazopanib AUC0-24, the Cmax, and the C24 values were similar after daily administration of doses of 800 to 2,000 mg. These results suggest that increasing the pazopanib dose to >800 mg once daily is not likely to result in consistently greater plasma concentrations when the one-day schedule was used. Four patients experienced DLTs. Sixty-one (97%) patients experienced at least one adverse event (AE) and 48 (76%) patients experienced drug-related AEs. The most frequently reported drug-related AEs were hypertension (33%), diarrhea (33%), hair depigmentation (32%), and nausea (32%). Overall, pazopanib was well tolerated and no treatment-related deaths were reported. Three patients achieved partial response (PR), of whom two with RCC. Fourteen patients achieved a prolonged stable disease (SD) of ≥6 months. Based on the safety profile, the saturation in exposure and the achievement of a threshold concentration that seems to be correlated with clinical activity, the 800-mg once-daily administration was decided to be evaluated in future studies (22).

A multinational Phase II randomized discontinuation trial of pazopanib (VEG102616) in patients with metastatic clear-cell RCC has been recently reported (23). A total of 225 patients (67% were treatment-naïve and 33% had failed one prior therapy) received pazopanib (p.o.) at the dose of 800 mg/day for 12 weeks, at which point patients who had SD were randomized 1:1 to continue pazopanib or receive placebo. Among the first 60 enrolled patients, an independent review board documented PR in 40% and SD in 42% of the patients after 12 weeks of treatment. Based on the significant level of 'early' activity, the independent data safety monitoring committee recommended discontinuation of the randomization part of the trial and, subsequently, all patients received pazopanib. The final analysis by an independent review revealed a clinical benefit rate of 79.5% [CR+PR+SD], with three confirmed CRs and 33.3% of patients achieving a PR (Table 2) (24).

The median duration of response was 68 weeks and the median time to response 12 weeks, as assessed by an independent review. Most common AEs included hypertension, hair color changes, transaminase elevation, diarrhea, nausea and fatigue (23, 24).

A randomized, placebo-controlled, multicenter international phase III (VEF105192) study evaluating pazopanib in treatment-naïve or cytokine-pretreated patients with advanced RCC has also recently completed accrual (14). In this study, patients (N=400 planned) were stratified and randomized (2:1) to pazopanib 800 mg/day or placebo. A total of 233 treatment-naïve and 202 cytokine-pretreated patients were enrolled (290 pazopanib; 145 placebo). The primary end-point was progression-free survival (PFS) based on independent review and secondary end-points included OS, response rate (RR), and safety. PFS was significantly prolonged with pazopanib in the entire study population (9.2 vs 4.2 months; HR: 0.46; 95% CI: 0.34, 0.62; p<0.0000001), in treatment-naïve patients (11.1 vs 2.8 months; HR: 0.40; 95% CI: 0.27, 0.60; p<0.0000001), and in cytokine-pretreated patients (7.4 vs 4.2 months; HR: 0.54; 95% CI: 0.35, 0.84; p<0.001). RR was 30% with pazopanib (and 3% with placebo) and median duration of response was 58.7 weeks. Median duration of exposure was 7.4 months for pazopanib and 3.8 months for placebo. The majority of AEs were grade 1 or 2 (diarrhea, hypertension, hair color change, nausea, anorexia and vomiting). The most common laboratory abnormality was ALT and AST elevation.

Table 3.
Primary Endpoint: Volumetric Response Rate at End of Treatment (24).

	All treated (N=35)	Evaluable (N=30)
Responders	2	2
Non –Responders	33	28
Response Rate (Responder)	5.7	6.7
95% Confidence Interval	(0.7-19.2)	(0.8-22.1)

Evaluable: subjects on therapy for at least 12 weeks but no more than 6 weeks with both the pre- and post-treatment HRCT scans
Responder: subjects achieving at least 50% tumor volume reduction from baseline

The conclusion is that pazopanib monotherapy was well tolerated and demonstrated a significant improvement in PFS and RR compared to placebo. Final OS results are awaited (14).

Based on these positive results, the European Medicines Agency (EMEA) approved pazopanib as an oral therapy for patients with advanced and/or metastatic RCC.

Patients with progressive disease on placebo were included in an open-label extension study (VEG107769) of pazopanib 800 mg/day (25). The primary end-point of this study was safety and secondary end-points included RR (according to the RECIST criteria) and PFS. Among the 70 placebo-treated (plus one pazopanib patient as an exemption due to symptom improvement) enrolled patients, 21 (30%) had died, 40 (56%) discontinued pazopanib and 31 (44%) were still on pazopanib. Most patients died or discontinued pazopanib due to PD. The majority of AEs (hypertension, hair color changes, diarrhea, anorexia and nausea) were grade 1-2. Grade 3 and 4 AEs were reported in 21% and 7% of patients, respectively. The most common grade 3 chemistry laboratory abnormalities were hypernatremia and elevated ALT and AST. RR was 32.4% (95% CI: 21.5-43.3) and the median PFS 8.3 months (95% CI: 6.1-11.4). The conclusion of this expansion access program was that patients with advanced RCC who developed PD on placebo in the above mentioned phase III study, achieved clinical benefit when pazopanib was administered (25).

Another phase III trial comparing pazopanib with sunitinib in patients with treatment-naïve RCC is ongoing and results are awaited (11).

MONOTHERAPY REGIMENS IN OTHER NEOPLASMS

Hepatocellular cancer (HCC)

A phase I trial (NCT00370513) of pazopanib, published to date in abstract form, enrolled 21 Asian patients with advanced HCC, a highly vascular tumor with increased levels of angiogenic factors (26). The maximum tolerated dose (MTD) was determined at 600 mg once daily. Although, the abstract of this phase I trial was not focused on activity, nevertheless, preliminary evidence of efficacy was provided. Best response was PR in two patients (7%) but SD lasting for >4 months was reported in 11 patients (41%). The median TTP was 137.5 days and the median PFS for the whole study population 17.7 weeks (95% CI: 11.9-23.9). The pharmacokinetic study in ascending doses of pazopanib in advanced HCC found that C24 values of at least 15μg/ml were achieved across the dose range of 200 mg q.d. to 800 mg q.d. (26).

Breast cancer (BC)

The activity of pazopanib in recurrent or metastatic breast cancer was evaluated in a phase II study (19); 21 patients (67% ER positive and all HER-2 negative) received pazopanib 800 mg/day. A PR was observed in one (5%) patient and SD in 11 (58%); the clinical benefit rate (CR, PR or SD for≥6 months) was 26%. The median TTP was 3.7 months and the estimated PFS at 3 and 6 months 55% and 28%, respectively. AEs were grade 3/4 elevations in AST (14%) and ALT (10%) and grade 3 hypertension and neutropenia (14% each). Other common AEs were grade 1-2 lymphopenia, neutropenia, diarrhea, fatigue, skin hypopigmentation, hypertension, nausea, vomiting, anorexia and headache. The study concluded that pazopanib is well tolerated and active in pretreated breast cancers with a SD rate and TTP comparable to other active agents in this setting (19).

