Issue 4 • Vol. 2

FCO

December 2011
www.forumclinicaloncology.org
(PRINTED VERSION)

FORUM of CLINICAL ONCOLOGY

Quarterly official publication of the Hellenic Society of Medical Oncology

ISSN: 1792-345X

Clinical practice guidelines in oncology: pros and cons

Neoadjuvant therapy for organ-confined prostate cancer

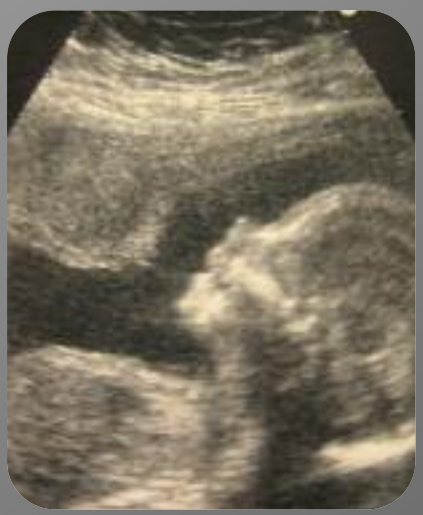
Pregnancy complicated by cancer. What do we know?

Consensus on diagnosis, treatment and management of non-infectious pneumonitis

Leprosy reactivation and lepromatous gangrene associated with chemotherapy for advanced gastric cancer

Recurrent multi-loculated symptomatic malignant pleural effusion after talc pleurodesis

Pancreatic metastasis from prostate cancer



1985

MINDWORK
BUSINESS SOLUTIONS LTD.
10, M. Botsari Street,
GR-14561 – Kifissia,
Athens, Greece

ΠΛΗΡΩΜΕΝΟ ΤΕΛΟΣ
PORT PAYÉ
Κ.Ε.Μ.Π.Α.
Αρ. Αδ. 4025
ΕΛΛΑΣ - HELLAS
B

ΕΛΤΑ
Hellenic Post

ΝΕΑ ΣΥΣΚΕΥΑΣΙΑ

TevaGrastim®
(filgrastim)

Νέα εποχή στη θεραπεία με G-CSF

Ultra Safe

TEVA Pharmaceuticals Hellas S.A.

Κηφισίας 166Α & Σοφοκλέους 2, 151 26 Μαρούσι, Ελλάδα
Τηλ.: +30210 72 79 099, www.tevapharm.com

Κάτοικος Άδειας Κυκλοφορίας: Teva Generics GmbH, Wasserstraße 50, D-01445 Radebeul, Γερμανία. **Tevagrastim 30 MIU/0,5 ml ενέσιμο διάλυμα ή διάλυμα για έγχυση:** Κάθε ml ενέσιμου διαλύματος ή διαλύματος για έγχυση περιέχει 60 εκατομμύρια διεθνείς μονάδες (MIU) (600 μg) φιλγραστίμης. Κάθε προγεμισμένη σύριγγα περιέχει 30 MIU (300 μg) φιλγραστίμης σε 0,5 ml ενέσιμου διαλύματος ή διαλύματος για έγχυση. **Tevagrastim 48 MIU/0,8 ml ενέσιμο διάλυμα ή διάλυμα για έγχυση:** Κάθε ml ενέσιμου διαλύματος ή διαλύματος για έγχυση περιέχει 60 εκατομμύρια διεθνείς μονάδες (MIU) (600 μg) φιλγραστίμης. Κάθε προγεμισμένη σύριγγα περιέχει 48 MIU (480 μg) φιλγραστίμης σε 0,8 ml ενέσιμου διαλύματος ή διαλύματος για έγχυση. **Τρόπος Διάθεσης (ΕΟΦ, 63424/31.01.2009):** Μόνο για Νοσοκομειακή ιατρική και μόνο από κλινικά Ογκολογικά και Αιματολογικά Κέντρα που έχουν πείρα στη χρήση του r-metHuG-CSF και τις σταφυλόκοκκους διογνωστικές δυνατότητες. Οι διαδικασίες κινητοποίησης και λευκαφαίρεσης θα πρέπει να πραγματοποιούνται σε συνεργασία με ένα ογκολογικό - αιματολογικό κέντρο που έχει εκπαιδευτική εμπειρία σε αυτόν τον τομέα και όπου ο έλεγχος των αιμοποιητικών προγονικών κυττάρων μπορεί να γίνει συχνά. **Περαιτέρω πληροφορίες διατίθενται από την TEVA HELLAS A.E.**

Publisher

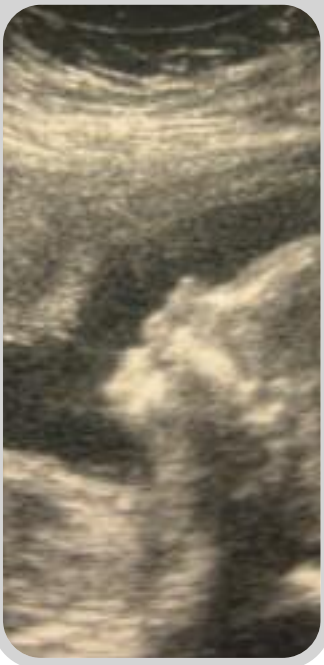
1985

Hellenic Society
of Medical Oncology
105, Alexandras Avenue,
Gr-11475 – Athens, Greece
tel./ fax: 0030 210 6457971
e-mail: hesmo@otenet.gr

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
website:
www.forumclinicaloncology.org

Printer: Lithoprint
I. Skourias Ltd.



Issue 4 • Vol. 2

FCO
FORUM of CLINICAL ONCOLOGY

December 2011
www.forumclinicaloncology.org
(PRINTED VERSION)

Quarterly official publication of the Hellenic Society of Medical Oncology

Contents

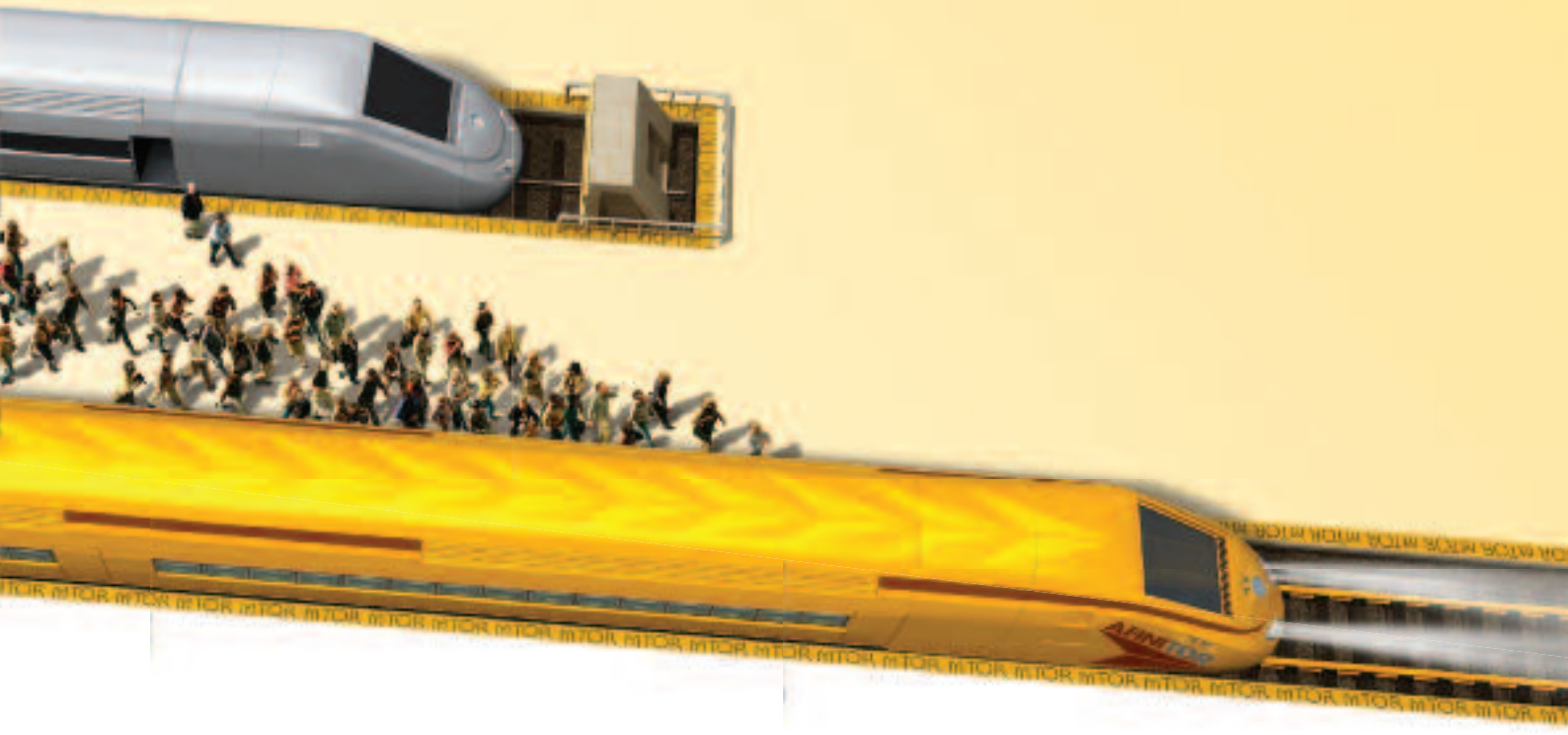
FCO FORUM of CLINICAL ONCOLOGY
Quarterly official publication of the Hellenic Society of Medical Oncology

Contents (suite)

Consensus

Case Reports

Somethink 8408.JUN/2010/AFT/AD/3



NOVARTIS ONCOLOGY

Novartis (Hellas) A.E.B.E.
Τ.Θ. 52001
144 10 Μεταμόρφωση
Τηλ.: 210 2811 712
www.novartis.gr

Γραφείο Θεσσαλονίκης
Βασ. Όλγας 216
551 33 Καλαμαριά
Τηλ.: 2310 424 039

ΦΑΡΜΑΚΟΕΠΑΓΡΥΠΝΗΣΗ: 210 2828 812

AFINITOR®
(everolimus) Tablets

Αλλάξτε όχημα

ΕΘΝΙΚΟ ΣΧΕΔΙΟ ΔΡΑΣΗΣ ΓΙΑ ΤΟΝ ΚΑΡΚΙΝΟ 2011-2015

ΓΙΑΤΙ;

ΓΙΑΤΙ ενώ ξέρουμε τι πρέπει να κάνουμε σε σχέση με τον καρκίνο, μένουμε στα λόγια;
ΓΙΑΤΙ κλείνουμε τα μάτια σε κάτι τόσο σημαντικό για εμάς και για αυτούς που αγαπάμε;
ΓΙΑΤΙ θεωρούμε ότι δε θα συμβεί σε μας ενώ συμβαίνει σε τόσους ανθρώπους γύρω μας;
ΓΙΑΤΙ αδιαφορούμε όταν πλέον με τις προληπτικές εξετάσεις:
4 στα 10 περιστατικά καρκίνου μπορούν να προληφθούν και 1 στους 3 καρκίνους
θεραπεύεται πλήρως αν γίνει έγκαιρα η διάγνωση και θεραπεία;

Η ζωή μας είναι πολύτιμη για να την αφήνουμε στη τύχη.
Κάνοντας προληπτικούς ελέγχους...

ΠΑΙΡΝΟΥΜΕ ΤΗ ΖΩΗ ΜΑΣ ΣΤΑ ΧΕΡΙΑ ΜΑΣ!

ΥΠΟΥΡΓΕΙΟ ΥΓΕΙΑΣ ΚΟΙΝΩΝΙΚΗΣ ΑΛΛΗΛΕΓΓΥΗΣ

ΕΣΠΑ 2007-2013

Νέο

Javlor®

vinflunine

Η 1η και μοναδική εγκεκριμένη θεραπεία του προχωρημένου ή μεταστατικού καρκινώματος από μεταβατικό επιθήλιο των ουροφόρων οδών μετά από αποτυχία με πλατίνα

Pierre Fabre
Farmaka SA

Λεωφ. Μεσογείων 350, 153 41 Αγ. Παρασκευή,
Τηλ.: 210 7234 582, Fax: 210 7234 589

Για περισσότερες πληροφορίες, παρακαλούμε συμβουλευτείτε τη ΠΑΠ του προϊόντος που διανέμεται από τη Pierre Fabre

Clinical practice guidelines are here to stay

Editorial

Vassilios Barbounis

The current issue of FCO features a very interesting article by professor Kappas (*Forum of Clinical Oncology* 2011; 2(4):11-22), entitled "Clinical practice guidelines in oncology: pros and cons".

Undoubtedly, the vast accumulation of knowledge from clinical trials, besides its obvious benefits, is associated with some intrinsic problems. Additionally globalization plays a major role, with respect to fast information flow, and has direct impact in good clinical practice.

Elaboration of clinical practice guidelines in Oncology by international and national organisations or consensus meetings comes with multiple advantages –reported in detail in professor Kappas' article– both for patients and healthcare professionals, as well as for the state and social security organisations.

There are, however, conflicting opinions arguing that such recommendations and guidelines might not be appropriate for the individual patient; they may lag behind astute clinical judgment and experience, and might not carry on as much as needed in real time the progress in medical science and practice.

All above arguments, both positive and negative, are scrutinized and extensively discussed in the article. Given the size of the article, it will be published in two parts in two consecutive FCO issues.

We are certain that this issue is well timed and will be widely discussed. Clinical practice guidelines are here to stay. Their value is indisputable; the medical oncology community should make proper use of CPGs in order to maximize their value –i.e. to assist healthcare professionals, not to substitute them.

ΓΙΑ ΤΟΥΣ ΑΣΘΕΝΕΙΣ ΜΕ ΟΣΤΙΚΕΣ ΜΕΤΑΣΤΑΣΕΙΣ
Η ΚΑΘΗΜΕΡΙΝΗ ΖΩΗ ΕΙΝΑΙ ΠΟΛΥΤΙΜΗ

ΠΡΟΣΤΑΤΕΨΤΕ ΤΗΝ με ZOMETA®

NOVARTIS
ONCOLOGY

Novartis (Hellas) A.E.B.E.
Τ.Θ.52001,
144 10 Μεταμόρφωση,
Τηλ.: 210 28 11 712
www.novartis.gr

Γραφείο Θεσσαλονίκης
12ο χλμ. Θεσσαλονίκης -
Ν. Μουδανιών
570 01 Θέρμη
τηλ.: 2310 424 039

ΦΑΡΜΑΚΟΕΠΑΓΡΥΠΝΗΣΗ: 210 2828812

ZOMETA®
zoledronic acid
Protect what is essential

Clinical practice guidelines in oncology: pros and cons - First Part

Constantin Kappas

Medical School of Larissa, Hellas

Correspondence:
Constantin Kappas, Professor,
Medical Physics Dept.,
University Hospital of Larissa,
41110, Viopolis, Larissa, Hellas (GR),
e-mail: kappas@med.uth.gr

ABSTRACT

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

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

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

INTRODUCTION

As many researchers describe, there is a sizeable gap between what could be provided to patients in optimal circumstances and what actually occurs in practice [1, 2, 3, 4]. This is more important for cancer patients due to cancer's high prevalence, and can reasonably be posited as responsible for a large number of avoidable cancer deaths.

The justification for changing a treatment approach could be based on different criteria, including the emergence of harmful treatment outcomes for individual patients when adhering to specific clinical recommendations, or the availability of new treatment interventions that improve clinical outcomes [5, 6, 7, 8].

A few decades ago, a clinician/oncologist was usually able to provide care to his patients or to change a treatment based on personal experience with the therapeutic agents available. This approach has become a much more stressing task in recent times as the number of available therapeutic modalities and the amount of literature relating to these therapies have increased.

Research in oncology has resulted in a proliferation of information that has made it difficult to reach clinical decisions on the basis of the available scientific findings [9, 10, 11, 12, 13, 14, 15]. While this is generally a positive thing [16, 17, 18], unfortunately the literature is of varying quality [19, 20, 21, 22, 23].

Complying with the experience of a notable number of clinicians, CPGs could be defined as follows:
"Systematically developed statements to assist practitioner and patient decisions about appropriate healthcare for specific clinical circumstances" [Institute of Medicine - USA, 24, 25].

In a broad sense:

- *"What the researchers call 'guidelines' are more like mandated treatment pathways"* [26].
- *"A related set of generalizations derived from past experience arranged in a coherent structure*

to facilitate appropriate responses to specific situations" [quoted from 27, 28].

- *"Guidelines (compared to textbooks) are more concerned with specifying treatment strategies for certain patient types, with healthcare quality, and the reduction of unjustifiable clinical variability and costs"* [quoted from 27, 28].
- *"Guidelines - like overviews - gather, appraise and combine evidence. Guidelines, however, go beyond most overviews in attempting to address all the issues relevant to a clinical decision and all the values that might sway a clinical recommendation. Like decision analysis, guidelines refine clinical questions and balance trade-off"* [quoted from 27, 28].

The wide interest today in Clinical Practice Guidelines (CPGs) has its origin not only in the intrinsic desire of healthcare professionals to offer, and of patients to receive, the best care possible as described above but also in issues that most healthcare systems face: rising healthcare costs; increased demand for care; more expensive technologies; ageing population; marked variation in physician practices, hospitals, and geographical regions.

Evidence-based guidelines are seen by clinicians, payers, managers and policy makers as a solution to these problems and as a tool for making care more consistent and efficient; a way of closing the gap between what clinicians do and the scientific evidence [15, 29, 30, 31, 32, 33, 34].

CPGs present advantages and disadvantages from a legal, political, social, financial and emotional point of view, but the overriding purpose of CPGs is to improve the quality of care for patients by decreasing inappropriate variation and expediting the application of effective advances in everyday practice [35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46].

In addition to the above, researchers [26, 47] surprisingly discovered that the public also finds arguments in favor of or against treatment guidelines.