Non-small cell lung cancer (NSCLC)

A phase II open-label multicenter clinical trial evaluated the safety and efficacy of pre-operative administration of pazopanib (800 mg/day orally for 2 to 6 weeks followed by a 7-day washout period prior to surgery) in 35 treatment-naïve patients with resectable NSCLC (adenocarcinoma 60%; squamous cell carcinoma 11%) (15,16,24). The primary end-point was volumetric response rate (VRR) defined as

the percentage of patients with a tumor volume reduction of at least 50% (Table 3) (24).

Secondary objectives included ORR and safety. According to the RECIST criteria, the ORR was 6.7% in the evaluable population and 5.7% in the all treated population with 2 PRs, respectively. Neither group achieved a CR. Although target VRR was not met, reductions in tumor volume from 0.71% to 85.79% were observed in 85.7% of the subjects. Most commonly reported AEs were hypertension, diarrhea, fatigue, nausea, ALT increase, headache and hair color changes. Five patients were withdrawn from study medication, four due to AEs and one for other unreported reasons (15,16).

Soft tissue sarcomas (STS)

Pazopanib (800 mg/day orally) has also been explored in the context of a phase II clinical trial in 142 patients with intermediate or high grade advanced or metastatic STS who were not eligible for chemotherapy or had received a maximum of two single cytotoxic agents for advanced disease (17). The progression-free rate at 12 weeks (PFR12weeks) was chosen as the primary end-point. Secondary end-points included overall PFS, RR, OS and safety. Synovial sarcomas, adipocytic STS, leiomyosarcomas and other STS comprised the four different strata that were studied. The adipocytic STS stratum was closed after the first stage due to insufficient activity (PFR12weeks 26%; five out of 19 patients). PFR12weeks was 44% (18 out of 41 patients) in the leiomyosarcomas cohort, 49% (18 out of 37 patients) in the synovial sarcomas cohort and 39% (16 out of 41 patients) in the other STS types. PFS and OS were prolonged in the three cohorts in whom the primary end-point was reached. A PR was achieved in nine patients (one with leiomyosarcomas, five with synovial sarcoma and three with other types). The most frequent drug-related AEs included hypertension, fatigue, hypopigmentation and nausea. Other toxicities included liver enzymes elevation, myelosuppression and proteinuria, all of which were mostly grade 1 to 2. The results of this trial strongly suggest that pazopanib has interesting antitumor activity in pretreated patients with STS; based on this data a double-blind placebo-controlled phase III trial of pazopanib in patients with different STS types has been initiated (17).

In addition, in a recent case report, an impressive tumor regression was noted in a patient with metastatic Merkel cell carcinoma when treated with pazopanib (27).

Ovarian cancer

Pazopanib has also been evaluated in 35 women with non bulky epithelial ovarian, fallopian tube and primary peritoneal cancers who relapsed following prior platinum-based chemotherapy (28). All patients had received 1 to 2 previous chemotherapy regimens; 39%, 33% and 28% of the patients had relapsed in <6 months, 6-12 months and >12 months after the previous chemotherapy regimen, respectively. Evaluation of response showed that pazopanib induced a >50% decrease in CA125 serum levels in 11 of 35 evaluable patients (31%) with a median time to response of 29 days and a median duration of response of 113 months (28).

Thyroid cancer

Pazopanib has been evaluated in 32 patients with advanced and progressive radioiodine insensitive differentiated thyroid

Table 4.

All-tumors published phase II trials' data.

Phase II trials	PR	SD	RR	TTP	PFS3 mo	PFS6 mo	>50% decrease in CA125	>50% decrease in TGA
BC (21 pts) (19)	5%	58%	26%	3.7 mo	55%	28%		
NSCLC (35 pts) (pre-operative administration) (15,16,24)			6.7%					
ADVANCED OR METASTATIC STS (142 pts) (17)								
leiomyosarcomas					44%			
synovial sarcomas					49%			
other STS					39%			
adipocytic STS					26%			
OVARIAN CANCER (28)				113 mo			31%	
THYROID CANCER (29)	19%							69%
MULTIPLE MYELOMA (30,31)	Absence of efficacy							

cancers that could have received up to 2 previous therapies. Five (19%) from the 26 evaluable patients developed PR; in addition, the thyreoglobulin (TGA) serum levels which were increased in 11 (69%) of 16 patients before treatment declined by >50%, whereas no patient with normal TGA levels before treatment experienced an increase (29).

Multiple myeloma (MM)

Pazopanib, by inhibiting VEGFR, is associated with a decreased in vivo growth of MM cells due to increased cell apoptosis and decreased angiogenesis, leading to prolonged survival in a mouse xenograft model of human MM (30,31). Preclinical data also demonstrates synergistic toxicity of low dose pazopanib with conventional and novel anti-multiple myeloma therapeutics. However, when pazopanib has been evaluated in 21 patients with extensively pre-treated MM, no objective response (CR, PR or SD) was observed and 10 patients experienced PD in the first 6 weeks. The absence of efficacy is consistent with the poor results obtained by other VEGFR inhibitors in MM (30,31).

Table 4 concentrates data from all-tumors published phase II trials.

COMBINATION REGIMENS

Combinations with lapatinib

As already mentioned above, pazopanib is an oral angiogenesis inhibitor targeting VEGFR, PDGFR and c-kit. Lapatinib, is an oral tyrosine kinase inhibitor of EGFR (ErbB1) and HER-2 (ErbB2). The combined VEGFR, PDGFR and ErbB1-2 inhibition could provide synergistic antitumor activity in some neoplasms, such as breast and cervical cancer and malignant gliomas (18,32-34).

Breast cancer (BC)

In a phase II multicenter, open–label, randomized clinical trial (NCT00347919), pazopanib was evaluated in combination with lapatinib versus lapatinib monotherapy in 141 patients with HER-2 positive advanced/metastatic breast cancer (32,33). Women with stage III/IV invasive HER-2 positive BC, with no prior chemotherapy or anti-HER-2 therapy were randomized to receive pazopanib 400 mg plus lapatinib 1000 mg once daily (69 patients) or lapatinib 1,500 mg once daily (72 patients). The primary end-point was progressive disease rate (PDR) at week 12 and secondary end-points included response rate at 12 weeks, time to response, response duration and OS. The PDR was 15.9% for patients receiving pazopanib plus lapatinib and 37.4% for those on lapatinib monotherapy. The RRs were 36.2% and 22.2%, respectively. Most of the patients in the combination arm developed reduction of the target lesions (32,33).