Arguments in favor of guidelines include:

- Doctors have financial incentives to provide inappropriate care
- Following guidelines will improve care for most patients
- Doctors don't keep up with the literature
- Doctors are unaware of better approaches followed elsewhere

Arguments against are:

- No outside group should come between doctors and patients
- Doctors will be unable to tailor care to the needs of individual patients
- Guidelines are vulnerable to abuse and corruption

Table 1.
Outcomes of cancer treatment [10]*

Measures of cancer response	These include measures of tumor response (e.g. complete and partial response; response duration; time to progression), biomarkers (e.g. CA-125), and cancer-induced abnormalities in common blood tests (e.g. alkaline phosphatase) [7, 49].
Survival	Whether overall, disease-free, progression-free, or event-free, this is the most important outcome. The quality of survival and cost of maintaining or improving it must also be assessed. Disease-free survival is especially important in the adjuvant setting, as is progression-free survival in metastatic disease [49].
Toxicity	It reduces QOL and can be life-threatening. Both short- and long-term toxicity is vitally important, with the latter being particularly critical in children because of its effects on growth and development. Three toxicity aspects need to be evaluated: frequency, severity and duration [50].
Global QOL	Cancer-related QOL is a multidimensional concept that evaluates the impact of cancer and its treatment on the following components of patient life: - physical (symptoms commonly caused by cancer and the toxicities of treatment, e.g. daily life activities, walking, climbing stairs), - psychological (effects of cancer and its treatment on cognitive function and emotional state, e.g. anxiety, optimism, depression) and - social (effects of cancer and its treatment on interpersonal relationships, school, work, recreation). In order to achieve an outcome, QOL measures must be sensitive to clinically meaningful changes produced by treatment [51, 52, 53].
Cost-effectiveness	Important to consider when the benefits of treatment are modest and/or costs are high [54, 55, 56].

* There is no mention of patient satisfaction as it is increasingly used to evaluate the effectiveness of healthcare delivery, but it is not important in technology assessment and guideline development, which are shaped by evidence from clinical trials on the benefits and risks [57].

- Payers will use guidelines to control costs and ration care
- Guidelines can't keep up with the pace of medical innovation

This behavior also needs to be explained and/or changed. The emerged controversial views of CPGs [48] feed the discussion about the usefulness of educational programs on how to implement CPGs both to assist generalists/oncologists in their daily clinical decisions and to support negotiations with politicians, administrators, insurance companies, etc.

OUTCOMES OF CANCER TREATMENT

The necessity of creating and applying CPGs originates from the duty to offer patients the best possible care. But best care of what? Patients, physicians, researchers, payers and policy makers all have different ideas about which outcomes of cancer are more important. Outcomes are defined [10] as the products, both good and bad, of cancer treatment and they are distinguished between cancer outcomes and patient outcomes (see also Table 1):

- *Cancer Outcomes* are the measures of cancer treatment effects (tumor response, biomarkers and cancer-induced abnormalities).
- *Patient Outcomes* are measures on the effect of treatment on patients, e.g. survival, toxicity and QOL. Patient outcomes should receive higher priority than cancer outcomes, but both are important in technology assessment and guideline development.

It must be pointed out that multiple outcomes should be taken into consideration because no single outcome adequately describes the results of cancer treatment. In general, there is no minimum benefit above which treatments are justified; rather, benefits should be balanced against toxicity and cost. Based on the above, CPG benefits and harms can be juxtaposed.

CPGS BENEFITS, HARMS & DEFICIENCIES, DEBATABLE EFFECTS FOR PATIENTS, HEALTH PROFESSIONALS AND THIRD PARTIES

Several organizations have performed audits to determine whether guidelines promote adherence to treatment recommendations and improve quality of care [1, 16, 17, 39, 42, 58, 59, 60, 61, 62, 63]. Additionally, publication of CPGs and (at least minimum) acceptance of these "standards" of care by third parties, will improve access to and increase acceptance of medical interventions which have been established in order to result in more beneficial outcomes [64, 65], e.g. screening programs (colon, breast and cervix cancers); standard surgical staging procedures (early stage ovarian cancer); and adjuvant hormonal or chemotherapy (breast cancer).

The more guidelines providing evidence that can be applied to individual patients, the more useful they will be for real life clinical decision making [5, 66]. In a significant proportion of clinical situations, guidelines could become a *lingua franca* providing patients, practitioners, scientists, and purchasers with an opportunity to share information more effectively. However, various problems with guidelines and their development that can impede their optimal use and profit have been reported by relatively recent studies [19, 20, 67].

Table 2 presents the main advantages and disadvantages of CPGs for patients, physicians and third parties.

Table 2.

CPG advantages (■), disadvantages (■) and debatable effects (■) for patients, healthcare professionals and third parties

Quality of care

■ **CPGs as audit tools for the improvement of clinical decisions quality**

- *Outdated or ineffective practices:* they depose the beliefs of doctors accustomed to outdated practices; alert clinicians to interventions unsupported by good practice; reinforce the importance and methods of critical appraisal; and call attention to ineffective, dangerous, and wasteful practices.
- *Care appropriateness:* they offer explicit recommendations for clinicians who are uncertain about how to proceed; improve the consistency of care; and provide authoritative recommendations that reassure practitioners about the appropriateness of their treatment policies.
- *Condition management:* CPGs review evidence; weigh various outcomes, both positive and negative; make recommendations; and provide a coherent and integrated view on how to manage a condition [5, 68].
- *Monitoring:* healthcare institutions or organizations can use CPGs to monitor the quality of care provided by specialists or non-specialists dealing with the cancer patient population.
- *Reward rather than fees:* doctors and hospitals could be supported by appropriate CPGs and be paid to provide quality of care as well as for their patients' outcomes, rather than simply for rendering services (i.e. fee for service) [1].

■ **Reduce morbidity and mortality and improve QOL**

CPGs that promote interventions of proven benefit and discourage ineffective ones have the potential of reducing morbidity and mortality and improving QOL -at least for some conditions.

■ **Justify elimination of unnecessary and inappropriate tests or procedures**

Oncologists may find CPGs useful in explaining to cancer patients (and their families) why certain tests or treatments are not being used, e.g. outdated biochemical or radiographic evaluations; discredited surgical techniques (e.g. the routine use of radical mastectomy in early stage breast cancer); ineffective salvage chemotherapy for refractory cancers (e.g. third line cytotoxic drug therapy for non-small cell lung cancer) [64].

■ **Answer specific clinical questions**

Answer specific clinical questions that stem from daily practice [69]. This allows clinicians to identify what sort of evidence they need to search for [70].

■ **The most important limitation: recommendations may be wrong for individual patients**

The value judgment made by a guideline development group could be considered as the best for patients overall but may be inappropriate or wrong for individual patients [5, 30]. Thus, a practice guideline should provide a thorough and accurate description of the population on which a recommendation is based on to allow clinicians to identify potential similarities; a starting point for the application of any evidence to an individual patient should determine how the patient in question is *similar* to those of the study groups and not how they differ [71].

■ **Risk of developing an oversimplified mentality of oncological care**

- *Diversity of human cancers:* it is not possible to adequately address all (or even a majority of the large number of) clinical variations involving common oncological conditions. CPGs can never substitute the importance of clinical judgement.
- *Effort to make CPGs easily understood:* there will likely be a tendency to oversimplify complex medical situations. This may lead to the erroneous conclusion that healthcare providers with limited training in oncology can manage many cancer-related medical interventions by "simply following what the guidelines tell one to do" [64].

Quality of CPGs and Scientific Evidence

■ **CPG objective evaluation of scientific knowledge**

- *Manpower:* CPGs are drawn up by specialists selected by scientific societies and/or groups of oncologists.
- *Popularity:* they usually include most cited articles in high impact journals and most downloaded files from specialty Society websites [72].
- *Objectivity:* CPGs are based on an objective evaluation of the relevant literature [15, 73].

■ **Evidence-based guidelines highlight gaps in the evidence**

- *Assessment Review:* several agencies have developed guidelines for the treatment of the most common cancers, based on a hierarchy of evidence from clinical trials (e.g. ASCO, ESMO, NCCN, CCO, SOR) [34, 71, 74, 75, 76, 77, 78, 79]. These CPGs are based on a review of the available evidence from clinical studies, and some of these groups have also assessed the quality of the sources (reviews, systematic reviews and meta-analyses) used for the development of guidelines that provide the evidence [80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91].
- *Presence/Absence of Evidence:* the methods of guideline development that emphasize systematic reviews focus attention on key research questions that must be answered to establish the effectiveness of an intervention [92, 93]. Critical appraisal of the evidence identifies design flaws in existing studies. Recognizing the presence and absence of evidence can redirect the work of investigators and encourage funding agencies to support studies that satisfy this effectiveness-based agenda.

■ **Lack of quality**

- *Non-adherence to existing standards:* a noticeable percentage of CPGs published in the peer-reviewed medical literature does not quite meet established methodological standards and is either not based on the best evidence or highlights vested interests of specific parties, including health-care industry guidelines [19, 20, 33, 39, 67, 94, 95, 96, 97, 98, 99, 100, 101].
- *Use of low-quality scientific techniques:* many CPGs used informal techniques such as narrative summaries prepared by clinical experts, a type of review shown to be of low mean scientific quality and reproducibility [102]. Flawed CPGs harm practitioners by providing inaccurate scientific information and clinical advice, thereby compromising the quality of care resulting in suboptimal, ineffective, or harmful practices.
- *Lack of feasibility:* in a high number of CPGs, the consequences in terms of acceptance by patients, and the resources, staff, skills and equipment needed for implementation are not considered during the development process.
- *Inflexible CPGs:* these may be harmful by leaving insufficient room for clinicians to examine closely and take into account patients' personal circumstances and medical history.
- *Improperly constructed and worded CPGs:* they may mislead or confuse doctors and patients and disrupt the doctor-patient relationship.
- *Conflicting CPGs (from different professional bodies):* they can confuse and frustrate practitioners.
- *Outdated recommendations:* they may perpetuate outmoded practices and technologies.

■ **Lack of evidence**

- *Lack of time, resources and skills:* guideline development groups often lack the time, resources, and skills to gather and scrutinize evidence. When evidence is missing, reliable procedures for including expert opinions and stakeholder preferences are required; such procedures are not present in many guideline development programs [103].

- *Bias and/or poor generalizability:* recommendations are influenced by the opinions, clinical experience and composition of the guideline development group. Tests and treatments that experts believe to be good for patients may in practice be inferior to other options, ineffective, or even harmful [104].
- *Interests before research reality:* there is a large grey area where expert opinions, practitioner and patient preferences as well as societal priorities are more important in the development of guidelines than research results [105].
- *"Binary or complex medicine":* algorithms that reduce patient care into a sequence of binary (yes/no) decisions often do injustice to the complexity of medicine and the parallel and iterative thought processes inherent in clinical judgment.

Difficulties in the translation of evidence into recommendations for practice

- *"Guidelines vs. Real Environment":* guideline users deal with a more heterogeneous population of patients and more complex health-care processes than those covered in the original research [106].
- *Multi- or Mono-disciplinary care pathway:* the majority of cancer clinical research deals with separate diagnostic or therapeutic decisions in selected samples of patients, while the practice of cancer care usually involves dealing with complex multidisciplinary care processes in a variety of patient groups [107].

Education & Research

CPGs can serve as educational tools

Tools for trainees (oncology specialists & clinicians) and information sources for individual oncologists for CPE. Useful tool also for the young resident oncologist who benefits from an ethical guide that complements his/her own experience [108, 109]. Used as instruments for self-assessment or peer review [65] and to learn about gaps in performance.

Avoid duplication of efforts and encourage research collaborations

- *Fuse similar strategies:* despite concrete improvements in diagnosis and treatment of cancer, marked differences in cancer survival exist worldwide [110, 111]. Currently, guideline programs in different countries use similar strategies to achieve similar goals. This results in unnecessary duplication of effort; inefficient use of resources; and suboptimum management of activities. A shared guideline development process could reduce costs and duplication of effort and improve the dissemination and implementation of CPGs that comply with internationally accepted quality criteria [18, 82, 85, 87, 110, 112, 113, 114, 115].
- *Opportunities for research collaborations:* e.g. the Guidelines Development Cycle [81, 116], provides a framework for the shared development of evidence-based recommendations. The collaboration between the SOR project and the CCOPGI has enabled a better understanding of the inconsistencies that can result between guideline recommendations based on the same evidence [18, 117, 118].

CPGs as control arms for randomized trials

CPGs could include a number of alternatives for the management of specific clinical settings. Investigators designing trials of new therapeutic approaches could compare these strategies to those established by a group of experts as "standard of care".

Biased research

CPGs recommend interventions for which there is evidence of effectiveness; in practice, options are often restricted to pharmaceutical interventions. There are two factors that bias research towards producing evidence for pharmaceutical interventions: Firstly, the currently accepted hierarchy of evidence privileges randomized controlled trials. Pharmaceutical interventions are ideally suited to production of placebos for use in trials, in contrast with other interventions, such as counseling, physical therapies and lifestyle interventions. Secondly, pharmaceutical companies are major funders of research [108, 109].

Discouragement of scientific progress and research

- *Definitive level of care:* one of the most serious concerns with the development of CPGs is the potential perception that these documents describe a "level of care" which cannot -and should not- be improved upon. This type of thinking would seriously hinder the development of much needed innovative new diagnostic and treatment strategies which hold the potential to significantly improve the QOL and survival of individuals with malignant diseases. CPGs should not be considered as being the definitive statement on cancer care but a temporary "state of the art" which must be easily and quickly modified with advances in basic and clinical research [64].
- *Deviations from CPG norms:* CPGs which conclude that a procedure or treatment lacks evidence of benefit may be misinterpreted by funding bodies as grounds for not investing in further research and for not supporting efforts to refine previously ineffective technologies. Under such circumstances any major (or even minor) deviations from the guidelines might be considered as "experimental/ investigational" or "unproven" treatment, and may not be allowed.

Standardization, Consistency of Care and Health Inequalities

Improvement in the consistency of care

Patients with identical clinical problems receive different care depending on their clinician, hospital, or location. CPGs make it more likely that patients will be

taken care of in the same manner regardless of where or by whom they are being treated [15, 36, 119, 120, 121]. Uniformity of procedures also allows patients to better approach their uncomfortable situation.

Potential increase in health inequalities

- *Socioeconomic factors:* the effects of socioeconomic status on health are well-established but difficult to overcome. This is because access to health services, the ability to act on health advice, and the capacity to modify health risk factors are all influenced by the circumstances in which people live and work [122]. These effects have largely been ignored in clinical guidelines.
- *"Inverse Care Law":* those most in need of care are the least likely to receive it ["Inverse Care Law - ICL", 123] and the quality of care received by people with lower socioeconomic positions is different than that of those with higher positions. CPGs have the potential to increase health inequalities by improving the health of the relatively health-advantaged more readily than that of the relatively disadvantaged [123, 124, 125, 126].
- *Patient Involvement:* variations in practice may be the result of active patient participation in choosing care options.

Ethical principles [108, 109, 127]

Positive contribution of CPGs

The use of guidelines must be ethically required, if using them supports ethical practice: Beneficence (act for the good of the patient); Non-maleficence (do no harm); Respect for patient autonomy (patients' right to make decisions about their care); and Justice (fairness in healthcare).

Economic assessments

Following a cost-effective guideline may forfeit the individual's best interests in favor of the greater good. Additionally, this population-focused approach may lead to inequitable results. E.g. risk factors identified in a national, evidence-based guideline for the prevention of a malignancy do not include ethnicity or socioeconomic status.

Medical and Scientific Malpractice

Negligence

- *Breach of duty and CPGs:* medical negligence is a combination of three essential elements. A plaintiff (the person bringing the action) must show that [quoted from 128]: 1) the defendant doctor owed the plaintiff a duty of care, and 2) the doctor breached this duty of care by failing to provide the required standard of medical care, and 3) this failure actually caused the plaintiff harm, a harm that should have been foreseeable and reasonably avoidable. CPGs could, in theory, influence the manner in which the courts establish the second element.
- *CPGs are not legal "gold standards":* CPGs could be introduced to a court by an expert witness as evidence of accepted and customary standards of care, but they cannot be introduced as a substitute for expert testimony; courts are unlikely to adopt standards of care advocated in CPGs as legal "gold standards" because the fact that a guideline exists does not in itself establish that compliance with it is reasonable in the circumstances, or that non-compliance is negligent [98, 128].

Legal protection

- *Against medical practice:* as CPGs become accepted in the clinical community, acting in accordance with a clinical guideline could in itself be viewed as acceptable medical practice. CPGs can be employed to defend a charge of "medical malpractice" [129] in a setting where it is claimed that an adverse outcome was the direct result of specific medical interventions [25, 104, 127, 128, 130, 131, 132, 133, 134, 135, 136].
- *Reduce litigation:* extensive insurance coverage for malpractice has resulted in increasing litigation. Encouraging compliance with the standard of care will reduce healthcare costs by reducing the use of defensive medicine. Furthermore, the promise of lower rates of malpractice litigation will promote the development of and greater compliance with guidelines, which will in turn improve the quality of medical practice and reduce costs associated with inappropriate care [132, 134].

Malpractice litigation

CPGs could be potentially harmful to doctors as citable evidence for malpractice litigation and because of their financial implications [129, 130, 132, 133, 136].

Scientific misconduct

Results of clinical studies are not infrequently biased in favor of new diagnoses, treatments or drugs. This bias can be attributed to conflicts of interest: medical research scientists are willing to produce scientifically sound results but, at the same time, do not decline the support of potential clients. These results are often adopted uncritically by health economists [74, 137, 138].

Financial Costs & Public Policy

Service reimbursement

In some healthcare systems, CPGs prompt government or private payers to provide coverage or to reimburse doctors for services.

Use of healthcare resources

- *Optimizing value for money:* CPGs can increase evidence-based management and compliance with CPGs can decrease financial costs [55, 127] and

improve patient outcomes [89]. Third party payers could use these guidelines to deny payment for medical care when deemed inappropriate or unnecessary.

- *Reduce outlays:* CPGs are used to make decisions about whether or not to fund expensive new treatments. Certain CPGs reduces outlays for various procedures, e.g. hospitalization, prescription drugs, surgery.
- *Free up resources:* in a cash-limited healthcare system, CPGs that improve the efficiency of healthcare free up resources needed for other (more equitably distributed) healthcare services.

■ CPGs can help patients by influencing public policy

- *Call attention to specific problems/groups:* under-recognised health problems, clinical services, and preventive interventions to neglected patient populations and high risk groups.
- *New services:* services that were not previously offered to patients may be made available as a response to newly-released guidelines.
- *Ethical matters:* CPGs developed with attention to the public good can promote distributive justice, advocating better delivery of services to those in need.

■ Improvement of public image

Publicizing adherence to guidelines may ameliorate public image, sending messages of commitment to excellence and quality. Such messages can promote good will, political support, and (in some healthcare systems) revenue.

■ Waste of limited resources

The costs of randomized studies and of developing CPGs are considerable [139, 140]. Some CPGs, especially those developed by medical and other groups unconcerned about financing, may advocate costly interventions that are unaffordable or that cut into resources needed for more effective services [39]. Note that more than half of all published guidelines do not mention costs at all, and only a small percentage provides any quantitative cost estimates [20].

■ Unreasonable cost cut

CPGs can be quite narrowly interpreted, in a way that only those diagnostic tests or therapeutic maneuvers specifically included within the document will be considered as "appropriate and necessary" for the condition and, thus, eligible for payment. Additionally, interventions not specifically mentioned or discussed in the CPGs could be excluded from payment.

Involve Patients in Treatment Decisions

■ Humane nursing perspective

Patients are regarded as individuals who are able to reflect on their existence and make autonomous choices based on their own personal values and norms [71, 141, 142, 143].

■ Enhance patient–doctor collaboration, empower patient position

- *Publications:* published (in magazines, news reports, and internet sites) guidelines empower patients to make more informed healthcare choices and to consider their personal needs and preferences [39, 142, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153] in selecting the best option.
- *Patient autonomy:* respect for patient self-determination is a fundamental principle of medical ethics, demonstrated in practice by facilitating patient choice [108, 151, 154]. The patient feels more protected and safeguarded instead of at the mercy of the physicians and their personal decisions.

■ Treatment decision involvement in the case of a serious illness

There is a need and an expressed desire by physicians and patients to involve the latter in treatment decision making. Especially when a patient presents with a serious illness (e.g. cancer) and different treatment options exist, the gains of treatment should be weighed against possible adverse effects, or when outcomes are uncertain. Research in newly-diagnosed cancer patients [155], in palliative cancer care patients [156], and in a healthy population [157] indicates that a higher educational attainment is associated with a preference for a more active role in decision making [151].

■ Practical concerns

- *Eliciting patient preferences:* additional time is needed and difficulties arise in eliciting patient preferences, exacerbated by limited appropriate information to support patient involvement.
- *Lack of physician competences:* doctors may not have the appropriate competences and patient preferences may also differ from those of their doctors or evidence-based guidelines.
- *Retain the imbalance of power:* some doctors may wish to retain the imbalance of power between themselves and their patients, and the latter may be reluctant to share their preferences if they consider their doctor as more powerful and knowledgeable.

■ CPGs do not systematically seek or integrate evidence on patient preferences

- *Preference evidence:* a clear taxonomy for studies of patient preferences does not exist, as there is no simple and generally accepted method to synthesize evidence on preferences. Moreover, only 5% of CPGs cite a method of identifying preference evidence [144].
- *Risks for patients with special needs:* CPGs which ignore patient preferences trying to create more consistent practice patterns and reduced variation may come at the expense of reducing individualized care for patients with special needs [29].

Abbreviations

ACCC	Association of Community Cancer Centers, USA
AGREE	Appraisal of Guidelines, Research, and Evaluation
AHCPR	Agency for Health Care Policy & Research
ASCO	American Society of Clinical Oncology
BASO	British Association of Surgical Oncology
BSP	Breast Screening Program
CCO or CCOPGI	Cancer Care Ontario Practice Guideline Initiative
CME	Continuing Medical Education
CoCanCPG	Coordination of Cancer Clinical Practice Guidelines in Europe is a Coordinated Action under the ERA-Net (European Research Area - Network) scheme, www.cocancpg.eu
CPE	Continuing Professional Education
CPGs	Clinical Practice Guidelines
EMEA	European Medicines Agency
ESMO	European Society for Medical Oncology
FDA	Food and Drug Administration - USA
FNCLCC	Fédération Nationale des Centres de Lutte Contre le Cancer
G-I-N PUBLIC	Guidelines International Network: promote ways to inform and involve the public in CPGs activity, www.g-i-n.net/activities/gin-public
MCRs	Minimum Clinical Recommendations
NCCN	National Comprehensive Cancer Network
NHS	National Health Service - UK
PROs	Patient-Reported Outcomes
QOL	Quality of Life
RCT	Randomized Controlled Trial
SIGN	Scottish Intercollegiate Guideline Network, www.sign.ac.uk/guidelines
SOR	Standards, Options & Recommendations
Third parties	Third party payers (e.g., insurance companies, employers, government), professional medical societies, and the courts

Terms [158, 69, 159, 160]

Academic detailing, educational outreach	Education of an individual physician by a healthcare professional, usually in the physician's office and most often in the area of prescribing.
Adoption	Healthcare provider commitment and decision to change their practices; the actual change in practices.
Conformance quality	The extent to which guidelines, once developed, are correctly and consistently applied [161].
Consumers	Patients and public.
Diffusion	Distribution of information and practitioners' natural, unaided adoption of policies and practices.
Dissemination	Communication of information to clinicians to improve their knowledge or skills; more active than diffusion, dissemination targets a specific clinical audience.
Educational intervention	Any strategy, program or maneuver intended to persuade physicians to change their performance and maintain their competence.
Evidence-Based Medicine (EBM)	Process of systematically finding, appraising and using contemporaneous research findings as the basis for clinical decisions. EBM is about asking questions, finding and appraising the relevant data, and harnessing information for everyday clinical practice [61, 69, 93, 162, 163].
Health-Related Quality of Life (HRQOL)	Broad multidimensional concept that usually includes self-reported measures of physical and mental health. HRQOL measures involve subjective patient assessment or evaluation of important aspects of well-being [164] that are affected by current disease and/or treatment. Prominent examples of cancer-related HRQOL tools are the EORTC QLQ-C30 and the Functional Assessment of Cancer Therapy General (FACT G) [165].

Implementation	Putting a guideline in place; active dissemination. It involves effective communication strategies and identifies and overcomes barriers to change by using administrative and educational techniques that are effective in the practice setting.
Inverse Care Law (ICL)	Principle stating that the availability of good medical or social care tends to vary inversely with the need of the population served. The law states that: *"The availability of good medical care tends to vary inversely with the need for it in the population served. This.... operates more completely where medical care is most exposed to market forces, and less so where such exposure is reduced."* [123].
Lack of awareness	Inability of a physician to correctly acknowledge the existence of a guideline.
Lack of familiarity	Inability of a physician to correctly answer questions about guideline content, as well as self-reported lack of familiarity.
Lack of outcome expectancy	Lack of expectation that a given behavior will lead to a particular consequence.
Opinion leaders, educationally influential clinicians	Clinicians identified by their colleagues in the community as being respected clinicians and effective communicators.
Patient-Reported Outcomes (PROs)	PROs have recently gained greater credibility with regulatory bodies aiming to standardize their use and interpretation in RCTs. PRO guidance from the EMEA and FDA has been valuable, and has raised the profile and active debate of PROs in oncology [145]. In oncological phase III RCTs and registration trials, PROs are increasingly used for providing information about HRQOL in patients who undergo new treatments. Both the FDA and EMEA increasingly appear to be willing to accept PROs in support of medicinal labeling claims or in the evaluation of medical products such as cancer drugs.
Providers	Healthcare professionals, including physicians.
Self-efficacy	Self-efficacy is the belief that one can actually perform a behavior.
Standards, Options & Recommendations (SOR) project	The SOR project was developed by the French National Federation of Cancer Centers [58] and the 20 French Comprehensive Cancer Centers (CRCC) in collaboration with specialists from French public universities, general hospitals, private clinics and scientific societies. SOR is a significant accomplishment with several lessons for guideline developers around the world [18]. SORs provide clinical algorithms as an aid for clinicians managing different clinical situations in daily practice [166].
Setting	Type of practice site implying aspects of workload, relevant healthcare team members, mix of patients and funding mechanisms.
Trialability	Degree to which an innovation may be experimented with, on a limited basis.

REFERENCES

1. Bach PB. Using practice guidelines to assess cancer care quality. J Clin Oncol 2005; 23:9041-9043.
2. Harlan L, Greene AL, Limin X, et al. Insurance status and the use of guideline therapy in the treatment of selected cancers. J Clin Oncol 2005; 23:9079-9088.
3. Kemper PD, Blumenthal D, Corrigan JM, et al. The design of the Community Tracking Study: a longitudinal study of health system change and its effects on people. Inquiry 1996; 33:195-206.
4. McGlynn EA, Asch SM, Adams J, et al. The quality of health care delivered to adults in the United States. N Engl J Med 2003; 348:2635-2645.
5. Gilmore A. Clinical practice guidelines: weapons for patients or shields for MDs? Can Med Assoc 1993; 148:429-31.
6. Glick M. Clinical guidelines. To follow or folly? You decide. JADA 2009; 140:825-826.
7. Therasse P, Arbuck SG & Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors - EORTC, NCI USA/Canada. J Nat Cancer Inst 2000; 92:205-216.
8. Tomlinson T. Futile care in oncology: when to stop trying. The Lancet Oncology 2001; 2:759-764.
9. ASCO Recommendations for the use of hematopoietic colony stimulating factors: evidence based clinical practice guidelines. J Clin Oncol 1994; 11:2471-2508.
10. ASCO Outcomes of cancer treatment for technology assessment and cancer treatment guidelines. J Clin Oncol 1996; 14:671-679.
11. Borbas C, Morris N, McLaughlin B, Asinger R & Gobel F. The Role of Clinical Opinion Leaders in Guideline Implementation and Quality Improvement. Chest 2000; 118:24S-32S.
12. Genuis SJ. The proliferation of clinical practice guidelines: professional development or medicine-by-numbers? J Am Board Fam Pract 2005; 18:419-425.
13. Kalemkerian G. Guidelines Are Never Enough: A Commentary on When Guidelines Are Not Enough. J Clin Oncol 2007; 25(13):1810-1811.
14. Mettlin C & Smart CR. Breast cancer detection guidelines for women aged 40 to 49 years rationale for the American Cancer Society reaffirmation of recommendations. Ca - A Cancer J for Clinicians 1994; 44:248-255.
15. Vannelli A, Poiasina E, Battaglia L, et al. Pitfalls and controversies of guidelines in oncology. Tumori 2008; 94(1):137-138.
16. Ray-Coquard I, Philip T, Lehmann M, Fervers B, et al. Impact of a clinical guidelines program for breast and colon cancer in a French cancer center. JAMA 1997; 278:1591-1595.
17. Ray-Coquard I, Philip T, de Laroche G, et al. A controlled 'before-after' study: impact of a clinical guidelines programme and regional cancer network organization on medical practice. Br J Cancer 2002; 86:313-321.
18. Fervers B, Hardy J & Philip T. Standards, options and recommendations - SOR. Clinical practice guidelines for cancer care from the French National Fe-

deration of Cancer Centres (FNCLCC). Br J Cancer 2001; 84 (Suppl 2):1-92.
19. Grilli R, Magrini N, Penna A, et al. Practice guidelines developed by specialty societies: the need for a critical appraisal. Lancet 2000; 355:103-106.
20. Shaneyfelt T, Mayo-Smith M & Rothwangl J. Are guidelines following guidelines? The Methodological Quality of Clinical Practice Guidelines in the Peer-Reviewed Medical Literature. JAMA 1999; 281(20):1900-1905.
21. Lomas J, Anderson GM, Domnick-Pierre K, et al. Do practice guidelines guide practice? The effect of a consensus statement on the practice of physicians. Engl J Med 1989; 321:1306-1311.
22. Weil RJ. When guidelines are not enough. J Clin Oncol 2007; 25(13):1807-1809.
23. Roberts KA. Best practices in the development of clinical practice guidelines. J Health Q 1998; 20:16-20, 32.
24. Field MJ & Lohr MJ. Clinical Practice Guidelines: Directions for a New Program. Field MJ & Lohr MJ, eds. Nat Acad Press 1990.
25. Lohr K. Guidelines for Clinical Practice: What They Are and Why They Count. J Law, Med & Ethics 1995; 23:49-56.
26. Williams D. Treatment guidelines pros and cons. Medpage Today's KevinMDCom 2011.
27. Schwartz PJ, Breithardt G, Howard AJ, Julian DG & Rehnqvist Ahlberg N. The legal implications of medical guidelines - a Task Force of the European Society of Cardiology. Eur Heart J 1999; 20:1152-1157.
28. Keffer J. Guidelines and Algorithms: Perceptions of Why and When They Are Successful and How to Improve Them. Clinical Chemistry 2001; 47(8):1563-1572.
29. Woolf SH. Barriers and Strategies to Influencing Physician Behavior. Am J Med Quality 2007; 22:5-7.
30. Woolf SH, Grol R, Hutchinson A, Eccles M & Grimshaw J. Clinical guidelines: the potential benefits, limitations, and harms of clinical guidelines. BMJ 1999; 318:527-530.
31. Austoker J. The potential and pitfalls for developing guidelines in oncology. Ann Oncol 2001; 12(9):1189-1190.
32. Winn RJ. The role of oncology clinical practice guidelines in the managed care era. Oncology (Huntingt) 1995; Suppl 9:177-183.
33. Grol R, Cluzeau FA & Burgers JS. Clinical practice guidelines: Towards better quality guidelines and increased international collaboration. Br J Cancer 2003; 89 (Suppl 1):S4-S8.
34. Oosterhuis W, Bruns D, Watine J, et al. Evidence-Based Guidelines in Laboratory Medicine: Principles and Methods. Clinical Chemistry 2004; 50(5):806-818.
35. Audet AM, Greenfield S & Field M. Medical practice guidelines: current activities and future directions. Ann Intern Med 1990; 113:709-714.
36. Chassin MR. Practice guidelines: best hope for quality improvement in the 1990s. J Occup Med 1990; 32:1199-1206.
37. DeVault KR & Castell DO. Guidelines for the diagnosis and treatment of gastro-esophageal reflux disease. Arch Intern Med 1995; 155:2165-2173.
38. Feder G, Eccles M, Grol R, Griffiths C & Grimshaw J. Using clinical guidelines. BMJ 1999; 318:728-730.
39. Grimshaw JM & Russell IT. Effect of clinical guidelines on medical practice: A systematic review of rigorous evaluations. Lancet 1993; 342(8883):1317-1322.
40. Mittman B, Tonesk X & Jacolson P. Implementing clinical practice guidelines: social influence strategies and practitioner behavior change. Quality Review Bulletin 1992; 18:413-422.
41. Tassinari D, B. Poggi B, Tamburini E, et al. Quality of care in clinical oncology: from the dreamworld to the real world of outcome assessment. Annals of Oncology 2006; 17(1):177-178.
42. Vardy J & Tannock IF. Quality of cancer care. Annals of Oncology 2004; 15:1001-1006.
43. Winn RJ. Oncology Practice Guidelines: Do They Work? J Natl Compr Canc Network 2004; 2:276-282.
44. Winn RJ & McClure J. The NCCN CPGs in Oncology: A Primer for Users. J Nat Compr Canc Network 2003; 1:5-13.
45. Winn RJ, Smith TJ. The American Society of Clinical Oncology guidelines program. Pharm Pract Manage Q 1996; 16:31-38.
46. Woolf SH. Practice guidelines, a new reality in medicine. Arch Intern Med 1992; 152:946-952.
47. Gerber AS, Patashnik EM, Doherty D & Dowling C. A national survey reveals public skepticism about research-based treatment guidelines. Health Aff (Millwood) 2010; 29(10):1882-1884.
48. ESMO Guidelines Task Force. ESMO minimum clinical recommendations - the beginning of a process. Ann Oncol 2001; 12:1037-1038.
49. O'Shaughnessy JA, Wittes RE, Burke G, et al. Commentary concerning demonstration of safety and efficacy of investigational anticancer agents in clinical trials. J Clin Oncol 1991; 9:2225-2232.
50. Leventhal BG & Wittes RE. Treatment Toxicity and Quality of Life. Raven eds. 3, NY 1988; 23-40.
51. Nayfield SG & Hailey BJ. Report of the Workshop on Quality of Life Research in Cancer Clinical Trials. Nayfield & Hailey editors. Nat Inst of Health - NIH, Bethesda 1990.
52. Moinpur CM, Feigl P, Metch B, et al. Quality of life end points in cancer clinical trials: Reviews and Recommendations. J Nat Cancer Inst 1989; 81:485-495.
53. Donovan K, Sanson-Fisher RW & Redman S. Measuring quality of life in cancer patients. J Clin Oncol 1989; 7:959-968.
54. Smith TJ, Hillner BE & Desch CE. Commentary. Efficacy and cost-effectiveness of cancer treatment: Rational allocation of resources based on decision analysis. J Nat Cancer Inst 1993; 85:1460-1474.
55. Shapiro DW, Lasker RD, Bindman AB & Lee PR. Containing costs while improving quality of care: the role of profiling and practice guidelines. Ann Re Public Health 1993; 14:219-241.
56. Eccles M & Mason J. How to develop cost-conscious guidelines. Health Technol Assess 2001; 5:1-69.
57. Rubin HR, Gandek B, Rogers WH, et al. Patients' ratings of outpatient visits in different practice settings. JAMA 1993; 270:835-840.
58. FNCLCC Recommandations pour la pratique clinique en Cancérologie. John Libbey EUROTEXT, Paris 2nd ed. FNCLCC 1998.
59. Grimshaw JM & Russell IT. Achieving health gain through clinical guidelines II: ensuring guidelines change medical practice. Qual Health Care 1994; 3:24-52.
60. Langmark F. Cancer in Norway: the cancer registry of Norway. Norwegian Cancer Registry, Oslo 1997; 98-99.
61. Rosenberg W & Donald A. Evidence-based medicine: an approach to clinical problem-solving. BMJ 1995; 310:1122-1126.
62. Sackett DL & Rosenberg W. The need for evidence-based medicine. J Royal Soc Med 1995; 88:620-624.
63. Siegel RD, Clause SB & Lyn JM. National Collaborative to Improve Oncology Practice: The NCI Community Cancer Centers Program Quality Oncology Practice Initiative Experience. J Onc Practice 2009; 5(6):276-281.
64. Markman M. Clinical practice guidelines in oncology: pros and cons. Cancer Res Clin Oncol 1996; 122:381-382.
65. Markman M. Quality assurance in oncology: More substance, more questions. Current Onc Reports 2006; 8(3):155-156.
66. Jackson R & Feder G. Guidelines for clinical guidelines. BMJ 1998; 317:427-430.
67. Burgers JS, Cluzeau FA, Hanna SE, Hunt C & Grol R, the AGREE Collaboration. Characteristics of high quality guidelines: evaluation of 86 clinical guidelines developed in ten European countries and Canada. Int J Technol Assess Health Care 2003; 19:148-157.
68. Cook DJ, Greengold NL, Ellrodt AG & Weingarten SR. The relation between systematic reviews and practice guidelines. Ann Intern Med 1997; 127:210-216.
69. Sackett DL, Richardson WS, Rosenberg W & Haynes RB. Evidence based medicine. How to practice and teach EBM. New York: Churchill Livingstone, 1996.
70. Burgers JS & van Everdingen J. Beyond the evidence in clinical guidelines. Lancet 2004; 364:392-393.
71. Scalzitti DA. Evidence-Based Guidelines: Application to Clinical Practice. Physical Therapy 2001; 81(10):1622-1628.
72. French J. Can Evidence-Based Guidelines & Clinical Trials Tell Us How to Treat Patients? Epilepsia 2007; 48(7):1264-1267.
73. Hoelzer S, Hundahl SA, Stewart A, et al. Confronting actual practice with practice guidelines in oncology. Qual Assur 1999; 7(3):163-71.
74. Hellbruck RP. Medical guidelines: a valid and reliable management tool? Int J Health Plann Manage 1997; 12:51-62.
75. Hensley M, Hagerty K, Kewalramani T, et al. ASCO: Clinical Practice Guide-