Malignant glioma

The combination of pazopanib and lapatinib in patients with relapsed malignant glioma was evaluated in a phase I/II study (34). The phase I part of the study determined the optimally tolerated regimen (OTR) of the pazopanib/lapatinib combination when administered with enzyme-inducing anticonvulsants (EIACs) and indicated that EIACs decrease the pazopanib and lapatinib plasma concentrations; the minimum active plasma levels, described in previous studies for both drugs, were approached at 600 mg bid and 1000 mg bid for pazopanib and lapatinib respectively when administered concurrently with EIACs. In the phase II part of the study, the efficacy of the daily pazopanib/lapatinib (400 mg/1,000 mg) regimen was evaluated in patients with relapsed Grade IV gliomas without concurrent administration of EIACs. As far as the efficacy of the combination is concerned, PR was achieved in three patients (11%) and SD lasting for ≥8 weeks in 13 patients (43%) during the phase I part of the study (30 pts); moreover, during the phase II part of the study (lapatinib 1,000 mg + pazopanib 400 mg once daily; n=41 patients) PR was observed in three patients and SD (lasting for at least 8 weeks) in 21. The combination had a manageable safety profile with a preliminary OTR with EIACs of pazopanib 600 mg bid/lapatinib 1,000 mg bid and with EIACs decreasing their plasma concentrations (34).

Cervical cancer

A randomized phase II trial evaluated the combination of pazopanib and lapatinib (400 mg/1,000 mg q.d. ascended to 800 mg/1,500 mg q.d. after the first 20 patients) versus 800 mg q.d. pazopanib or 1,500 mg q.d. lapatinib monotherapy (randomization 1:1:1) in 235 patients with advanced and recurrent cervical cancer (18). Pazopanib and lapatinib both demonstrated a favorable toxicity profile. This study demonstrated a significant prolongation of PFS and OS in favor of the pazopanib monotherapy arm with a median OS of 50.7 vs 39.1 weeks. RRs were 9 and 5% for pazopanib and lapatinib, respectively (18).

Other combinations

Phase I combination trials in solid tumors

The combination of pazopanib (400 to 800 mg/day orally) and paclitaxel (15 to 80 mg/m^2 on days 1, 8 and 15 every 28 days) was evaluated in a phase I clinical trial in 25 patients with advanced solid tumors including BC, esophageal cancer and NSCLC. The maximum tolerated doses were defined at 800 mg for pazopanib and 80 mg/m^2 for paclitaxel with five out of 16 patients experiencing PR and 10 patients experiencing SD for at least 12 weeks. The pharmacokinetic results indicated that pazopanib increases the mean paclitaxel AUC (the mean area under the plasma concentration) and Cmax by 45 and 40% respectively (35).

Pazopanib was also assessed in a phase I trial (NCT00387387) in combination with FOLFOX 6 (oxaliplatin, 5-fluorouracil and folinic acid) or CapOX (capecitabine and oxaliplatin) in patients with previously untreated advanced or metastatic

colorectal cancer and adequate organ function (36). Patients were assigned to pazopanib with FOLFOX 6 or CapOX with escalated doses of pazopanib starting at 400 mg daily. The optimal tolerated regimen (OTR) was the combination dose at which <1/6 patients experienced dose-limiting toxicity and was achieved at 800 mg pazopanib with full-dose FOLFOX 6 and at 800 mg pazopanib with CapOX when capecitabine was reduced to 850 mg/m^2 twice daily. Efficacy and pharmacokinetic analyses are ongoing (36).

Several phase I combination therapy trials are ongoing and actually evaluate different pazopanib-based combinations. The NCT00678977 trial investigates the combination of pazopanib with gemcitabine and gemcitabine plus cisplatin in patients with advanced solid tumors (expected accrual n=39 patients); other studies evaluate the combination of pazopanib with irinotecan and cetuximab in patients (n=40) with CRC (NCT00540943), pazopanib with epirubicin or doxorubicin in advanced solid tumors (NCT00722293), whereas, the NCT00619424 trial compares the pazopanib/erlotinib combination with the pazopanib/pemetrexed combination in patients (n=55) with advanced solid tumors (21,24).

In Table 5 combination trials of pazopanib with other targeted and/or chemotherapeutic agents and respective tumors are summarized.

DISCUSSION

Pazopanib (Votrient) is a multi-target tyrosine kinase inhibitor of VEGF -1, -2, -3, PDGFR –α and –β and c-kit tyrosine kinases. It has demonstrated encouraging antineoplasmatic activity in different tumor types with tolerable and manageable toxicity (4).

Phase I studies of pazopanib as monotherapy and in combination with other agents in patients with advanced solid tumors have reported encouraging activity. Based on the safety profile, the saturation in exposure and the achievement of a threshold concentration which is correlated with clinical activity, the 800-mg once-daily administration was decided to be considered for phase II trials (4,13,21-22,24). Moreover, phase II clinical trials of pazopanib (either as monotherapy or in combination with other drugs) have reported interesting results with a favorable tolerability profile (17-19,23-24). Finally, a randomized phase III study of pazopanib versus placebo in patients with advanced RCC demonstrated that the administration of pazopanib was associated with a significant clinical benefit both in terms of PFS and ORR (14,25). In all studies pazopanib has been associated with an acceptable toxicity profile. Liver function abnormalities, hypertension, diarrhea, hair color change and nausea were the most frequent side effects.

Until recently, interferon A2 and IL-2 were the only available drugs with proven efficacy against metastatic RCC (5). Improved understanding of the biology of RCC led to the development and approval of several new drugs such as sunitinib, sorafenib, temsirolimus and everolimus for the treatment of metastatic RCC; however, none of them is associated with significant rates of long-term disease-free survival (1,3,5,12). Further clinical research led to the discovery of pazopanib, a drug that received FDA and EMEA approval for the treatment of patients with advanced RCC, with the recommended dose of 800 mg orally once daily without food (22). Besides that, pazopanib has shown encouraging efficacy results in other tumor types, such as BC (19), CRC (36), HCC (26), NSCLC (15-16), multiple gliomas (34), fallopian tube, ovarian and peritoneal tumors (28), STS (17), cervical cancer (18) and other solid tumors. As far as RCC is concerned, pazopanib is already incorporated in our daily therapeutic choices; it is probable that, soon, it will be approved for other types of cancer as well, giving us more options for the benefit of our patients (4).

Table 5.
Combination trials of pazopanib.