line Update: Use of Chemotherapy and Radiation Therapy Protectants. J Clin Oncol 2008; 27(1):127-145.
76. Maltoni M, Caraceni A, Brunelli C, et al. Prognostic Factors in Advanced Cancer Patients: Evidence-Based Clinical Recommendations - A Study by the Steering Committee of the European Association for Palliative Care. J Clin Oncol 2005; 23:6240-6248.
77. McGivney WT. The NCCN guidelines: how do they relate to community oncology practice? Community Oncol 2004 July/Aug; 98-102.
78. Olesen F & Lauritzen T. Do general practitioners want guidelines? Attitudes toward a county-based and a national college-based approach. Scand J Prim Health Care 1997; 15:141-145.
79. Poonacha T & Go R. Level of Scientific Evidence Underlying Recommendations Arising from the National Comprehensive Cancer Network CPGs. J Clin Oncol 2011; 29(2):186-191.
80. Bahtsevani C, Uden G & Willman A. Outcomes of evidence-based clinical practice guidelines: a systematic review. Int J Technol Assess Health Care 2004; 20(4):427-433.
81. Browman GP, Levine MN, Mohide EA, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995; 13:502-512.
82. Burgers JS, Fervers B, Haugh M, et al. Intern. Assessment of the Quality of Clinical Practice Guidelines in Oncology Using the Appraisal of Guidelines and Research and Evaluation Instrument. J Clin Oncol 2004; 22:2000-2007.
83. Chalmers I & Altman DG. Systematic Reviews. BMJ Publishing Group, London 1995.
84. Counsell C. Formulating questions and locating primary studies for inclusion in systematic reviews. Ann Intern Med 1997; 127:380-387.
85. Fervers B, Fervers J, Haugh M, et al. Predictors of high quality clinical practice guidelines: examples in oncology. Int J Qual Health Care 2005; 17(2):123-132.
86. Lee SJ, Earle CC & Weeks JC. Outcomes research in oncology: history, conceptual framework, and trends in the literature. J Nat Cancer Inst 2000; 92:195-204.
87. Fervers B, Fervers J, Haugh M, et al. Adaptation of clinical guidelines: literature review and proposition for a framework and procedure. Int J Qual Health Care 2006; 18(3):167-176.
88. Meade MO & Richardson SW. Selecting and appraising studies for a systematic review. Ann Intern Med 1997; 127:531-537.
89. Smith TJ & Hillner BE. Ensuring Quality Cancer Care by the Use of Clinical Practice Guidelines and Critical Pathways. J Clin Oncol 2001; 19(11):2886-2897.
90. Vigna-Taglianti F, Vineis P, Liberati A & Faggiano F. Quality of systematic reviews used in guidelines for oncology practice. Ann Oncol 2006; 17:691-701.
91. Woolf SH. Manual for Conducting Systematic Reviews. Agency for Health Care Policy and Research Rockville, Md. 1996.
92. Cook DJ, Mulrow CD & Haynes RB. Systematic reviews: synthesis of best evidence for clinical practice. Ann Int Med 1997; 126:376-380.
93. Lewison G & Sullivan R. The impact of cancer research: how publications influence UK cancer clinical guidelines. Br J Cancer 2008; 98:1944-1950.
94. Cluzeau F, Littlejohns P & Grimshaw J. Appraising clinical guidelines - towards a 'Which' guide for purchasers. Quality in Health Care 1994; 3:121-122.
95. Cluzeau F, Littlejohns P, Grimshaw J, Feder G & Moran S. Development and application of a generic methodology to assess the quality of clinical guidelines. Int J Qual Health Care 1999; 11:21-28.
96. Cluzeau FA, Burgers JS, Brouwers M, et al. (The AGREE Group). Development and validation of an international appraisal instrument for assessing the quality of clinical practice guidelines: the AGREE project. Qual Saf Health Care 2003; 12:18-23.
97. Fahey TP & Peters TJ. What constitutes controlled hypertension? Patient based comparison of hypertension guidelines. BMJ 1996; 313:93-96.
98. Grol R, Dalhuijsen J, Thomas S, Veld C, Rutten G & Mokkink H. Attributes of clinical guidelines that influence use of guidelines in general practice: observational study. BMJ 1998; 317:858-861.
99. Psaty BM & Furberg CD. British guidelines on managing hypertension. Provide evidence, progress, and an occasional missed opportunity. BMJ 1999; 319:589-590.
100. Shekelle PG, Woolf SH, Eccles M & Grimshaw J. Clinical Guidelines. Developing guidelines. BMJ 1999; 318:593-596.
101. Ward JE, Grieco V. Why we need guidelines for guidelines: A study of the quality of clinical practice guidelines in Australia. Med J Aust 1996; 165:574-576.
102. Oxman AD & Guyatt GH. The science of reviewing research. Ann NY Acad Sci 1993; 703:125-134.
103. Burgers JS, Grol R, Klazinga NS, Makela M & Zaat J. The AGREE Collaboration Towards evidence-based clinical practice: an International Survey of 18 clinical guideline programmes. Int J Qual Health Care 2003; 15:31-45.
104. Kane RL. Creating practice guidelines: the dangers of over-reliance on expert judgment. J Law Med Ethics 1995; 23(1):62-64.
105. Naylor CD. Grey zones of clinical practice: some limits to evidence based medicine. Lancet 1995; 345:840-842.
106. Van Weel C & Knottnerus JA. Evidence-based interventions and comprehensive treatment. Lancet 1999; 353:916 -918.
107. Miller J & Petrie J. Development of practice guidelines. Lancet 2000; 355(9198):82-83.
108. Rogers W. Are guidelines ethical? Some considerations for general practice. Br J of General Practice 2002; 52:663-669.
109. Hope T. Evidence-based medicine and ethics. J Med Ethics 1995; 21:259-260.
110. Fervers B, Philip T, Haugh M, Cluzeau F, Browman G. Clinical-practice guidelines in Europe: time for European co-operation for cancer guidelines. The Lancet Oncology 2003; 4:139-140.
111. Sant M, Capocaccia R, Coleman MP, et al. (EUROCARE Working Group). Cancer survival increases in Europe, but international differences remain wide. Eur J Cancer 2001; 37:1659-1667.
112. Eisinger F, Geller G, Burke W & Holtzman NA. Cultural basis for differences between US and French clinical recommendations for women at increased risk of breast and ovarian cancer. Lancet 1999; 353:191-200.
113. Haines A & Feder G. Guidance on Guidelines. BMJ 1992; 305:785-786.
114. Petrie JC, Grimshaw JM & Bryson A. The Scottish Intercollegiate Guidelines Network initiative: getting validated guidelines into local practice. Health Bull 1995; 53:345-348.
115. Fervers B, Philip T, Browman G. Clinical appraisal of the Minimal Critical Recommendations (MCR) of ESMO: challenges for a European framework for the development of clinical practice guidelines. Ann Oncol 2002; 13:1507-1510.
116. Browman GP, Newman TE, Mohide EA, et al. Progress of clinical oncology guidelines development using the Practice Guidelines Development Cycle: The role of practitioner feedback. J Clin Oncol 1998; 16:1226-1231.
117. Browman GP. Improving clinical practice guidelines for the 21st century: Attitudinal barriers and not technology are the main challenges. Int J Technol Assess Health Care 2000; 16:959-968.
118. Browman GP. 'Background to clinical guidelines in cancer': SOR, a programmatic approach to guideline development and aftercare. British J Cancer 2001; 84 (Suppl 2):1-3.
119. Storme G. Clinical practice guidelines in cancer: the European perspective. British J Cancer 2001; 84 (Suppl 2):6-7.
120. Quinn MJ, Martinez-Garcia C & Berrino F. Variations in survival from breast cancer in Europe by age and country, 1978-1989. Eur J Cancer 1998; 34:2204-2211.
121. Manna DR, Bruijnzeels MA, Mokkink HGA & Berg M. Ethnic specific recommendations in clinical practice guidelines: a first exploratory comparison between guidelines from the USA, Canada, the UK, and the Netherlands. Qual Saf Health Care 2003; 12:353-358.
122. Aldrich R, Kemp L, Williams SJ, et al. Using socioeconomic evidence in clinical practice guidelines. BMJ 2003; 327:1283.
123. Hart JT. The inverse care law. Lancet 1971; 297:405-412.
124. Whitehead M. The concepts and principles of equity and health. WHO Copenhagen, Reg. Office for Europe 1990.
125. Kidd KE & Altman DG. Adherence in social context. Control Clin Trials 2000; 21 (suppl 1):S184-187.
126. National Health & Medical Research Council - Australia. Using socioeconomic evidence in clinical practice guidelines. Canberra: NHMRC, 2003:95. Available from: www.nhmrcGoau/publications/synopses 2003.

127. Pauly M. Practice guidelines: can they save money? Should they? J Law Med Ethics 1995; 23(1):65-74.
128. Hurwitz B. Legal and political considerations of clinical practice guidelines. BMJ 1999; 318:661-664.
129. Fluechter D & Dearlove O. Clinical guidelines examined by High Court. BMJ 1999; 318:661.
130. Brennan T. Practice guidelines and malpractice litigation: collision or cohesion? J Health Polit Policy Law 1991; 16:67-85.
131. Havighurst C. Practice Guidelines as Legal Standards Governing Physician Liability. Law & Contemporary Problems 1991; 54(2):87-117.
132. Hyams AI, Brandenburg FA, Lipsitz SR, et al. Practice guidelines and malpractice litigation: a two-way street. Ann Intern Med 1995; 122:450-455.
133. Jutras D. Clinical practice guidelines as legal norms. Can Med Assoc J 1993; 148:905-908.
134. Mozaffarieh M & Wedrich A. Malpractice in ophthalmology: guidelines for preventing pitfalls. Med Law 2006; 25:257-265.
135. Samanta A, Samanta J, Gunn M. Legal considerations of clinical guidelines: will NICE make a difference? J R Soc Med 2003; 96:133-138.
136. Zweig FM & Witte HA. Assisting judges in screening medical practice guidelines for health care litigation. Jt Comm J Qual Impro 1993; 19:342-354.
137. Gotzsche P. Clinical practice should reflect clinical science. In: Health Telematics for Clinical Guidelines and Protocols. Gordon & Christensen Eds. Amsterdam: IOS Press: 1994; 17-25.
138. Freemantle N & Maynard A. Something rotten in the state of clinical & economic evaluations? Health Economics 1994; 3:63-67.
139. Brook RH. A method for the detailed assessment of the appropriateness of medical technologies. J Techn Asses in Health Care 1986; 2:53-63.
140. Brook RH. Practice guidelines and practicing medicine. Are they compatible? JAMA 1989; 262(21):3027-3030.
141. Benner P & Wrubel J. The primacy of caring: stress and coping in health and illness. Menlo Park, CA: Addison-Wesley 1989.
142. Ramfelt E & Lützén K. Patients with Cancer: their approaches to participation in treatment plan decisions. Nursing Ethics 2005; 12(2):143-156.
143. Watson J. Nursing: Human science and human care. A theory of nursing. National League for Nursing, NY, USA 1999.
144. Chong C, Chen I, Naglie G & Krahn MD. How Well Do Guidelines Incorporate Evidence on Patient Preferences? J Gen Intern Med 2009; 24(8):977-982.
145. Bottomley A, Jones D & Claassens L. Patient-reported outcomes: Assessment and current perspectives of the guidelines of the Food and Drug Administration and the reflection paper of the European Medicines Agency. Eur J Cancer 2009; 45:347-353.
146. Elwyn G, Edwards A, Gwyn R & Grol R. Towards a feasible model for shared decision making: focus group study with general practice registrars. BMJ 1999; 319:753-756.
147. Fettings JH. Principles of practice guidelines. Patient outcomes and guidelines. Am Soc of Cl Onc - ASCO (ed): Educ. Book. Alexandria, VA, 1994.
148. Hlatky MA. Patient preferences and clinical guidelines. JAMA 1995; 273:1219-1220.
149. Lipscomb J, Gotay CC & Snyder C. Patient-reported outcomes in cancer: a review of recent research and policy initiatives. CA Cancer J Clin 2007; 57:278-300.
150. Oppenheim PI, Sotiropoulos G & Baraff LJ. Incorporating Patient Preferences into Practice Guidelines: Management of Children with Fever without Source. Annals of Emerg Med 1994; 24(5):836-841.
151. Pieterse AH, Baas-Thijssen MCM, et al. Clinician and cancer patient views on patient participation in treatment decision-making: a quantitative and qualitative exploration. Br J Cancer 2008; 99:875-882.
152. Say R & Thomson R. The importance of patient preferences in treatment decisions - challenges for doctors. BMJ 2003; 327:542-545.
153. Woo B, Woo B, Cook EF, Weisberg M & Goldman L. Screening procedures in the asymptomatic adult: comparison of physicians' recommendations, patients' desires, published guidelines, and actual practice. JAMA 1985; 254:1480-1484.
154. Guadagnoli E, Ward P. Patient participation in decision-making. Soc Sci Med 1998; 47:329-339.
155. Degner LF, Kristjanson LJ, Bowman D, Sloan JA, Carriere KC, O'Neil J, Bilodeau B, Watson P & Mueller B. Information needs and decisional preferences in women with breast cancer. JAMA 1997; 277:1485-1492.
156. Rothenbacher D, Lutz MP & Porzsolt F. Treatment decisions in palliative cancer care: patients' preferences for involvement and doctors' knowledge about it. Eur J Cancer 1997; 33:1184-1189.
157. O'Donnell M & Hunskaar S. Preferences for involvement in treatment decision-making generally and in hormone replacement and urinary incontinence treatment decision-making specifically. Patient Educ Couns 2007; 68:243-251.
158. Davis DA, Taylor-Vaisey A. Translating guidelines into practice. Can Med Assoc J 1997; 157:408-416.
159. Rogers EM. Diffusion of Innovations. Free Press 4th ed. New York, NY 1995.
160. Lomas J. Diffusion, dissemination, and implementation: Who should do what? Ann NY Acad Sci 1993; 703:226-237.
161. Kedikoglou S, Syrigos K, Skalkidis Y, et al. Implementing clinical protocols in oncology: quality gaps and the learning curve phenomenon. Eur J Public Health 2005; 15(4):368-371.
162. EBM Working Group. Evidence-based medicine: a new approach to teaching the practice of medicine. J Am Med Assoc 1992; 268:2420-2425.
163. Pavlidis N. Evidence-based medicine: Development and implementation of guidelines in oncology. Eur J Cancer 2009; 45:468-470.
164. Lipscomb J, Gotay CC & Snyder C. Introduction to outcomes assessment in cancer. In: Lipscomb et al. eds. Outcomes assessment in cancer. Cambridge University Press 2005; 1-14.
165. Bottomley A & Aaronson NK. EORTC. International perspective on health-related quality-of-life research in cancer clinical trials: the EORTC experience. J Clin Oncol 2007; 25(32):5082-5086.
166. Dickman PW, Hakulinen T, Luostarinen T, et al. Survival of cancer patients in Finland 1955-1994. Acta Oncol 1999; 38 (Suppl 12):1-103.

Neoadjuvant therapy for organ-confined prostate cancer

Athanasios Athanasiadis, Georgia Lambrodimou and Fotios Zarzoulas

Oncology Unit,
General Hospital of Larissa,
Thessaly, Greece

Correspondence:
Athanasios Athanasiadis,
Oncology Unit, General Hospital of Larissa,
Tsakalof 1, 41221 Thessaly, Greece,
e-mail: athanasiadis.athanasios@yahoo.com

ABSTRACT

Most of patients with organ-confined prostate cancer are treated successfully and can be cured with definitive local therapy (radical prostatectomy or radiation therapy) but approximately 30%-60% of them will finally experience local or incurable systemic relapse. Patients with advanced clinical stage (T2c-3), and/or serum prostate-specific antigen (PSA) levels ≥20ng/mL, or high-grade tumors (Gleason score 7-10) are at higher risk of disease relapse and death, despite the implementation of local therapy. Neoadjuvant systemic therapy could theoretically eradicate the occult locally or disseminated micrometastatic disease and improve cure rates of prostate cancer patients with unfavorable prognosis.