COMBINATION TRIALS	TUMORS
Pazopanib + lapatinib (phase II) (32,33)	HER-2 positive advanced or metastatic breast cancer patients
Pazopanib + lapatinib (phase I/II) (34)	Relapsed malignant glioma
Pazopanib + lapatinib (phase II) (18)	Advanced or recurrent cervical cancer
Pazopanib + paclitaxel (phase I) (35)	Advanced solid tumors (BC, esophageal cancer, NSCLC)
Pazopanib + FOLFOX or CapOX (phase I) (36)	Previously untreated advanced or metastatic CRC
Pazopanib + gemcitabine (phase I) (21)	Advanced solid tumors
pazopanib + irinotecan + cetuximab (phase I) (21)	CRC
pazopanib + epirubicin or doxorubicin (phase I) (21)	Advanced solid tumors
Pazopanib + erlotinib vs pazopanib + pemetrexed (phase I) (21)	Advanced solid tumors

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Cancer cachexia syndrome: a review

Ioannis Gioulbasanis, Panagiotis Vlachostergios, Athanassios Zafiriou, Christos Papandreou

Department of Medical Oncology, University Hospital of Larissa, University of Thessaly, School of Medicine, Larissa, Greece

Correspondence:
Ioannis Gioulbasanis
Department of Medical Oncology, University Hospital of Larissa, University of Thessaly, School of Medicine, Larissa, Greece.
e-mail: rodopatis@gmail.com

Abstract: Cancer cachexia syndrome is a clinical entity often observed in patients with neoplastic diseases and characterized by loss of muscle mass, leading to increased morbidity, quality of life deterioration, reduced tolerance and response to treatment and shortened survival. The syndrome is often under-diagnosed due to lack of clinical suspicion, particularly in patients with elevated body mass index.

Recently, a new scientific definition as well as diagnostic criteria have been proposed, including - but not limited to - weight loss. The use of screening questionnaires as well as computed tomography image analysis software for the quantification of muscle and fat body composition are expected to further enhance diagnosis and response to treatment assessment.

The principal pathophysiological features of the cancer cachexia syndrome include abnormalities in energy intake-waste balance, presence of inflammation, and an altered lipid and muscle metabolism favoring lipolysis, reduced muscle synthesis, and increased muscle degradation.

Although no therapeutic interventions may, thus far, be considered successful, a better combination of existing treatment modalities based on randomized clinical trials, as well as the development of innovative pharmacological agents is expected to lead to a more effective and beneficial therapeutic approach for these patients.

Key words: Cancer, cachexia, sarcopenia, inflammation, cytokines.

INTRODUCTION

Introduction – definition

The term "cachexia" is a composite word, first used by Hippocrates to describe patients in poor clinical condition. Even after all those years of progress in biomedical sciences, the underlying mechanisms responsible for the pathogenesis of this syndrome have not been fully elucidated and there has been a long-going debate about its exact definition.

Finally, a uniform agreement on a clinical determination of the syndrome was reached as late as 2008 (1). According to that, "cachexia is a complex metabolic syndrome associated with underlying diseases and characterized by loss of muscle mass with or without loss of fat tissue. The principal clinical feature in adults is weight loss (corrected for fluid retention) while in children growth restriction is the most frequent clinical finding (with the exception of endocrine-related disorders). Anorexia, inflammation, insulin resistance and muscle degradation are often related to cachexia. However, cachexia is different from starvation, age-related muscle loss, depression, malabsorption and hyperthyroidism and has increased morbidity".

Evidently, this definition is not specific for cancer cachexia but is relevant to all end-stage diseases potentially implicated as causative factors such as heart failure, chronic obstructive pulmonary disease, acquired immunodeficiency syndrome, etc.

Diagnosis and incidence of cachexia

The same authors (1) propose the following diagnostic criteria for cachexia:

Weight loss >5% during ≤12 months (or BMI <20 kg/m^2) and 3/5 of:

1. Reduced muscle strength
2. Fatigue
3. Anorexia
4. Low free fat index
5. Abnormal lab values:
   i. Increased inflammation markers [C-reactive protein (CRP), interleukin (IL)-6]
   ii. Anemia (Hb <12 g/dL)
   iii. Low serum albumin (<3.2 g/dL)

Based on the classic study by Dewys et al. (2) in the early '80s, >5% weight loss may occur in up to 80% of late-stage cancer patients, is correlated with poor prognosis and constitutes the major cause of death in 20% of said cases, due to respiratory muscle degradation and respiratory failure (3). Syndrome incidence is greater in patients with lung and gastrointestinal cancers (4,5).

In clinical practice, the percentage of weight loss during a set period of time is usually the only screening tool currently in use, either for prognostic purposes or for decision making on starting nutritional interventions. However, monitoring of this parameter alone, irrespective of existing discrepancies in the exact values and time interval necessary for treatment (6), appears as a rather simplified diagnostic approach (7).

Nutritional status assessment may be better supported by the use of specific screening questionnaires (7,8), such as Patient-Generated Subjective Global Assessment (PG-SGA) (9) and Mini Nutritional Assessment (MNA) (10), combining subjective data with objective measurements. Recently we suggested that MNA may have a better predictive and prognostic value compared to percentage (%) of weight loss as baseline nutritional evaluation in patients with metastatic lung cancer (11).

Sarcopenic obesity

Intriguingly, the most important reason for under-diagnosis of cachexia is increased body weight which is also responsible for increased cancer risk (12). In these cases, muscle degradation is masked under a fat tissue layer without being practically detectable (13). This results from the progressive loss of muscle mass at a level greater than 2 standard deviations (SD) from the median age-adjusted value (14) – this is a common definition of sarcopenia – and, simultaneously, a body mass index (BMI) value so high that would never raise clinical suspicion of malnutrition.

Recently, the development of software that enables analysis and accurate calculation of muscle and fat tissue mass has evolved from computed tomography imaging (15). In a study involving patients with pancreatic cancer, only 10% of patients could be considered malnourished based on classic criteria, but the same group of patients was found over 55% when calculated using muscle mass as an index (13). Sarcopenia in overweight patients is correlated with poor survival (15) as well as increased treatment-induced toxicity (16).

Pathophysiology of cancer cachexia (Figure 1)

The energy balance in cachexia

As in all thermodynamic systems, total body mass is regulated by the balance between energy intake and consumption. The most important pathophysiological disorders in cachexia result in aberration of this balance.

Anorexia

Anorexia is defined as loss of the desire to eat (loss of appetite). However, even in this case, diagnosis is not completely clear (17). The use of visual analogical scales is a useful epidemiological tool, but does not seem to be very reliable particularly in cases with only minor loss of appetite (18). Alternatively, assessment of anorexia could be based on the analysis of secondary symptoms related with reduced food intake (19). Thus, patients suffering from at least one of the following symptoms, without any other evident cause, may be characterized as anorectic:

1. Early saturation
2. Taste alterations
3. Smell alterations
4. Meat consumption repulsion
5. Nausea/Vomiting

It has been calculated that 50% of patients exhibit feeding problems at diagnosis (2), which is even higher at later stages of the disease (20).