The present article reviews the available data regarding androgen deprivation therapy and chemotherapy in the neoadjuvant setting, as well as the current role of this approach in clinical practice and future perspectives.

Key words: prostate cancer; neoadjuvant therapy; hormonal therapy; radical prostatectomy; radiation therapy.

INTRODUCTION

Organ-confined prostate cancer can be treated with curative intent with radical local therapy, prostatectomy or radiation therapy, yet a subset of patients with adverse features, such as high-grade tumors (Gleason score ≥7), high baseline PSA level ≥20ng/mL, and/or advanced clinical stages (T2c-3) have a higher risk for biochemical, local or systemic relapse; the former ultimately leading to the latter. Local therapy is not sufficient to guarantee cure for the majority of patients with unfavorable prognosis, therefore a combination of effective local therapy with an active systemic therapy could probably increase the disease cure rate [1, 2, 3].

Patient groups of low, intermediate or high risk should be classified accordingly prior to radical treatment, using T-stage; PSA value; and Gleason score, corresponding to rates of disease-specific survival [4, 5].

Predictive variables have been combined in useful and accurate pretreatment nomograms [6, 7].

Based on pretreatment assessment, patients with less favorable prognosis can be selected as candidates for multimodality therapeutic approach.

Relapse of prostate cancer after radical local treatment could be explained by the presence of occult micrometastatic disease at the time of diagnosis, or by inadequate implementation of local therapy.

The concept of neoadjuvant systemic therapy is based on the possibility of eradication of all subclinical local or systemic disease prior to definitive local therapy. Theoretical advantages of the neoadjuvant therapeutic approach are: disease downstaging and consequential increase of the number of patients, who could effectively receive local treatment; immediate assessment of disease responsiveness; acquisition of prognostic and predictive information; and rapid evaluation of the implemented treatment's effectiveness.

Conventional process of phase I to phase III trials for definitive evaluation of the efficacy of a promising therapy is time-consuming, and the rapid evaluation of newer therapies is a crucial issue in cancer therapeutics. Furthermore, phase I trials are conducted by enrolling patients with significantly advanced, heavily pretreated disease -a population that may in fact be biologically different from patients with early-stage disease. The neoadjuvant therapeutic approach offers an attractive model for the evaluation and development of newer

drugs in prostate cancer and allows collection of pre- and post-treatment tumor tissue for translational research.

Difficulties related to the neoadjuvant therapy are: accurate and objective evaluation of organ-confined disease and the assessment of neoadjuvant therapy efficacy based on pathological criteria, since complete response is a rather rare outcome.

The difficulty in accurately evaluating disease response necessitates the use of surrogate endpoints. The effect of neoadjuvant therapy in the case of radical prostatectomy can be assessed by the rate of negative excision margins; the rate of organ-confined disease; and lymph node negativity.

The evaluation of neoadjuvant systemic therapy response is even more difficult and less accurate after radiation therapy. Newer imaging modalities, such as endorectal magnetic resonance imaging and magnetic resonance spectroscopy may provide a more precise assessment of tumor volume and response to treatment [8].

NEOADJUVANT ANDROGEN DEPRIVATION THERAPY (ADT)

Androgen deprivation therapy is the cornerstone of advanced prostate cancer treatment, because of the androgen-dependent growth of the vast majority of prostate cancer cells. ADT has been studied in the neoadjuvant setting, as induction therapy before radical prostatectomy and external beam radiation therapy as well.

NEOADJUVANT ADT AND RADICAL PROSTATECTOMY

Initially the role of the ADT in the neoadjuvant setting was investigated as induction therapy before radical prostatectomy, mainly because the immediate evaluation of induction treatment effects is feasible by objective pathological assessment of tissue specimen after prostatectomy. Response evaluation is more complicated when external beam radiation therapy is the local therapeutic approach.

Studies on neoadjuvant ADT before radical prostatectomy used various efficacy endpoints such as rate of positive surgical margins; change in tumor volume as assessed by imaging methods; pathological changes; rate of objective responses; and biochemical response to therapy.

Klotz *et al.* [9] in a randomized study which enrolled 213 prostate cancer patients with T1b - T2c disease, compared the neoadjuvant therapy with cyproterone acetate for 3 months before radical prostatectomy to prostatectomy alone and found lower rates of positive surgical margins for the neoadjuvant therapy group (27.7% vs. 64.8%, p=0.001), but no difference in biochemical relapse between the two groups. Similar results were reported by Soloway *et al.* [10] and Aus *et al.* [11] in two randomized trials comparing the addition of 3 months of neoadjuvant therapy with leuprolide plus flutamide and triptorelin, respectively to radical prostatectomy alone.

In a large randomized trial conducted by Schulman *et al.* [12], 402 prostate cancer patients with T2-3N0M0 disease were randomized to 3-month ADT with goserelin and flutamide prior to radical prostatectomy or to radical prostatectomy alone. Pathological downstaging occurred in 15% and 7% of cases in the preoperatively treated group and in the direct radical prostatectomy group, respectively (p<0.01). The rate of negative surgical margins also favored the group of neoadjuvant ADT group, but this advantage did not translate into a significantly better PSA progression free rate (p=0.18). However, when evaluating local control rate in the subset of patients with clinically T2 tumors, the authors reported a statistically significant lower local recurrence rate for neoadjuvant ADT group (3% vs. 11%, p=0.03).

In these studies, the higher rate of negative surgical margins and the downstaging effect of the neoadjuvant ADT unfortunately did not lead to a clinically significant benefit. This observation could be due to greater sensitivity of tumor cells in the prostate gland, while the disseminated prostate cancer cells are less sensitive to the androgen ablation or to the fact that a brief course of 3-month ADT is unable to eradicate the occult systemic disease. The concept that a short course of ADT is unable to eradicate the extraprostatic disseminated disease is supported by the observations of the small case control study conducted by Wood *et al.* [13]. In this study, 60 patients with cT2b-c or T1c-2a disease and PSA ≥10ng/mL, were analyzed for the presence of disseminated tumor cells (DTCs) in bone marrow specimens by reverse transcriptase polymerase chain reaction amplification (RTPCR) of the PSA mRNA. Thirty-one patients were treated with neoadjuvant ADT prior to radical prostatectomy and 29 patients with prostatectomy alone. Patients preoperatively treated with ADT had a higher probability of having organ-confined disease (58% vs. 24%, p=0.03). However, in the neoadjuvant group, 46% and 28% of patients with extraprostatic and organ-confined disease, respectively, were RTPCR positive (p=0.29). For patients who were RTPCR positive, 45% of the neoadjuvant group had organ-confined disease, compared to 6% in the radical-prostatectomy-alone patients (p=0.018). This data suggests that in a subset of patients from the neoadjuvant group the disease was converted to organ-confined, without eliminating the bone marrow cancer cells. ADT before radical prostatectomy probably decreases the occurrence of extraprostatic disease, but cannot eradicate disseminated prostate cancer cells. This hypothesis may partially explain why hormonal therapy before radical prostatectomy does not improve disease-free survival.

NEOADJUVANT ADT AND RADIATION THERAPY (EBRT)

The combination of ADT with radiation therapy is promising. Preclinical data favors neoadjuvant androgen blockade prior to radiation therapy. Zietman AL *et al.* conducted a study evaluating the best sequence between androgen suppression and radiation therapy. The androgen-dependent Shionogi adenocarcinoma allografts in athymic mice were significantly more sensible to radiation, when orchiectomy was implemented prior to radiation (neoadjuvant therapy), in comparison

to orchiectomy after radiation (adjuvant therapy) [14].

Large phase III trials have evaluated the role of ADT before and during definitive radiation therapy.

The RTOG 8610 trial included 456 patients with T2-4, any N (1988 American Joint Committee on Cancer TNM staging system) disease, which were randomly assigned to receive combined ADT consisted of two months of goserelin and flutamide before EBRT (neoadjuvant) and concurrently with EBRT or to receive EBRT alone. The study was powered to detect a difference in overall survival. Ten-year overall survival estimates (43% vs. 34%) and median survival times (8.7 vs. 7.3 years) favored neoadjuvant ADT and EBRT; however these differences did not reach statistical significance (p=0.12). There was a statistically significant improvement in 10-year disease-specific mortality (23% vs. 36%; p=0.01), distant metastasis rate (35% vs. 47%; p=0.006), disease free survival (11% vs. 3%; p<0.0001), and biochemical failure (65% vs. 80%; p<0.0001) on addition of neoadjuvant ADT to EBRT [15, 16].

Laverdière J *et al.* randomized 120 prostate cancer patients with clinical stage T2-4, between EBRT alone; 3 months of neoadjuvant anti-androgen therapy with LHRH-agonist and flutamide prior to EBRT; and a third group receiving combination therapy 3 months before, during, and 6 months after EBRT. Patients treated with neoadjuvant androgen blockade had a significantly lower rate of positive biopsies at 12 and 24 months after the end of radiation therapy as compared to those treated with radiation therapy alone [17].

To date, RTOG 9413 is the only study that addressed certain issues regarding volume and sequencing of radiation (RT) and hormone therapy (HT) [18]. In this study 1,323 patients with localized prostate cancer, PSA ≤100ng/mL, and an estimated risk of lymph node involvement of 15% were randomly assigned to whole pelvis irradiation (WP RT) and neoadjuvant and concurrent hormonal therapy (NCHT), pelvic only irradiation (PO RT) and NCHT, WP RT and adjuvant hormonal therapy (AHT) or PO RT and AHT. Patients treated with NCHT experienced a 4-year PFS of 52% versus 49% for AHT (p=0.56). WP RT + NCHT improved significantly PFS compared with PO RT + NCHT, PO RT + AHT, and WP RT +AHT, suggesting that there is a favorable biological interaction between WP RT and NCHT.

In a retrospective study, the addition of a short course of neoadjuvant ADT to transperineal interstitial permanent brachytherapy failed to show an improvement in PSA-relapse-free survival in the matched-pair analysis [19]. The lack of benefit from NCHT when combined with PO RT reported by the RTOG 9413 study could probably explain the observed lack of benefit in the addition of neoadjuvant ADT in patients receiving brachytherapy.

NEOADJUVANT CHEMOTHERAPY BEFORE DEFINITIVE LOCAL THERAPY

Before the 1990s, objective response rates with available chemotherapeutic agents in the treatment of advanced prostate cancer were disappointing. Besides, the difficulty in defining target lesions in advanced prostate cancer encumbered the development of chemotherapy in this disease, and imposed the use of appropriate surrogate endpoints in phase II trials. Tolerability of systemic chemotherapy in prostate cancer was also of concern, since most patients are elderly and many have comorbidities [20].

Tannock *et al.* comparing in a phase III trial the combination of docetaxel plus prednisone to mitoxantrone plus prednisone in hormone-refractory prostate cancer patients showed that docetaxel, given every three weeks, was associated with increased median survival (18.9 months), higher rate of more than 50% decrease in the serum PSA, and improved quality of life [21].

Increasing evidence that prostate cancer is from its onset a polyclonal disease, with varying degrees of hormone sensitivity, provides a theoretical basis for the evaluation of chemotherapy in the neoadjuvant setting.

Today there are no phase III trials investigating the role of cytotoxic therapy prior to radical therapy, and only small phase II studies are available. Common finding of studies on neoadjuvant chemotherapy prior to radical prostatectomy was the lack of pathological complete remissions.

Hussain MA *et al.* studied the combination of docetaxel (every 21 days) plus short course of estramustine (days 1 to 3) in 21 prostate cancer patients selected on one or more of the following criteria: clinical stage T2b or greater; PSA ≥15ng/mL; and/or Gleason score of 8 to 10.Three to six cycles of chemotherapy were followed by local therapy, radical prostatectomy or EBRT -as deemed appropriate. Induction chemotherapy was well-tolerated and feasible with promising results. Ten patients underwent radical prostatectomy, with negative surgical margins in 7 of them, and 11 received EBRT with negative pre-radiotherapy biopsies in 2 [22].

Febbo PG *et al.* enrolled 19 patients with high-risk localized prostate cancer (Gleason score of 8 to 10, PSA>20ng/mL, and/or clinical stage T3) in a pilot trial to determine the clinical, pathological, and molecular effect of neoadjuvant chemotherapy with docetaxel.

Therapy consisted of weekly docetaxel (36mg/m^2) for 6 months, followed by radical prostatectomy. All patients were monitored with serum PSA measurements, and endorectal magnetic resonance imaging (MRI). Frozen tumor specimens were also collected for microarray analysis [23].

Chemotherapy was well-tolerated, PSA declined by >50% in 11 of 19 patients and endorectal MRI showed tumor volume reduction of at least 25% in 13 of 19 patients and at least 50% in 4 patients. Sixteen patients completed chemotherapy and had radical prostatectomy, but no patient achieved pathological complete response. Microarray analysis identified coordinate upregulation of genes involved in androgen metabolism associated with docetaxel therapy. Specifically, RNA expression of genes that decrease cellular levels of

bioactive androgens was proportionally increased in response to chemotherapy.

The authors hypothesized that prostate cancer cells, surviving docetaxel therapy, altered their androgen metabolism by lowering the availability of active androgens; divided less often; and were less sensitive to the anti-mitotic effects of docetaxel's microtubule-stabilizing properties. The observed alteration of androgen metabolism as a mechanism of resistance to docetaxel raises some concern on combining androgen ablation with docetaxel, but such findings are too preliminary to reject the combination of docetaxel with antiandrogen therapy [24].

In a recent study, Darshan MS *et al.* investigated the association between androgen receptor (AR) subcellular localization in circulating tumor cells (CTCs) and patient clinical response to chemotherapy with taxane. Analysis of CTCs isolated from the peripheral blood of hormone refractory prostate cancer (HRPC) patients receiving taxane chemotherapy, revealed a significant correlation between AR cytoplasmic sequestration and clinical response to therapy. These results indicate that in HRPC patients, taxanes act at least in part by inhibiting AR nuclear transport and signaling following microtubule stabilization [25].

The impact of neoadjuvant ADT combined with docetaxel chemotherapy on pathological and long-term outcomes is still unknown. Neoadjuvant therapy followed by prostatectomy is feasible and provides a paradigm for evaluating the activity, mechanism of action and resistance to new treatments [26, 27].

CONCLUSION

To optimize the therapy of high-risk localized prostate cancer, neoadjuvant systemic therapy before a definitive local one is under active evaluation.

Neoadjuvant hormonal therapy with radiation therapy is promising, increases significantly both clinical and biochemical progression free survival, and probably the overall survival in subsets of patients. The optimal duration of neoadjuvant ADT needs to be further defined.

In contrary, neoadjuvant ADT before radical prostatectomy does not improve survival parameters, despite the increase in the rate of organ-confined disease and the rate of negative surgical margins. It is still unclear why patients undergoing radiation therapy benefit from neoadjuvant ADT while patients with prostatectomy do not.

Chemotherapy as induction before radical prostatectomy is feasible and its impact on long-term clinical outcome, as well as its pathological and biological effects, are investigated by ongoing phase III clinical trials.

REFERENCES

1. Epstein JI, Epstein JI, Partin AW, et al. Prediction of progression following radical prostatectomy. A multivariate analysis of 721 men with long-term follow-up. Am J Surg Pathol 1996; 20:286-292.
2. Kupelian PA, Elshaikh M, Reddy CA, et al. Comparison of the Efficacy of Local Therapies for Localized Prostate Cancer in the PSA Era: A Large Single-Institution Experience with Radical Prostatectomy and EBRT. J Clin Oncol 2002; 20(16):3376-3385.
3. Shipley WU, Thames HD, Sandler HM, et al. Radiation therapy for clinically localized prostate cancer: a multi-institutional pooled analysis. JAMA 1999 May 5; 281(17):1598-1604.
4. D'Amico AV, Whittington R, Malkowicz SB, et al. Estimating the impact on prostate cancer mortality of incorporating prostate-specific antigen testing into screening. Urology 2001 Sep; 58(3):406-10.
5. Partin AW, Mangold LA, Lamm DM, Walsh PC, et al. Contemporary update of prostate cancer staging nomograms (Partin Tables) for the new millennium. Urology 2001 Dec; 58(6):843-8.
6. Kattan MW, Eastham JA, Stapleton AM, Wheeler TM, Scardino PT. A preoperative nomogram for disease recurrence following radical prostatectomy for prostate cancer. J Natl Cancer Inst 1998; 90:766-771.
7. Kattan MW, Zelefsky MJ, Kupelian PA, et al. Pretreatment Nomogram for Predicting the Outcome of Three-Dimensional Conformal Radiotherapy in Prostate Cancer. JCO 2000 Oct 19; 18(19):3352-3359.
8. Carroll PR, Coakley FV, Kurhanewicz J. Magnetic Resonance Imaging and Spectroscopy of Prostate Cancer. Rev Urol 2006; 8 (Suppl 1):S4-S10.
9. Klotz LH, Goldenberg SL, Jewett M, et al. CUOG randomized trial of neoadjuvant androgen ablation before radical prostatectomy: 36-month post-treatment PSA results. Urology 1999; 53:757-763.
10. Soloway MS, Pareek K, Sharifi R, et al. Neoadjuvant androgen ablation before radical prostatectomy in cT2bNxM0 prostate cancer: 5-year results. J Urol 2002; 167:112-116.
11. Aus G, Abrahamsson P-A, Ahlgren G, et al. Three-month neoadjuvant hormonal therapy before radical prostatectomy: a 7-year follow-up of a randomized controlled trial. BJU Int 2002; 90:561-566.
12. Schulman CC, Debruyne FMJ, Forster G, et al. Four-year follow-up results of a European prospective randomized study on neoadjuvant hormonal therapy prior to radical prostatectomy in T2-3N0M0 prostate cancer. Eur Urol 2000; 38:706-713.
13. Wood DP, Beamean A, Banerjee M, et al. Effect of neoadjuvant androgen deprivation on circulating prostate cells in the bone marrow of men undergoing radical prostatecotmy. Clin Cancer Res 1998; 4:2119-2123.
14. Zietman AL, Prince EA, Nakfoor BM, Park JJ. Androgen deprivation and radiation therapy: sequencing studies using the Shionogi in vivo tumor system. Int J Radiat Oncol Biol Phys 1997; 38(5):1067-70.
15. Pilepich MV, Winter K, John MJ, et al. Phase III RTOG trial 86-10 of androgen deprivation adjuvant to definitive radiotherapy in locally advanced carcinoma of the prostate. Int J Radiat Oncol Biol Phys 2001; 50(5):1243-52.
16. Roach M III, Bae K, Speight J, et al. Short-Term Neoadjuvant Androgen Deprivation Therapy and External-Beam Radiotherapy for Locally Advanced Prostate Cancer: Long-Term Results of RTOG 8610. J Clin Oncol 2008 Feb 1; 26(4):585-591.
17. Laverdière J, Gomez JL, Cusan L, et al. Beneficial effect of combination hormonal therapy administered prior and following external beam radiation therapy in localized prostate cancer. Int J Radiat Oncol Biol Phys 1997 Jan 15; 37(2):247-52.
18. Roach M III, DeSilvio M, Lawton C, et al. Phase III Trial Comparing Whole-Pelvic Versus Prostate-Only Radiotherapy and Neoadjuvant Versus Adjuvant Combined Androgen Suppression: Radiation Therapy Oncology Group 9413. J Clin Oncol 2003 May 15; 21(10):1904-1911.
19. Potters L, Torre T, Ashley R, et al. Examining the role of neoadjuvant androgen deprivation in patients undergoing prostate brachytherapy. J Clin Oncol 2000 Mar; 18(6):1187-1192.