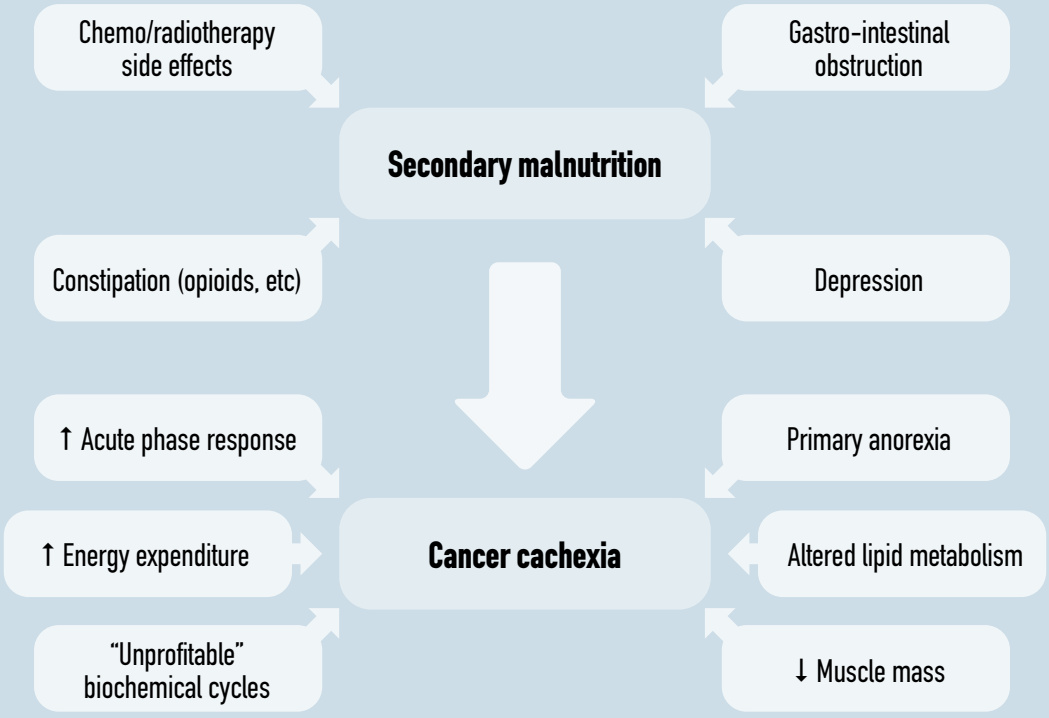
Many factors are implicated in the syndrome's pathophysiology, mainly peripheral signals, particularly hormones like insulin, leptin and ghrelin, as well as energy signals such as malonic coenzyme A, which is increased due to abnormal fatty acids metabolism leading to reduced food intake (17). Peripheral signals being detected in hypothalamic centers may trigger or inhibit energy intake (21). There are indications that these pathways are disrupted during cancer cachexia, partly due to the presence of cytokines, such as interleukin (IL)-6, tumor necrosis factor (TNF)-α and interferon (INF)-γ (17). Recent data support the presence of "micro-inflammation" in the aforementioned brain centers (22).

Nonetheless, the presence of anorexia alone could not entirely explain the changes in body composition during cachexia (23). For instance, body weight loss observed in anorexia is mainly caused by fat loss, whereas in cancer cachexia equal amounts of fat and muscle mass are lost (24). This means that syndrome reversal may not be possible with simple calorie replenishment (23). In contrast, anorexia caused by anticancer treatment responds to nutritional dietary supplements (25), which translates to better survival rates (26).

The energy expenditure

Seventy percent of the totally expended energy is lost during non-stress conditions. It is modified according to the tumor primary site (e.g. it increases in lung and pancreatic cancer but remains unaffected in gastric and colon cancer) (27) and increases in end-stage patients (28). Depression is often observed in patients with pancreatic cancer (29) and results in reduction of physical activity and therefore of voluntary energy loss (30), at the cost of quality of life.

Figure 1.
Pathophysiology of cancer cachexia.



It seems that increased energy loss under non-stress conditions is due to increased thermogenesis in cinereous fat tissue and muscles. This is caused by activated unconjugated proteins (UCPs) located in the inner mitochondrial membrane that participate in the proton flow and control the production of free radical species (23). There are indications that certain cytokines and tumor factors (e.g. lipid mobilizing factor, LMF) are able to modify UCP levels (23).

The role of "unprofitable" biochemical cycles

Most cancer cells use glycolysis as the only way of ATP production (also known as Warburg process) (31) and this is caused by mitochondrial dysfunction due to mitochondrial DNA mutations (32).

Moreover, hypoxia and activation of hypoxia inducible factor (HIF)-1 promote the activation of glycolytic enzymes (33) while at the same time inhibit the action of pyrouvate dehydrogenase resulting in the production of lactic acid instead of acetyl-coenzyme A (34). This is an extremely energy-wasting process, demanding a 40-fold higher supply of nutritional elements for the production of the same number of ATP molecules as under aerobic conditions (35). It has been calculated that this process results in additional loss of 300 kcal/day in cancer patients (36).

Furthermore, glycerol produced by the hydrolysis of triglycerides, and amino-acids as constituents of muscle proteins produced by neoglycogenesis, offer lower amounts of energy (23). Due to the coexisting insulin resistance, the process of neoglycogenesis is not subjected to an analogous negative regulation (37).

Acute phase inflammatory response

The presence of acute phase inflammatory response, often confirmed by increased CRP levels (CRP>10 mg/l), is associated with reduced survival in patients with cachexia (38). An important role is played by soluble mediators, particularly pro-inflammatory cytokines (39), which are produced as a response from leukocytes infiltrating the tumor microenvironment (40). The inflammatory response is also related with the production of free radical species which may further promote cytokine production (41).

Although the exact mechanism through which the acute phase inflammatory reaction leads to muscle atrophy is not clear, it is possibly related with a change of liver metabolism during which muscle degradation products

are used to generate acute phase proteins (42). It has been calculated that the degradation of 2.6 g of muscle protein is required to produce only 1 g of fibrinogen (43). In a study of pancreatic cancer patients with cachexia it has been demonstrated that calorie replenishment as a sole dietary intervention is not only ineffective but may even worsen the overproduction of fibrinogen by the liver, resulting in further loss of muscle mass (44).

Lipid metabolism

The loss of fat tissue is mostly caused by increased lipolysis resulting in the increased production of glycerol and free fatty acids (45). However, the extent of lipolysis could not be explained solely by the tumor energy needs (23).

Interestingly, a glycoprotein termed zing a2-glycoprotein (ZAG) has been isolated from the urine of patients with cachexia, sharing great homology with LMF which was initially identified in an adenocarcinoma mouse model (46). These glycoproteins promote lipolysis through cyclic mono-phosphate adenosine (cAMP) (47). Eicosapentaenoic acid (EPA), which has been used as a treatment for cachexia, seems to reduce lipolysis through attenuation of the action of ZAG (48).

The cytokines TNFα, INFγ and IL-1β seem to play a less important role by inhibiting the action of lipoprotein lipase which normally hydrolyses fatty acids from plasma lipoproteins to enable their storage in lipocytes (49).

Muscle mass

The reduction of muscle mass observed in cachexia stems both from decreased synthesis and increased muscle degradation. This is the principal cause responsible for the poor survival of patients with cachexia (50).

Muscle synthesis

Reduced protein synthesis has been described in mouse models with or without cachexia suggesting that it constitutes an independent mechanism (51).

The combination of two pro-inflammatory cytokines, TNFα and INFγ, reduces expression of transcription factor MyoD resulting, in turn, in reduced production of heavy chain myosin (52).