20. Tannock IF. Is there evidence that chemotherapy is of benefit to patients with carcinoma of the prostate? J Clin Oncol 1985; 3:1013-1021.
21. Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med 2004; 351:1502-1512.
22. Hussain M, Smith DC, El-Rayes BF, et al. Neoadjuvant docetaxel and estramustine chemotherapy in high-risk/locally advanced prostate cancer. Urology 2003 Apr; 61(4):774-80.
23. Febbo PG, Richie JP, George DJ, et al. Neoadjuvant Docetaxel before Radical Prostatectomy in Patients with High-Risk Localized Prostate Cancer. Clin Cancer Res 2005; 11(14):5233-5240.
24. Eastham JA, Kelly WK, Grossfeld GD, et al. CALGB 90203: a randomized phase 3 study of radical prostatectomy alone versus estramustine and docetaxel before radical prostatectomy for patients with high-risk localized disease. Urology 2003; 62 (Suppl 1):55-62.
25. Darshan MS, Loftus MS, Thadani-Mulero M, et al. Taxane-induced blockade to nuclear accumulation of the androgen receptor predicts clinical responses in metastatic prostate cancer. Cancer Res 2011 Sep 15; 71(18):6019-29.
26. Garzotto M, Higano CS, O'Brien C, et al. Phase 1/2 study of preoperative docetaxel and mitoxantrone for high-risk prostate cancer. Cancer 2010 Apr 1; 116(7):1699-708.
27. Sonpavde G, Palapattu GS. Neoadjuvant therapy preceding prostatectomy for prostate cancer: rationale and current trials. Expert Rev Anticancer Ther 2010; 10(3):439-50.

Pregnancy complicated by cancer. What do we know?

Evangelos Voulgaris[1,2], Nikolaos Pavlidis[2]

[1]217 Military Hospital, Ioannina, Greece
[2]Department of Medical Oncology, University Hospital of Ioannina, Greece

Correspondence:
Evangelos Voulgaris,
Department of Medical Oncology,
University Hospital of Ioannina, Greece,
e-mail: evoulg@gmail.com

ABSTRACT

Background: As most women today tend to delay childbearing, the complex situation of cancer in pregnancy has become more frequent.

Patients & Methods: Review of literature on the issues of diagnosis, staging and treatment in pregnant patients.

Results: Due to the paucity of large/randomized trials and the relatively limited experience, cancer management in pregnancy is challenging and requires increased awareness. As in non-pregnant patients, every effort should be made to provide the maximal benefit and best prognosis to the pregnant patient. In most cases, in order to avoid any harm to the fetus, different diagnostic approaches should be incorporated and treatment should be tailored to each pregnant woman. Patients should be properly informed and their wishes and beliefs respected.

Conclusion: Treatment of cancer during pregnancy with normal fetal outcome is feasible but should be executed by experienced specialists using strict protocols. The cooperation of multidisciplinary teams including medical and radiation oncologists, surgeons, obstetricians, neonatologists and experienced nursing staff is necessary to provide optimal care for the patient with minimal harm to the fetus..

Key words: cancer; pregnancy; diagnosis; treatment.

INTRODUCTION

Diagnosis of cancer during pregnancy is a relatively rare phenomenon with an incidence of approximately 1 in 1000-1500 pregnancies, resulting in 3000-5000 new patients a year in Europe [1]. The physiological changes during pregnancy require a different diagnostic and therapeutic approach to patient treatment so as to achieve maximal benefit for the mother with minimal harm to the fetus. As women tend to delay childbearing, the incidence of gestational cancer will increase over the next years. In this literature review we present the current data on the complicated issues of diagnosis, management and outcome of cancer diagnosed during pregnancy.

DIAGNOSTIC WORK-UP IN PREGNANT WOMEN WITH CANCER

As with any other patient, a detailed history and a thorough physical examination should be the basis for the diagnostic work-up in pregnant women. The clinical presentation is not different from those of non-pregnant patients but, due to the physiological changes during pregnancy, the presenting symptoms may be overlooked resulting in late diagnosis. Biopsies or fine needle aspirations may be performed and, with cautious use of sedatives and analgesics, the risk is limited for the fetus. Minor or major operations may also be performed during pregnancy with a slightly increased risk for fetal loss in the 1st trimester due to general anesthesia [2].

Many diagnostic imaging modalities, with appropriate shielding, expose the fetus to smaller doses of radiation than the recommended safe limits [3]. Irradiation is proven to be highly teratogenic, with the radiation effect on the fetus being dose-dependent and directly related to gestational age, irradiation field and fractionation [4]. The use of Computerized Tomography (CT) should be avoided due to the fact that internal scatter of radiation to the fetus cannot be avoided [5]. Instead, magnetic resonance (MRI) may be used, if deemed necessary [6, 7]. Gadolinium-based MR contrast agents should not be routinely provided to pregnant patients as no controlled

trials have been performed in humans and their administration should be based on overwhelming potential benefit to the patient against the risks of fetal exposure [6, 8]. Mammography, with new imaging equipment and appropriate shielding, presents little risk to the fetus, while diagnostic ultrasound (US) has no documented adverse effects [9]. Positron emission tomography and computed tomography (PET/CT) exposes the fetus to high radiation doses due to the combination of 18F-FDG uptake as well as CT dose and should therefore be performed after delivery [10].

OPTIONS FOR THE MANAGEMENT OF CANCER IN PREGNANCY

Recent developments in medical and radiation oncology, in combination with the experience gained by small studies, have changed the practice in gestational cancer. Surgery, chemotherapy and radiotherapy during pregnancy can now be compatible with normal fetal outcome.

Surgery

Open as well as laparoscopic surgery may be performed safely and effectively in all trimesters of pregnancy by experienced teams of surgeons and anesthesiologists [11, 12]. Although the use of most anesthetic drugs is considered safe for the fetus, the potential risk for intraoperative as well as postoperative complications still exists [11].

Chemotherapy, pharmacokinetics

Most of the data available on the teratogenic risks of specific chemotherapeutic agents during pregnancy are based on case reports and small studies. Chemotherapy has been associated with both immediate and delayed effects on the fetus, as it directly damages the DNA and/or interferes with DNA replication, repair, and the processes of chromosome segregation during cell division (Table 1) [13]. The teratogenicity of these agents has been demonstrated when fetal exposure occurs during the first trimester of pregnancy [14, 15].

Enhanced renal excretion of drugs during pregnancy; increased or decreased hepatic function; different gastrointestinal absorption or enterohepatic circulation; and altered plasma protein binding can affect chemotherapeutic agent pharmacokinetics [16]. Drugs with molecular weight less than 600kDa may traverse the placenta, unless strongly protein-bound [17]. Agents that are lipophilic or remain in the un-ionized state may also easily cross the placenta [18]. The dosage, route and scheduling of administration is important. Short infusions may cause higher toxicity, while orally-administered drugs may have reduced absorption [16]. It should be noted that many agents may cause adverse effects regardless of the gestational age, while some seem to be relatively safe if administered after the 1st trimester. Use of chemotherapy in the first trimester may result to spontaneous abortion, fetal death or major malformations in 10-20% of the cases [19, 20]. Exposure to chemotherapy during the 2nd and 3rd trimester may also cause functional defects of late-forming tissues but, given the overwhelming data on the use of chemotherapy during this period, such risks remain minimal and acceptable, given the potential benefits for the mother.

Radiotherapy

The data regarding pregnant women exposed to radiation therapy are scarce and based on animal studies; data from *in utero* exposure to diagnostic procedures or from women and children survivors of nuclear disasters [21, 22]. Estimation of the fetal size and position, as well as projected growth over the duration of the treatment, are essential in radiotherapy planning so as to minimize fetal radiation exposure [3]. Successful radiotherapy during pregnancy and birth of healthy children has been reported [23-30]. A general rule is that if radiotherapy cannot be delayed until the post-partum period, it should be administered by an experienced team of physicists and radiation oncologists after careful planning, with the use of purpose-built shielding devices and low fractional doses over a longer time period [3, 22]. Administering radiation therapy during pregnancy is a decision that needs to be taken by a multidisciplinary team

Table 1.

Impact of chemotherapy on fetal health in different stages of embryonal development (Reproduced with permission: Pentheroudakis et al. *Cancer and pregnancy: Poena magna, not anymore*. EJC, Volume 42, Issue 2, January 2006, Pages 126-140)

Gestational stage	Embryonal/fetal development	Impact
Weeks 0-2	Undifferentiated multicellular organism	"All or nothing", spontaneous abortion or normal development
Weeks 3-12	Organogenesis	Spontaneous abortion, major congenital anomalies
2nd and 3rd trimester	Intrauterine growth and maturation, continuing development of CNS, gonads, teeth-palate, eyes, ears	Functional defects and minor anomalies of late-forming tissues, still birth, intrauterine growth retardation, premature delivery, myelosuppression

following thorough discussion with the patient and taking into account the possible risks and benefits. Irradiation during the 3rd trimester should be avoided due to the small distance between the uterus and the irradiated supradiaphragmatic sites [31].

MANAGEMENT OF THE MOST COMMON MALIGNANCIES DURING PREGNANCY

The frequency of the phenomenon cannot be accurately estimated for each type of cancer, as most studies are based on small number of patients. The most common malignancies associated with pregnancy are reported to be breast cancer, cervical cancer, hematological malignancies, melanoma, and thyroid cancer [32-34]. Ovarian, lung and gastrointestinal cancers are less often [35-37]. The incidence of malignant tumors during pregnancy is shown in Table 2.

Table 2.
Incidence of malignant tumors per pregnancies

Tumor Type	Incidence
Breast cancer	1 : 3,000-10,000
Cervical cancer	1 : 2,000-10,000
Hodgkin's lymphoma	1 : 1,000-6,000
Leukemias	1 : 75,000-100,000
Melanoma	2-5 : 100,000
Thyroid cancer	14 : 100,000
Ovarian cancer	4-8 : 100,000
Colorectal cancer	1 : 13,000

Breast cancer

It is estimated that up to 3% of breast cancers are diagnosed during pregnancy [38]. Due to the physiological changes during pregnancy, breast cancer diagnosis may be delayed from 2 to 18 months compared to non-pregnant women [39]. Approximately, 65 to 90% of pregnant patients are diagnosed at stage II and III, as compared to 45-65% of non-pregnant ones [40]. The histopathological features are similar to those of same age non-pregnant women breast cancer [33]. A common finding is a higher frequency of estrogen (ER) and progesterone (PR) negative tumors than for non-pregnant women of the same age [40, 41]. Due to the small number of studies, no definite conclusions can be drawn about differences in the incidence of HER2/*neu* amplification between pregnant and non-pregnant women [42].

Modified radical or conservative surgery with axillary lymph node dissection (ALND) can be performed during all trimesters of pregnancy with minimal risk to the fetus [39, 43, 44]. Sentinel lymph node biopsy (SLNB) is considered safe, and blue dye is not recommended because of possible allergic or anaphylactic reactions [45]. Due to the small number of patients in studies and the fact that concerns do exist regarding increased rates of false-negative results, patients should be duly informed about the risks and benefits. ALND could be performed instead. Chemotherapy during the first trimester is contraindicated and should be postponed. The dosage should be the same as for non-pregnant patients based on patient height and weight [44]. Most reports on the systemic therapy of PABC are retrospective. Based on these studies, anthracyclines remain the best choice for adjuvant therapy. In the majority of retrospective studies, the use of the FAC (5-FU, doxorubicin, cyclophosphamide) chemotherapy regimen is described. In the largest of them, eleven patients were treated during the second/third trimester and no congenital malformations were detected [46]. The use of FAC has been reported in a prospective study by Hahn *et al.* from the MD Anderson Cancer Center with favorable outcome [47]. Anthracycline-based regimens like FEC (5-FU, epirubicin, cyclophosphamide); AC (doxorubicin, cyclophosphamide); EC (epirubicin, cyclophosphamide) have also been reported with normal outcomes after 1st trimester exposure. Peccatori *et al.* [48] from the European Institute of Oncology have reported favorable outcomes with the use of weekly epirubicin in their prospective study. Use of taxanes, as single agents or in combination with anthracyclines, has also been reported in few patients without adverse effects for the pregnancy or the fetus [46, 49-51]. Since the safety of taxanes is less documented, it remains the second best choice for breast cancer during pregnancy. Based on recent preclinical data and the clinical experience of approximately 40 cases, the use of taxanes appears feasible during the 2nd and 3rd trimesters of pregnancy with limited risk to the mother and fetus [52]. CMF (5-FU, methotrexate, cyclophosphamide) should be avoided due to the potential teratogenic effects of methotrexate and the superiority of the anthracycline-based regimens [42]. Based on animal studies, case reports of congenital anomalies and lack of robust data on fetal outcome, women using tamoxifen should be strongly advised to discontinue its use in case of pregnancy [53, 54].

For patients diagnosed in the first or early second trimester, radiation therapy can be delayed until after delivery, if neoadjuvant or adjuvant chemotherapy is needed. For patients diagnosed during the late second or third trimester, radiation therapy should be postponed until after delivery [45]. If radiation therapy cannot be delayed, it can be administered during the 1st or 2nd trimester with all the precautions described earlier [44]. According to retrospective studies, survival of women with breast cancer during pregnancy is worse, regardless of the age of the mother [55-59]. Conversely, other studies report that the prognosis is similar to that of non-pregnant patients of similar stage, grade and hormonal status [33, 60, 61]. The prognosis remains an open issue.

Cervical cancer

Cervical cancer is the second most common solid tumor encountered during pregnancy [32]. Cervical carcinomas

during pregnancy are predominately of squamous histology (80-90%) and their prognosis does not seem to be influenced by pregnancy [62]. Cervical cancer in pregnant women is diagnosed at earlier stages, possibly because of the routine visual inspection and cytological examination of the cervix as part of the prenatal check-up [63]. For pre-invasive lesions, a conservative approach is advised with new colposcopy every six to eight weeks so as to monitor the disease and definite treatment should be delayed until after delivery [64, 65].

The treatment of invasive cervical cancer depends on histology, disease stage, gestational age of the fetus and patient's wishes regarding pregnancy termination. For stage Ia1 disease, conization during the second trimester and close follow-up of the patient is required until delivery [64, 66]. For patients wishing to preserve their pregnancy, platinum-based neoadjuvant chemotherapy may be given during the 2nd and 3rd trimester with a minimum of two and a maximum of four cycles until fetal maturity is attained [64]. In the absence of nodal metastasis, the French recommendations describe it as an option for stage Ib1~4cm, while the European consensus recommendations consider it an option even for stage Ib1<2cm [64, 67]. For these patients conservative surgery (i.e. trachelectomy) may be considered after neoadjuvant therapy, but this approach entails a high risk of pregnancy loss and cannot be considered standard [64]. Immediate treatment with sacrifice of the fetus is advised in cases of i) stage Ia1 with positive margins, Ia2, Ib or IIa discovered prior to 12 weeks gestation; ii) locally advanced; and iii) small cell histological subtype, poorly differentiated squamous or adenocarcinoma or disease progression [64]. In locally advanced cervical carcinoma, neoadjuvant chemotherapy is an option for patients refusing to terminate their pregnancy in order to stabilize the disease and allow fetal viability [64]. The mode of delivery is also controversial. Most reports suggest that survival is not affected by the mode of delivery if the cervix is cleared from the tumor but since fatal recurrences in episiotomy sites have been reported after vaginal delivery, a cesarian delivery is often advocated [64, 67, 68]. When preservation of pregnancy is not the aim, definitive treatment should be started immediately upon disease diagnosis.

Melanoma

Melanoma represents approximately 8% of all cancers diagnosed during pregnancy [69]. Wide surgical excision with 1-3 cm margins according to primary lesion thickness is the treatment of choice. Sentinel lymph node biopsy could be performed with the same limitations as for breast cancer. Adjuvant treatment regimens with high dose interferon have not been studied in pregnant patients with melanoma and are not routinely recommended [70-72]. In the metastatic setting, the use of chemotherapy is palliative and termination of pregnancy should be discussed with the patient. Dacarbazine-based chemotherapy during the 2nd and 3rd trimester has been reported, resulting in one case of minor fetal malformation (syndactyly) and 1 fetal death [73]. Shorter survivals have been reported in the literature, possibly due to enhanced lymphangiogenesis during pregnancy and shortened time to nodal metastasis [74-77] but three recent studies have not shown any difference in survival between pregnant and non-pregnant women with melanoma [62, 78, 79].

Hematological malignancies

Acute myeloid leukemia (AML) represents two thirds of all acute leukemias which occur during pregnancy and **acute lymphoblastic leukemia (ALL)** represents the remaining third [37]. Immediate therapy initiation is required upon diagnosis. When the diagnosis is made during the 1st trimester and treatment is initiated, there are high rates (nearly 50%) of adverse fetal outcomes [80]. During the 2nd and 3rd trimester the same induction and consolidation regimens as for non-pregnant patients are used. The combinations of cytarabin and daunorubicin or idarubicin (and vincristine for ALL) are most frequently reported in the literature with high rates of congenital anomalies and fetal deaths even if administered after the 1st trimester of pregnancy [80]. The use of doxorubicin could be considered for induction therapy for patients with AML or ALL who are not willing to proceed with pregnancy termination [80].

The incidence of **Hodgkin's lymphoma** ranges from 1 in 1,000 to 1 in 6,000 pregnancies [32]. Diagnosis should be based on excisional lymph node biopsy. When diagnosed early in the first trimester, termination of pregnancy should be considered -especially if any delay in treatment endangers the life of the mother (i.e. bulky disease, B-symptoms). If pregnancy preservation is the aim, a "watch-and-wait" approach until the 2nd trimester is preferred. For patients diagnosed in the 2nd and the 3rd trimester, the gold standard regimen ABVD (doxorubicin, bleomycin, vinblastin, dacarbazine) can be safely administered [80]. Prognosis for pregnant patients with HL does not seem to be inferior to that of non-pregnant patients [81, 82].

Non-Hodgkin's lymphoma during pregnancy is rare and few reports exist in the literature. When diagnosis is made, chemotherapy should be initiated immediately. In a review of 45 cases, where standard regimens were administered (even in the first trimester), no fetal adverse outcomes were registered [80]. Prognosis for pregnant patients with NHL does not seem to be inferior to that of non-pregnant patients [83].

Thyroid cancer

Thyroid cancer has been reported to occur with an incidence of 14 cases per 100,000 pregnancies [36]. All thyroid nodules measuring 1 cm or larger should be evaluated by FNA. Any patient with a malignant nodule or nodule(s) growing rapidly should undergo surgery during the 2nd trimester of

pregnancy. Pregnant patients should maintain normal T4 values, low but measurable thyroid-stimulating hormone and should be carefully monitored to avoid adverse fetal development [84]. Radioactive iodine should not be provided in women who are breastfeeding. There has not been reported decreased survival in pregnant thyroid cancer patients when compared with non-pregnant patients [85].

Ovarian cancer

Four to eight cases of ovarian cancer per 100,000 pregnancies is the estimated incidence reported in the literature [86, 87]. For early stage (IA) grade 1 epithelial tumors the surgical staging is similar to that of non-epithelial tumors [88]. Bilateral salpingo-oophorectomy may be performed after the 7th week of gestation [89]. For advanced stage disease, termination of pregnancy and complete surgical debulking is recommended. If preservation of pregnancy is the aim, hysterectomy may be performed as soon as a viable fetus is delivered. Current literature suggests that the use of platinum agents is feasible during the second and third trimester of pregnancy but further reports of platinum use during pregnancy are warranted to confirm the safety of these drugs. Based on a better toxicity profile, carboplatin is recommended instead of cisplatin [64, 90]. For non-epithelial ovarian cancer the use of BEP (bleomycin, etoposide, cisplatin); EP (etoposide, cisplatin); and PVB (cisplatin, vinblastin, bleomycin) have been reported with no major adverse fetal effects. Although data is limited, prognosis of patients with gestational ovarian cancer is reported to be similar to that of the non-pregnant patients [91].

Colorectal cancer

The incidence of colorectal cancer during pregnancy has been reported as one case per 13,000 pregnancies [32]. When diagnosis of colon or rectal cancer is made during the first 20 weeks of gestation, surgery can be performed safely and if adjuvant chemotherapy (or radiotherapy) is needed it can be offered post-partum. If it is diagnosed in the second half of pregnancy, surgery should be delayed until a viable fetus is delivered [92]. A cesarean delivery should be performed if the birth canal is tumor-obstructed. Only 2 cases of chemotherapy use during pregnancy have been reported. In both cases 5-FU with oxaliplatin was used after the 1st trimester without adverse effects on the fetus [93, 94].

Lung cancer

The incidence of lung cancer during pregnancy is rising due to the smoking habits of young women in western societies. Less than 50 cases have been reported in the literature with very poor prognosis for the patients. Eight patients were treated with systemic therapies during the course of gestation with normal fetal outcome and no evidence of fetal or placental metastases [95].

USE OF TARGETED AGENTS

Special concerns arise regarding the use of targeted agents during pregnancy as they are increasingly used in the everyday practice of oncology.

Trastuzumab has significantly improved outcomes in HER2 positive breast cancer [96, 97]. Few reports exist regarding the use of trastuzumab during pregnancy. Despite the fact that the majority of patients were exposed during the first trimester, no congenital anomalies were reported. It is proposed that the minimal materno-fetal transfer of IgG that occurs during the first trimester can account for these results [98]. The use of trastuzumab resulted in oligohydramnios or anhydramnios and caused neonatal deaths in four cases, as well as transient respiratory or renal failure in three [99-104]. These complications seem to be associated with prolonged exposure (more than one trimester) to trastuzumab and are reversible on stopping the mAb [105]. Six cases of *in utero* exposure to **rituximab** during the 2nd trimester and one during the 1st trimester of gestation have been reported with no congenital anomalies in the newborns. In three out of seven neonates, CD19+ B cells were decreased or undetectable at birth or shortly after. The condition was reversible within 3-6 months [106-110].

For the tyrosine kinase inhibitor **imatinib** preclinical models have shown teratogenic effects in mice and rats and thus the drug is not labeled for use in pregnancy [111]. In 2008, Pye *et al.* reported a series of 180 patients exposed to imatinib during pregnancy [112]. Of the 125 pregnancies that had known outcomes, twelve (9.6%) resulted in infants with fetal abnormalities. **Dasatinib** is a multi-targeted kinase inhibitor of bcr/abl and Src kinases and related proteins. Cortes *et al.* from the MD Anderson Cancer Center reported at a scientific meeting the outcomes of pregnancies of eight women who conceived during treatment. Three had therapeutic abortions, two spontaneous abortions and three delivered the babies. None of these women or their infants experienced serious adverse outcomes [113]. Conchon *et al.* recently reported the successful pregnancy and delivery of a healthy newborn exposed to dasatinib for approximately 8 weeks after conception [114]. No clinical data about the TKIs **sunitinib** and **sorafenib** during human pregnancy has been noted in the literature to date. Patyna *et al.* [115] recently reported embryo-fetal developmental toxicity of sunitinib in rats and rabbits due to angiogenesis inhibition, as typically observed for potent inhibitors TKIs and the monoclonal antibody bevacizumab. **Erlotinib** has been shown to cause embryo/fetal lethality in animal models. A case of fetal exposure to erlotinib during the 1st trimester has been reported [116]. The pregnancy was uncomplicated and continued until term without congenital anomalies being encountered. Due to limited clinical data and until larger studies with robust data are available, conception during treatment with TKIs is not recommended and effective contraception should be used. During pregnancy, the use of TKIs should be avoided -especially during the 1st trimester.

SUPPORT TREATMENT

Very limited data exists regarding the safety of **granulocyte colony stimulating factors (G-CSF)**. The drug may be considered for the management of febrile neutropenia in pregnant women [108, 117, 118]. **Recombinant human erythropoietin (rhEPO)** does not cross the placenta and the development of teratogenic effects is unlikely [119-121], but since data is scarce it should only be used if blood transfusion is not an option. In humans, the safety information on **bisphosphonates** during pregnancy is basically based upon case reports and small studies. On the basis of approximately 50 cases, exposure does not seem to be linked with anomalies to the embryo or fetus, but infants should be monitored for hypocalcemia [122]. In another study, the risk of birth defects and abortion was not higher when bisphosphonates were used during pregnancy [123]. Despite the above results and until definite data becomes available, bisphosphonates should be avoided during pregnancy. The **antiemetics** metoclopramide and ondasentron have been found to be safe during pregnancy in prospective trials and can be used during pregnancy [124, 125]. **Acetaminophen** can be the analgesic and antipyretic of choice during all phases of pregnancy.

TERMINATION OF PREGNANCY

Termination of pregnancy may be considered when immediate treatment is needed for abdominal or pelvic tumors; for aggressive neoplastic disease; in advanced stage cancers with dismal prognosis; and in cases of parents' reluctance to accept the risk associated with *in utero* exposure to chemotherapy or radiotherapy [89]. As personal, social, ethical and religious issues may arise, patients should be thoroughly informed and all their wishes acknowledged. Management should be individualized and psychological support offered, if required. No difference in prognosis for the patients with cancer has been shown after termination, if appropriate anti-cancer therapy is applied [20, 32, 126].

SUBSEQUENT PREGNANCIES AND LONG-TERM HEALTH OUTCOME OF THE CHILDREN

Women diagnosed with cancer during pregnancy may opt for further child-bearing as soon as the first 2-5 years postpartum (critical period for potential recurrence) are completed. During this time, contraception should be used and strict follow-up should be pursued [89]. In case of relapse, salvage therapy should be initiated and further pregnancies should be avoided in women with recurrent disease and poor prognosis. Based on the results of a recent large meta-analysis (1,244 cases and 18,145 controls), pregnancy in women with history of breast cancer is safe and does not seem to compromise their overall survival [127]. Hence, breast cancer survivors should not be denied the opportunity of future conception.

The results of a large study (both retrospective and prospective) presented at the 2011 European Multidisciplinary Cancer Congress, showed that children who were exposed to chemotherapy *in utero* did not appear to suffer any detrimental effects in terms of general health and neurological and cardiac functioning. The median follow-up was almost 2 years, although some of the children were followed for up to 18 years. At birth, no congenital heart defects were observed, and cardiac function was normal. Most of the children had adequate neurological function and normal cardiac function; rates were similar to those seen in the general population. High rates of premature birth were observed and, although cognitive development was in the normal range for the majority of the cohort, children who fell below the normal parameters tended to be premature. Normal findings were observed in 90% of the children, which conformed to the general population. On the basis of these results, as well as the results of previous studies, it seems that chemotherapy may be administered after the first trimester with reasonable safety for the children [47, 128-131].

EPILOGUE

Based on the clinical experience and cooperation of multidisciplinary teams, treatment of gestational cancer with normal fetal outcomes is feasible. Benefits from the use of surgery, chemotherapy and/or radiotherapy as well as the mother's health and wishes need to be factored into recommendations and treatment planning. As the incidence of cancer-complicated pregnancy rises, and due to the phenomenon's relative rarity, the need for multicenter cooperation continues to grow.

REFERENCES

1. Van Calsteren K, Heyns L, De Smet F, Van Eycken L, Gziri MM, Van Gemert W, et al. Cancer during pregnancy: an analysis of 215 patients emphasizing the obstetrical and the neonatal outcomes. J Clin Oncol Feb 1; 28(4):683-9.
2. Duncan PG, Pope WD, Cohen MM, Greer N. Fetal risk of anesthesia and surgery during pregnancy. Anesthesiology 1986 Jun; 64(6):790-4.
3. Kal HB, Struikmans H. Radiotherapy during pregnancy: fact and fiction. Lancet Oncol 2005 May; 6(5):328-33.
4. Osei EK, Faulkner K. Fetal doses from radiological examinations. Br J Radiol 1999 Aug; 72(860):773-80.
5. Kennedy EV, Iball GR, Brettle DS. Investigation into the effects of lead shielding for fetal dose reduction in CT pulmonary angiography. Br J Radiol 2007 Aug; 80(956):631-8.
6. Kanal E, Barkovich AJ, Bell C, Borgstede JP, Bradley WG, Jr., Froelich JW, et al. ACR guidance document for safe MR practices: 2007. AJR Am J Roentgenol 2007 Jun; 188(6):1447-74.
7. Kanal E, Borgstede JP, Barkovich AJ, Bell C, Bradley WG, Felmlee JP, et al. American College of Radiology White Paper on MR Safety. AJR Am J Roentgenol 2002 Jun; 178(6):1335-47.
8. Leyendecker JR, Gorengaut V, Brown JJ. MR imaging of maternal diseases of the abdomen and pelvis during pregnancy and the immediate postpartum

period. Radiographics 2004 Sep-Oct; 24(5):1301-16.
9. Abramowicz JS, Kossoff G, Marsal K, Ter Haar G. Safety Statement, 2000 (reconfirmed 2003). International Society of Ultrasound in Obstetrics and Gynecology (ISUOG). Ultrasound Obstet Gynecol 2003 Jan; 21(1):100.
10. Devine CE, Mawlawi O. Radiation safety with positron emission tomography and computed tomography. Semin Ultrasound CT MR 2010 Feb; 31(1):39-45.
11. Moran BJ, Yano H, Al Zahir N, Farquharson M. Conflicting priorities in surgical intervention for cancer in pregnancy. Lancet Oncol 2007 Jun; 8(6):536-44.
12. Jackson H, Granger S, Price R, Rollins M, Earle D, Richardson W, et al. Diagnosis and laparoscopic treatment of surgical diseases during pregnancy: an evidence-based review. Surg Endosc 2008 Sep; 22(9):1917-27.
13. Povirk LF, Shuker DE. DNA damage and mutagenesis induced by nitrogen mustards. Mutat Res 1994 Dec; 318(3):205-26.
14. Murray CL, Reichert JA, Anderson J, Twiggs LB. Multimodal cancer therapy for breast cancer in the first trimester of pregnancy. A case report. JAMA 1984 Nov 9; 252(18):2607-8.
15. Zemlickis D, Lishner M, Erlich R, Koren G. Teratogenicity and carcinogenicity in a twin exposed in utero to cyclophosphamide. Teratog Carcinog Mutagen 1993; 13(3):139-43.
16. Wiebe VJ, Sipila PE. Pharmacology of antineoplastic agents in pregnancy. Crit Rev Oncol Hematol 1994 Apr; 16(2):75-112.
17. Pacifici GM, Nottoli R. Placental transfer of drugs administered to the mother. Clin Pharmacokinet 1995 Mar; 28(3):235-69.
18. Zenk KE. An overview of perinatal clinical pharmacology. Clin Lab Med 1981 Jun; 1(2):361-75.
19. Zemlickis D, Lishner M, Degendorfer P, Panzarella T, Sutcliffe SB, Koren G. Fetal outcome after in utero exposure to cancer chemotherapy. Arch Intern Med 1992 Mar; 152(3):573-6.
20. Cardonick E, Iacobucci A. Use of chemotherapy during human pregnancy. Lancet Oncol 2004 May; 5(5):283-91.
21. International Commission on Radiological Protection. Pregnancy and medical radiation. Ann ICRP 2000; 30(1):iii-viii, 1-43.
22. Streffer C, Shore R, Konermann G, Meadows A, Uma Devi P, Preston Withers J, et al. Biological effects after prenatal irradiation (embryo and fetus). A report of the International Commission on Radiological Protection. Ann ICRP 2003; 33(1-2):5-206.
23. Ngu SL, Duval P, Collins C. Foetal radiation dose in radiotherapy for breast cancer. Australas Radiol 1992 Nov; 36(4):321-2.
24. Antypas C, Sandilos P, Kouvaris J, Balafouta E, Karinou E, Kollaros N, et al. Fetal dose evaluation during breast cancer radiotherapy. Int J Radiat Oncol Biol Phys 1998 Mar 1; 40(4):995-9.
25. Spitzer M, Citron M, Ilardi CF, Saxe B. Non-Hodgkin's lymphoma during pregnancy. Gynecol Oncol 1991 Dec; 43(3):309-12.
26. Nisce LZ, Tome MA, He S, Lee BJ, 3rd, Kutcher GJ. Management of coexisting Hodgkin's disease and pregnancy. Am J Clin Oncol 1986 Apr; 9(2):146-51.
27. Mazonakis M, Varveris H, Fasoulaki M, Damilakis J. Radiotherapy of Hodgkin's disease in early pregnancy: embryo dose measurements. Radiother Oncol 2003 Mar; 66(3):333-9.
28. Haba Y, Twyman N, Thomas SJ, Overton C, Dendy P, Burnet NG. Radiotherapy for glioma during pregnancy: fetal dose estimates, risk assessment and clinical management. Clin Oncol (R Coll Radiol) 2004 May; 16(3):210-4.
29. Mazonakis M, Damilakis J, Theoharopoulos N, Varveris H, Gourtsoyiannis N. Brain radiotherapy during pregnancy: an analysis of conceptus dose using anthropomorphic phantoms. Br J Radiol 1999 Mar; 72(855):274-8.
30. Yu C, Jozsef G, Apuzzo ML, MacPherson DM, Petrovich Z. Fetal radiation doses for model C gamma knife radiosurgery. Neurosurgery 2003 Mar; 52(3):687-93; discussion 93.
31. Fenig E, Mishaeli M, Kalish Y, Lishner M. Pregnancy and radiation. Cancer Treat Rev 2001 Feb; 27(1):1-7.
32. Pavlidis NA. Coexistence of pregnancy and malignancy. Oncologist 2002; 7(4):279-87.
33. Loibl S, von Minckwitz G, Gwyn K, Ellis P, Blohmer JU, Schlegelberger B, et al. Breast carcinoma during pregnancy. International recommendations from an expert meeting. Cancer 2006 Jan 15; 106(2):237-46.
34. Borden EC. Melanoma and pregnancy. Seminars in oncology 2000 Dec; 27(6):654-6.
35. Ahn BY, Kim HH, Moon WK, Pisano ED, Kim HS, Cha ES, et al. Pregnancy- and lactation-associated breast cancer: mammographic and sonographic findings. J Ultrasound Med 2003 May; 22(5):491-7; quiz 8-9.
36. Smith LH, Danielsen B, Allen ME, Cress R. Cancer associated with obstetric delivery: results of linkage with the California cancer registry. Am J Obstet Gynecol 2003 Oct; 189(4):1128-35.
37. Shapira T, Pereg D, Lishner M. How I treat acute and chronic leukemia in pregnancy. Blood Rev 2008 Sep; 22(5):247-59.
38. White TT. Carcinoma of the breast and pregnancy; analysis of 920 cases collected from the literature and 22 new cases. Ann Surg 1954 Jan; 139(1):9-18.
39. Navrozoglou I, Vrekoussis T, Kontostolis E, Dousias V, Zervoudis S, Stathopoulos EN, et al. Breast cancer during pregnancy: a mini-review. Eur J Surg Oncol 2008 Aug; 34(8):837-43.
40. Middleton LP, Amin M, Gwyn K, Theriault R, Sahin A. Breast carcinoma in pregnant women: assessment of clinicopathologic and immunohistochemical features. Cancer 2003 Sep 1; 98(5):1055-60.
41. Berry DL, Theriault RL, Holmes FA, Parisi VM, Booser DJ, Singletary SE, et al. Management of breast cancer during pregnancy using a standardized protocol. J Clin Oncol 1999 Mar; 17(3):855-61.
42. Ring AE, Smith IE, Jones A, Shannon C, Galani E, Ellis PA. Chemotherapy for breast cancer during pregnancy: an 18-year experience from five London teaching hospitals. J Clin Oncol 2005 Jun 20; 23(18):4192-7.
43. Keleher AJ, Theriault RL, Gwyn KM, Hunt KK, Stelling CB, Singletary SE, et al. Multidisciplinary management of breast cancer concurrent with pregnancy. J Am Coll Surg 2002 Jan; 194(1):54-64.
44. Amant F, Deckers S, Van Calsteren K, Loibl S, Halaska M, Brepoels L, et al. Breast cancer in pregnancy: recommendations of an international consensus meeting. Eur J Cancer Dec; 46(18):3158-68.
45. Amant F, Deckers S, Van Calsteren K, Loibl S, Halaska M, Brepoels L, et al. Breast cancer in pregnancy: recommendations of an international consensus meeting. Eur J Cancer 2010 Dec; 46(18):3158-68.
46. Garcia-Manero M, Royo MP, Espinos J, Pina L, Alcazar JL, Lopez G. Pregnancy associated breast cancer. Eur J Surg Oncol 2009 Feb; 35(2):215-8.
47. Hahn KM, Johnson PH, Gordon N, Kuerer H, Middleton L, Ramirez M, et al. Treatment of pregnant breast cancer patients and outcomes of children exposed to chemotherapy in utero. Cancer 2006 Sep 15; 107(6):1219-26.
48. Peccatori FA, Azim HA, Jr., Scarfone G, Gadducci A, Bonazzi C, Gentilini O, et al. Weekly epirubicin in the treatment of gestational breast cancer (GBC). Breast Cancer Res Treat 2009 Jun; 115(3):591-4.
49. Potluri V, Lewis D, Burton GV. Chemotherapy with taxanes in breast cancer during pregnancy: case report and review of the literature. Clin Breast Cancer 2006 Jun; 7(2):167-70.
50. Gonzalez-Angulo AM, Walters RS, Carpenter RJ, Jr., Ross MI, Perkins GH, Gwyn K, et al. Paclitaxel chemotherapy in a pregnant patient with bilateral breast cancer. Clin Breast Cancer 2004 Oct; 5(4):317-9.
51. Nieto Y, Santisteban M, Aramendia JM, Fernandez-Hidalgo O, Garcia-Manero M, Lopez G. Docetaxel administered during pregnancy for inflammatory breast carcinoma. Clin Breast Cancer 2006 Feb; 6(6):533-4.
52. Calsteren KV, Verbesselt R, Devlieger R, De Catte L, Chai DC, Van Bree R, et al. Transplacental transfer of paclitaxel, docetaxel, carboplatin, and trastuzumab in a baboon model. Int J Gynecol Cancer 2011 Dec; 20(9):1456-64.
53. Barthelmes L, Gateley CA. Tamoxifen and pregnancy. Breast 2004 Dec; 13(6):446-51.
54. Iguchi T, Hirokawa M, Takasugi N. Occurrence of genital tract abnormalities and bladder hernia in female mice exposed neonatally to tamoxifen. Toxicology 1986 Dec 1; 42(1):1-11.
55. Daling JR, Malone KE, Doody DR, Anderson BO, Porter PL. The relation of reproductive factors to mortality from breast cancer. Cancer Epidemiol Biomarkers Prev 2002 Mar; 11(3):235-41.
56. Bladstrom A, Anderson H, Olsson H. Worse survival in breast cancer among women with recent childbirth: results from a Swedish population-based register study. Clinical Breast Cancer 2003 Oct; 4(4):280-5.