Furthermore, alterations have been observed in patients with cachexia with regard to the eukaryotic initiation factor 2 (eIF2) phosphorylation status which exerts a translational regulatory role in myosin synthesis (23).

From a treatment-oriented point of view, the role of lateral chain amino-acids seems to be important, particularly leukine (53), which abrogates the effect of an eIF2 kinase (54). Whether the use of such agents has any effect on tumor growth rate has not been fully clarified, although there are several indications suggesting that this may not be the case (55).

Muscle degradation

There are three systems involved in muscle degradation: the lysosomal system, the intracellular calcium release system and the ubiquitin-proteasome system, which is particularly important in patients with severe weight loss (56). In contrast, during the early phase of cachexia, the lysosomal system seems to play a major role (57). An additional contribution to muscle atrophy is made by myocyte apoptosis, given the increased activity of certain caspases (58).

Proteolysis-inducing factor (PIF) is a glycoprotein produced by tumor cells and modifies proteasome activity through the activation of nuclear factor-kappa B (NF-κB) (59) while simultaneously causes cytokine production from monocytes and Kupffer cells (60). The activation of NF-κB may also be effected by TNFα (61) and angiotensin II (62) in a similar manner, whereas IL-6 possibly promotes muscle mass loss indirectly, by increasing tumor burden (63).

Finally glucocorticosteroids cause muscle degradation via the ubiquitin-proteasome system but through a different mechanism involving the Forkhead box O transcription factors (FOXO) but not NF-κB (64). Further, they reduce the signal intensity of the IGF-1/PI3K/Akt pathway resulting in activation of the lysosomal system (24).

Treatment of cachexia

Today, no treatment may be considered successful in the management of cachexia. This does not necessarily mean that there are no effective drugs available but, that, they may have been used inappropriately (65).

One of the most important prerequisites for a successful "anti-cachectic" therapy is starting the treatment early, before the condition becomes irreversible (8,44). Indeed, the term "pre-cachexia" has been proposed to describe a condition of limited weight loss not accompanied by anorexia or signs of generalized inflammatory reaction (44). Towards this direction it would be really useful to develop sensitive biological markers. By now, the only easily measurable biomarker in clinical use is CRP, which has been extensively studied (38). Other potentially helpful biological markers could be insulin, cortisol, angiotensin II and appetite-regulating hormones, involving leptin and ghrelin (38).

From another aspect, certain single nucleotide polymorphisms (SNPs) of genes encoding pro-inflammatory cytokines (66) or being associated with muscle atrophy (67) are related to a genetic predisposition for cachexia. Interestingly, such a polymorphism has been recently described for an anti-inflammatory cytokine, IL-10 (68).

The ideal target of an anti-cachectic therapy is not clear. A typical example is the use of megestrol acetate which acts by increasing appetite and thus increases body weight but this is mostly due to the accumulation of fat and water retention, without affecting other clinical parameters (65,69).

Table 1.
Current and future potential anti-cachectic agents.

Current treatment options
• Progestagens (Megestrol acetate, Medroxyprogesterone acetate)
• Corticosteroids
Drugs that failed in clinical trials
• Cannabinoids
• Pentoxifylline
• Monoclonal antibodies against cytokines
• Proteasome inhibitors
Promising agents
• Eicosapentaenoic acid (EPA)
• Thalidomide
• Non steroid anti-inflammatory drugs (NSAIDS)
• Ghrelin
• Anabolic steroids
• Angiotensin converting enzyme (ACE) inhibitors

It has been made clear by regulatory authorities that the approval of an anti-cachexia therapy should postulate the improvement of both body composition and physical activity (44). The quantification of muscle mass via CT analysis (16) combined with the use of new, objective methods of physical activity evaluation (e.g. monitoring of slight muscle electrical activity [70]) may be truly helpful in this perspective.

Nutritional support and parenteral feeding

A global healthcare approach of patients with cachexia necessitates a nutritional evaluation. In a study of patients undergoing radiation therapy, the contribution of nutritionists was proven equally or even more important than the use of high-calorie nutriments (71). There are many different guidelines among different associations on when parenteral feeding should be started, depending on clinical experience and references from specific expert groups (committees). According to European Society for Parenteral and Enteral Nutrition (ESPEN) directions, the calorie replenishment should start immediately in already malnourished patients, if feeding is not possible for over 7 days and if there is a reduction of calorie intake greater than 60% for more than 10 days (72).

Although there are no randomized trials, it is supported that enteral nutrition in patients with cancer cachexia should be enriched with fat, given the normal and/or increased lipid metabolism (73) and the disturbance in glucose metabolism (37,74). Moreover, there are no clear data on the minimal protein content of nutriments and various guidelines suggest an intake of 1.2 to 2 g per kg of body weight per day (75).

The aim of parenteral nutrition in patients with progressive weight loss is stabilization and/or improvement of their nutritional status which would result in maintaining a good quality of life. This seems to be feasible in the absence of systemic inflammatory response (25). However, when inflammation is present, it is extremely difficult to restore cellular mass by energy supplementation alone (43,44). In such cases it is supported that any dietary intervention needs to be combined with pharmacological agents modifying the inflammatory response (72).

Pharmacological agents (Table 1)

Until now, the only acceptable pharmacological intervention is the administration of megestrol acetate as its effects have been extensively studied (at least 15 clinical trials and a systematic review) in patients with cancer cachexia (69). Although the exact mechanism of action has not been fully elucidated, it is believed to involve an excitation of neuropeptide Y activity, which is part of the hypothalamic axis of appetite regulation (21), or suppression of pro-inflammatory cytokine synthesis (76). As mentioned before, increased appetite and/or weight attained in some of the studies was due to the increase of fat and water and did not lead to the expected improvement in quality of life.

Steroids, acting through an increase in appetite, have been found to improve both food intake and memory of patients

(77). However, they are responsible for aggravating muscle degradation and therefore their long-term use should be discouraged (44).

EPA, which is classified as a polysaturated fatty acid, inhibits muscle degradation by modulating the action of PIF-induced NF-κB (78), while simultaneously enabling fat tissue conservation by reducing ZAG synthesis (46). Furthermore, though less effective than megestrol acetate, it seems to promote appetite (79). EPA has been mostly used in combination with high-calorie nutritional supplements with some studies showing improvement of food intake (80) and physical activity (81). However, a meta-analysis of 5 randomized trials failed to reach a definite conclusion regarding the role of EPA in patients with cancer cachexia (82).

In addition, there are other drugs that did not meet the expected outcomes. Such an example is the use of cannabinoids (83), which has shown only slight clinical benefit despite acting through increasing appetite and attenuation of cytokine production (84). Furthermore, administration of pentoxifylline, a methylxanthine theoretically intended to reduce TNFα mRNA levels (85) did not show any efficacy (86) which was also the case for infliximab, a monoclonal antibody against TNFα, when administered together with gemcitabine in pancreatic cancer patients with cachexia (87).

Finally, a study on the use of bortezomib, a proteasome inhibitor, failed to demonstrate any benefit in cancer patients with weight loss (88).

Other therapeutic agents have shown some positive results without leading to safe conclusions. In this group of drugs, thalidomide promotes the degradation of TNFα mRNA and inhibits NF-κB–regulated gene expression (89). Non-steroidal anti-inflammatory drugs (NSAIDS) reduce the loss of energy under basal, non-stress conditions and also CRP levels (90). Ghrelin is a peptide hormone that increases appetite, muscle mass and intestinal mobility (91). Anabolic steroids promote protein synthesis, thus positively affecting the nitrogen balance (92). Angiotensin converting enzyme (ACE) inhibitors reduce TNFα production by monocytes and also act on angiotensin II levels (93).

Based on existing data regarding the pathophysiology of the syndrome and relevant clinical experience, the co-administration of enteral nutrition and available drugs in the context of better designed clinical trials is being tested. Furthermore, new drugs are being developed with the aim of inhibiting the action of pro-inflammatory cytokines, modifying intracellular signals, inhibiting degradation and promoting synthesis of structural components (44,49,65,92).

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A Case of Fiber in an Ovarian Cyst

Georgios P. Rigakos, Stefanos V. Labropoulos, Ioulia A. Evangelou, Dimitra G. Giannopoulou, Maria N. Kordoni, Evangelia D. Razis

1st Department of Medical Oncology, Hygeia Hospital, Athens, Greece

Correspondence:
Georgios Rigakos, 54-56 Eyboias Street, 11362, Athens, Greece,
e-mail: grigos1@hotmail.com

Abstract: Gastrointestinal perforation is a rare but possibly fatal side effect of bevacizumab treatment. In this report, we present a unique case of bevacizumab-associated gastrointestinal perforation with atypical presentation and clinical course that led to the remarkable finding of a dietary fiber in the lumen of an inflamed ovarian cyst. Our case report underlines to the physicians prescribing bevacizumab the relatively uncommon appearance of bevacizumab-associated gastrointestinal perforation and is accompanied with a concise review of the literature.

Key words: Bevacizumab, non-small cell lung cancer, fistula, gastrointestinal perforation.

CASE PRESENTATION

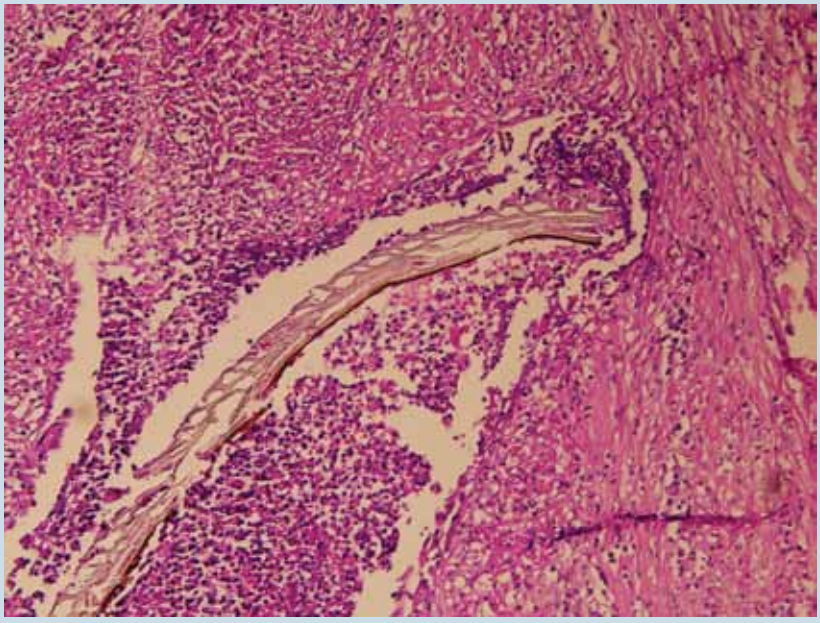
A 64-year-old female smoker appeared in November 2007 with cough, dyspnoea and haemoptysis. Her chest X-ray revealed a dilated mediastinum and a left upper lobe mass. Past medical history included a chocolate cyst of the ovary and fully treated pulmonary tuberculosis with residual fibrotic findings on CT scans in 2001. The patient had a chest CT scan that showed a 3.8 cm tumor in the right middle lobe with enlarged lymph nodes in the right hilum and mediastinum, two micronodular densities in the right lung and one in the left as well as one lesion in the upper left lobe consistent with previous TB. At bronchoscopy there was a fungating mass in the orifice of the right middle bronchus and enlarged subcarinal and paratracheal lymph nodes. Biopsies and cytology revealed adenocarcinoma. Staging tests that included brain, abdominal and pelvic MRI, bone scintigraphy and PET/CT scan were negative for metastatic disease but revealed some cysts in the liver and one cyst in the left ovary. The final staging was T2 N3 MX, due to the uncertain nature of the small nodular bilateral lesions.

The patient received 3 21-day cycles of paclitaxel (200 mg/m^2) and carboplatin (AUC 6) with bevacizumab (7.5 mg/kg) from cycle 2 onwards, and had CT scans that showed her to be unresponsive. Therefore the treatment was changed in January 2008 to pemetrexed (500 mg/m^2 every 3 weeks) with folic acid and vitamin B6 support in combination with bevacizumab (400 mg/cycle) because it was considered that after 2 infusions one may not experience its full benefit.

In the months that followed the patient had vague, fleeting GI symptoms of short duration manifesting with mild abdominal pain and constipation alternating with diarrhoea that resolved with conservative treatment. Hospital admission was needed in one occasion for persistent constipation and fever but the patient responded to conservative treatment quickly. Meanwhile she responded well to the pemetrexed bevacizumab combination and it was thus decided to continue with maintenance therapy with the same regimen beyond the standard 6 cycles.

Two weeks after completion of the 9th cycle of pemetrexed (and a total of 11 of bevacizumab) the patient reported constipation for over a week. In the following days her clinical status gradually deteriorated with diffuse abdominal pain and fever up to 37.8°C and finally she appeared in the emergency room with abdominal distension, left iliac fossa tenderness and signs of peritoneal inflammation. The patient was admitted and evaluated by the surgical and infectious disease teams. She was diagnosed with incomplete bowel obstruction and treated empirically with ciprofloxacin, metronidazol and linezolid for bacterial colitis on the basis of fever, abdominal tenderness and a white blood count of 13000/μl with an absolute neutrophil count of 10400/μl. The plain abdominal X-rays showed large amounts of gas and stool in the colon, loops of distended bowel and an air fluid level in the rectosigmoid. While on nothing by mouth and on parenteral nutrition, she had an abdominal CT scan that showed

Figure 1.
A dietary fiber is clearly depicted inside the inflamed ovarian cyst.



distension of an ileal loop adjacent to a solid mass of unknown origin with associated bowel wall thickening. An MRI of the abdomen was also performed to rule out microscopic disease that could have been missed on CT but there were no additional findings. As the concern of disease progression in the abdomen persisted, the patient had a PET/CT scan that showed increased uptake in the area of the lesion (SUV max 6.3) consistent with inflammation or possibly a metastatic implant on the mesentery. The PET/CT was otherwise negative. As the patient had recently been treated with bevacizumab, conservative management was continued but her condition did not improve, so 5 weeks after the last bevacizumab infusion, an exploratory laparotomy with omentectomy and excision of the inflamed pelvic mass was performed. The mass was found to contain gas and pus and there was inflammation in the surrounding tissues but no evidence of inflammatory or ischemic colitis. In fact, the bowel appeared intact.

The pathology report described the lesion as an infected serous ovarian cystadenoma with accompanying pyosalpinx along with inflamed segments of omentum, intestine and peritoneum. There was no evidence of malignancy. A fiber was identified in the lumen of the cystic mass (Figure 1). This finding, along with the clinical information that the lesion was full of gas, led to the conclusion that there had been communication between the cyst and the gastrointestinal tract, most likely due to perforation of a diverticulum and subsequent fistula formation, which had since closed off and healed.

The patient had an uncomplicated postoperative course and recovery and was not treated with bevacizumab or pemetrexed again.

DISCUSSION

Bevacizumab is a humanized monoclonal antibody that targets vascular endothelial growth factor (VEGF) thereby acting as an angiogenesis inhibitor and is approved for the treatment of various forms (1) of cancer. Its use has been shown to improve overall and progression-free survival in patients with non-squamous non-small cell lung cancer (NSCLC) and it is thus approved (2) as first line treatment along with chemotherapy for this disease.

Reported side effects of bevacizumab include hypertension, proteinuria, impaired wound healing, increased risk of haemorrhage and gastrointestinal perforation (3,4). The latter is a fairly rare complication but can be fatal. It is has been described in patients with various types of cancer treated with bevacizumab (5) but the majority of cases are in colorectal and ovarian cancer. Bowel perforation has been described in patients on bevacizumab for lung cancer (5,6) and a recent meta-analysis of randomized clinical trials that directly compared cancer patients treated with and without bevacizumab showed an increased dose-related risk for gastrointestinal perforation in the bevacizumab group, which was overall higher when it was given for non-small cell lung cancer compared to other malignancies (7).

The pathophysiology behind bevacizumab – associated bowel perforation is unclear although some possible mechanisms have been proposed (8). These included (1) necrosis of intramural tumor that can lead to weakening of the intestinal wall, (2) impaired wound healing in the case of bowel injury, (3) ischemic damage due to thrombosis and vasoconstriction of mesenteric vessels and (4) existing risk factors such as diverticulitis, prior bowel surgery and bowel obstruction (8). In ovarian cancer large

intraperitoneal tumor burden and heavy pretreatment were also associated with bowel perforations in bevacizumab-treated patients (9). Additionally, in patients with colorectal cancer, perforation was associated with colitis due to chemotherapy or intra-abdominal inflammation (10). A review on the management of bevacizumab-associated bowel perforation in 24 patients with various malignancies was recently published. Recognized baseline risk factors were abdominal irradiation, non-steroid anti-inflammatory drug use, diverticulosis and intact primary tumor. The authors note that tumor was present at the perforation site in 9 out of 24 cases, 8 patients had peritoneal carcinomatosis and in 4 cases the perforation occurred at the anastomotic site of previous gastrointestinal surgery. At the time of perforation, 2 patients had concurrent diverticulitis, 4 other had presented with GI obstruction and in most cases there was abscess formation at the perforation site (5).

It is worthy of note here that a case of typhlitis was described in a febrile neutropenic patient after a single course of pemetrexed as second line treatment for NSCLC (11). Similarly to our case the patient presented with food intolerance, fever and abdominal pain and CT scan showed extended inflammation of the colon. Typhlitis, in the setting of chemotherapy-induced neutropenia and direct chemotherapy toxicity of the intestinal mucosa, was originally described in patients treated with chemotherapy for leukemia. A recent review though showed that patients with leukemia or solid tumors are equally likely to develop chemotherapy-related typhlitis (12). However, only ten cases of chemotherapy-associated colitis in patients with lung cancer have been described so far (11). Of those, only the one mentioned above was related to pemetrexed and none of the patients had received bevacizumab.

Clearly one cannot identify the degree to which bevacizumab and pemetrexed contributed to the pathophysiology of bowel inflammation and perforation in this case. However the non-neutropenic status of the patient at the time of the event and the intact appearance of the colon as described by the surgeons make the possibility of neutropenic, pemetrexed-induced colitis less likely. Also, the course of events in our case may indicate that the bowel–ovary fistula occurred in a non-inflammatory setting and the abscess was formed secondarily. Therefore we believe that this unique case of bowel to ovarian cyst fistula was mainly driven by bevacizumab.

CONCLUSION

Bevacizumab has significantly improved progression-free and overall survival (13,2) in patients with NSCLC. However its use does not come without the cost of some serious, potentially fatal side-effects that include hypertension, proteinuria, impaired healing and increased risk of haemorrhage. Gastrointestinal perforation is a rare, potentially fatal side-effect and, as reported here, it can manifest in not readily recognizable forms, masked under vague and confusing symptoms that can be misleading and troubling in their proper interpretation. The physician prescribing bevacizumab must always bear in mind the possibility of a gastrointestinal fistula, especially in the presence of risk factors such as diverticulosis, peritoneal implant or bowel surgery.

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	Study Phase	Indication	Setting
LUX-Lung 1	Phase IIb/III	Stage IIIB/IV NSCLC	2nd line treatment after CTx and EGFR TKI
LUX-Lung 2	Phase II	Stage IIIB/IV NSCLC	1st / 2nd line, EGFR mut+ patients
LUX-lung 3	Phase III	Stage IIIB/IV NSCLC	1st line, EGFR mut+ patients
LUX-Lung 5	Phase III	Stage IIIB/IV NSCLC	Patients with PD after CTx and EGFR TKI treatment
LUX-Breast 1	Phase III	HER2+ MBC	Patients after failing trastuzumab treatment

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In addition, the LUME clinical trial programme, which is investigating an anti-angiogenic inhibitor (BIBF1120[1]) in combination with chemotherapy regimens for patients with advanced NSCLC and Ovarian Cancer, is ongoing.

	Study Phase	Indication	Setting
LUME-Lung 1	Phase III	Stage IIIB/IV or recurrent NSCLC	2nd line treatment in patients with PD
LUME-Lung 2	Phase III	Stage IIIB/IV or recurrent NSCLC (Non-Squamous)	2nd line treatment in patients with PD
LUME-Ovar 1	Phase III	Stage IIB–IV Ovarian Cancer	1st line treatment

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[1]BIBW 2992 and BIBF 1120 are investigational agents and are not approved for the treatment of cancer. Their efficacy and safety have not yet been established.

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