57. Whiteman MK, Hillis SD, Curtis KM, McDonald JA, Wingo PA, Marchbanks PA. Reproductive history and mortality after breast cancer diagnosis. Obstetrics and Gynecology 2004 Jul; 104(1):146-54.

58. Rodriguez AO, Chew H, Cress R, Xing G, McElvy S, Danielsen B, et al. Evidence of poorer survival in pregnancy-associated breast cancer. Obstetrics and Gynecology 2008 Jul; 112(1):71-8.

59. Bonnier P, Romain S, Dilhuydy JM, Bonichon F, Julien JP, Charpin C, et al. Influence of pregnancy on the outcome of breast cancer: a case-control study. Societe Francaise de Senologie et de Pathologie Mammaire Study Group. International Journal of Cancer 1997 Sep 4; 72(5):720-7.

60. Beadle BM, Woodward WA, Middleton LP, Tereffe W, Strom EA, Litton JK, et al. The impact of pregnancy on breast cancer outcomes in women < or = 35 years. Cancer 2009 Mar 15; 115(6):1174-84.

61. Halaska MJ, Pentheroudakis G, Strnad P, Stankusova H, Chod J, Robova H, et al. Presentation, management and outcome of 32 patients with pregnancy-associated breast cancer: a matched controlled study. The Breast Journal 2009 Sep-Oct; 15(5):461-7.

62. Stensheim H, Moller B, van Dijk T, Fossa SD. Cause-specific survival for women diagnosed with cancer during pregnancy or lactation: a registry-based cohort study. J Clin Oncol 2009 Jan 1; 27(1):45-51.

63. Jones WB, Shingleton HM, Russell A, Fremgen AM, Clive RE, Winchester DP, et al. Cervical carcinoma and pregnancy. A national pattern of care study of the American College of Surgeons. Cancer 1996 Apr 15; 77(8):1479-88.

64. Amant F, Van Calsteren K, Halaska MJ, Beijnen J, Lagae L, Hanssens M, et al. Gynecologic cancers in pregnancy: guidelines of an international consensus meeting. Int J Gynecol Cancer 2009 May; 19 Suppl 1:S1-12.

65. Amant F, Brepoels L, Halaska MJ, Gziri MM, Calsteren KV. Gynaecologic cancer complicating pregnancy: an overview. Best Pract Res Clin Obstet Gynaecol 2009 Feb; 24(1):61-79.

66. Weisz B, Meirow D, Schiff E, Lishner M. Impact and treatment of cancer during pregnancy. Expert Rev Anticancer Ther 2004 Oct; 4(5):889-902.

67. Morice P, Narducci F, Mathevet P, Marret H, Darai E, Querleu D. French recommendations on the management of invasive cervical cancer during pregnancy. Int J Gynecol Cancer 2009 Dec; 19(9):1638-41.

68. Van Calsteren K, Vergote I, Amant F. Cervical neoplasia during pregnancy: diagnosis, management and prognosis. Best Pract Res Clin Obstet Gynaecol 2005 Aug; 19(4):611-30.

69. Potter JF, Schoeneman M. Metastasis of maternal cancer to the placenta and fetus. Cancer 1970 Feb; 25(2):380-8.

70. Roth MS, Foon KA. Alpha interferon in the treatment of hematologic malignancies. Am J Med 1986 Nov; 81(5):871-82.

71. Baer MR, Ozer H, Foon KA. Interferon-alpha therapy during pregnancy in chronic myelogenous leukaemia and hairy cell leukaemia. Br J Haematol 1992 Jun; 81(2):167-9.

72. Hiratsuka M, Minakami H, Koshizuka S, Sato I. Administration of interferon-alpha during pregnancy: effects on fetus. J Perinat Med 2000; 28(5):372-6.

73. Pages C, Robert C, Thomas L, Maubec E, Sassolas B, Granel-Brocard F, et al. Management and outcome of metastatic melanoma during pregnancy. Br J Dermatol 2010 Feb 1; 162(2):274-81.

74. Reintgen DS, McCarty KS, Jr., Vollmer R, Cox E, Seigler HF. Malignant melanoma and pregnancy. Cancer 1985 Mar 15; 55(6):1340-4.

75. Slingluff CL, Jr., Reintgen DS, Vollmer RT, Seigler HF. Malignant melanoma arising during pregnancy. A study of 100 patients. Ann Surg 1990 May; 211(5):552-7; discussion 8-9.

76. Pages C, Robert C, Thomas L, Maubec E, Sassolas B, Granel-Brocard F, et al. Management and outcome of metastatic melanoma during pregnancy. Br J Dermatol Feb 1; 162(2):274-81.

77. Khosrotehrani K, Nguyen Huu S, Prignon A, Avril MF, Boitier F, Oster M, et al. Pregnancy promotes melanoma metastasis through enhanced lymphangiogenesis. The American Journal of Pathology 2011 Apr; 178(4):1870-80.

78. Lens MB, Rosdahl I, Ahlbom A, Farahmand BY, Synnerstad I, Boeryd B, et al. Effect of pregnancy on survival in women with cutaneous malignant melanoma. J Clin Oncol 2004 Nov 1; 22(21):4369-75.

79. O'Meara AT, Cress R, Xing G, Danielsen B, Smith LH. Malignant melanoma in pregnancy. A population-based evaluation. Cancer 2005 Mar 15; 103(6):1217-26.

80. Azim HA, Jr., Pavlidis N, Peccatori FA. Treatment of the pregnant mother with cancer: a systematic review on the use of cytotoxic, endocrine, targeted agents and immunotherapy during pregnancy. Part II: Hematological tumors. Cancer Treat Rev 2010 Apr; 36(2):110-21.

81. Lishner M, Zemlickis D, Degendorfer P, Panzarella T, Sutcliffe SB, Koren G. Maternal and foetal outcome following Hodgkin's disease in pregnancy. Br J Cancer 1992 Jan; 65(1):114-7.

82. Gobbi PG, Attardo-Parrinello A, Danesino M, Motta C, Di Prisco AU, Rizzo SC, et al. Hodgkin's disease and pregnancy. Haematologica 1984 May-Jun; 69(3):336-41.

83. Gelb AB, van de Rijn M, Warnke RA, Kamel OW. Pregnancy-associated lymphomas. A clinicopathologic study. Cancer 1996 Jul 15; 78(2):304-10.

84. Abalovich M, Amino N, Barbour LA, Cobin RH, De Groot LJ, Glinoer D, et al. Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2007 Aug; 92(8 Suppl):S1-47.

85. Moosa M, Mazzaferri EL. Outcome of differentiated thyroid cancer diagnosed in pregnant women. J Clin Endocrinol Metab 1997 Sep; 82(9):2862-6.

86. Oehler MK, Wain GV, Brand A. Gynaecological malignancies in pregnancy: a review. Aust N Z J Obstet Gynaecol 2003 Dec; 43(6):414-20.

87. Whitecar MP, Turner S, Higby MK. Adnexal masses in pregnancy: a review of 130 cases undergoing surgical management. Am J Obstet Gynecol 1999 Jul; 181(1):19-24.

88. Amant F, Brepoels L, Halaska MJ, Gziri MM, Calsteren KV. Gynaecologic cancer complicating pregnancy: an overview. Best Pract Res Clin Obstet Gynaecol 2010 Feb; 24(1):61-79.

89. Pentheroudakis G, Pavlidis N. Cancer and pregnancy: poena magna, not anymore. Eur J Cancer 2006 Jan; 42(2):126-40.

90. Han SN, Van Calsteren K, Amant F. Use of chemotherapy during pregnancy in the treatment of ovarian malignancies. European Journal of Obstetrics, Gynecology, and Reproductive Biology 2011 Jun; 156(2):237.

91. Ferrandina G, Distefano M, Testa A, De Vincenzo R, Scambia G. Management of an advanced ovarian cancer at 15 weeks of gestation: case report and literature review. Gynecol Oncol 2005 May; 97(2):693-6.

92. Walsh C, Fazio VW. Cancer of the colon, rectum, and anus during pregnancy. The surgeon's perspective. Gastroenterol Clin North Am 1998 Mar; 27(1):257-67.

93. Gensheimer M, Jones CA, Graves CR, Merchant NB, Lockhart AC. Administration of oxaliplatin to a pregnant woman with rectal cancer. Cancer Chemother Pharmacol 2009 Jan; 63(2):371-3.

94. Kanate AS, Auber ML, Higa GM. Priorities and uncertainties of administering chemotherapy in a pregnant woman with newly diagnosed colorectal cancer. J Oncol Pharm Pract 2009 Mar; 15(1):5-8.

95. Azim HA, Jr., Peccatori FA, Pavlidis N. Lung cancer in the pregnant woman: to treat or not to treat, that is the question. Lung Cancer 2010 Mar; 67(3):251-6.

96. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, Goldhirsch A, Untch M, Smith I, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. The New England Journal of Medicine 2005 Oct 20; 353(16):1659-72.

97. Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. The New England Journal of Medicine 2001 Mar 15; 344(11):783-92.

98. Israel EJ, Simister N, Freiberg E, Caplan A, Walker WA. Immunoglobulin G binding sites on the human foetal intestine: a possible mechanism for the passive transfer of immunity from mother to infant. Immunology 1993 May; 79(1):77-81.

99. Weber-Schoendorfer C, Schaefer C. Trastuzumab exposure during pregnancy. Reprod Toxicol 2008 Apr; 25(3):390-1; author reply 2.

100. Warraich Q, Smith N. Herceptin therapy in pregnancy: continuation of pregnancy in the presence of anhydramnios. J Obstet Gynaecol 2009 Feb; 29(2):147-8.

101. Beale JM, Tuohy J, McDowell SJ. Herceptin (trastuzumab) therapy in a twin pregnancy with associated oligohydramnios. Am J Obstet Gynecol 2009 Jul; 201(1):e13-4.

102. Witzel ID, Muller V, Harps E, Janicke F, Dewit M. Trastuzumab in pregnancy associated with poor fetal outcome. Ann Oncol 2008 Jan; 19(1):191-2.

103. Bader AA, Schlembach D, Tamussino KF, Pristauz G, Petru E. Anhydramnios associated with administration of trastuzumab and paclitaxel for metastatic breast cancer during pregnancy. Lancet Oncol 2007 Jan; 8(1):79-81.

104. Shrim A, Garcia-Bournissen F, Maxwell C, Farine D, Koren G. Favorable pregnancy outcome following Trastuzumab (Herceptin) use during pregnancy - Case report and updated literature review. Reprod Toxicol 2007 Jun; 23(4):611-3.

105. Azim HA, Jr., Azim H, Peccatori FA. Treatment of cancer during pregnancy with monoclonal antibodies: a real challenge. Expert Review of Clinical Immunology 2010 Nov; 6(6):821-6.

106. Cordeiro A, Machado AI, Borges A, Alves MJ, Frade MJ. Burkitt's lymphoma related to Epstein-Barr virus infection during pregnancy. Arch Gynecol Obstet 2009 Aug; 280(2):297-300.

107. Rey J, Coso D, Roger V, Bouayed N, Belmecheri N, Ivanov V, et al. Rituximab combined with chemotherapy for lymphoma during pregnancy. Leuk Res 2009 Mar; 33(3):e8-9.

108. Decker M, Rothermundt C, Hollander G, Tichelli A, Rochlitz C. Rituximab plus CHOP for treatment of diffuse large B-cell lymphoma during second trimester of pregnancy. Lancet Oncol 2006 Aug; 7(8):693-4.

109. Friedrichs B, Tiemann M, Salwender H, Verpoort K, Wenger MK, Schmitz N. The effects of rituximab treatment during pregnancy on a neonate. Haematologica 2006 Oct; 91(10):1426-7.

110. Kimby E, Sverrisdottir A, Elinder G. Safety of rituximab therapy during the first trimester of pregnancy: a case history. Eur J Haematol 2004 Apr; 72(4):292-5.

111. Hensley ML, Ford JM. Imatinib treatment: specific issues related to safety, fertility, and pregnancy. Semin Hematol 2003 Apr; 40(2 Suppl 2):21-5.

112. Pye SM, Cortes J, Ault P, Hatfield A, Kantarjian H, Pilot R, et al. The effects of imatinib on pregnancy outcome. Blood 2008 Jun 15; 111(12):5505-8.

113. Cortes J, O'Brien S, Ault P, Borthakur G, Jabbour E, Bradley-Garelik B, Debreczeni K, Yang D, Liu D, Kantarjian H. Pregnancy Outcomes among Patients with Chronic Myeloid Leukemia Treated with Dasatinib. Blood (ASH Annual Meeting Abstracts) 2008; 112(Abstract 3230).

114. Conchon M, Sanabani SS, Serpa M, Novaes MM, Nardinelli L, Ferreira PB, et al. Successful Pregnancy and Delivery in a Patient with Chronic Myeloid Leukemia while on Dasatinib Therapy. Adv Hematol 2010; 2010:136252.

115. Patyna S, Haznedar J, Morris D, Freshwater K, Peng G, Sukbuntherng J, et al. Evaluation of the safety and pharmacokinetics of the multi-targeted receptor tyrosine kinase inhibitor sunitinib during embryo-fetal development in rats and rabbits. Birth Defects Res B Dev Reprod Toxicol 2009 Jun; 86(3):204-13.

116. Zambelli A, Prada GA, Fregoni V, Ponchio L, Sagrada P, Pavesi L. Erlotinib administration for advanced non-small cell lung cancer during the first 2 months of unrecognized pregnancy. Lung Cancer 2008 Jun; 60(3):455-7.

117. Lam MS. Treatment of Burkitt's lymphoma during pregnancy. Ann Pharmacother 2006 Nov; 40(11):2048-52.

118. Papantoniou N, Daskalakis G, Marinopoulos S, Anastasakis E, Mesogitis S, Antsaklis A. Management of pregnancy in adolescence complicated by acute lymphoblastic leukemia. Fetal Diagn Ther 2008; 23(2):164-7.

119. Scott LL, Ramin SM, Richey M, Hanson J, Gilstrap LC, 3rd. Erythropoietin use in pregnancy: two cases and a review of the literature. Am J Perinatol 1995 Jan; 12(1):22-4.

120. Lin CP, Huang MJ, Liu HJ, Chang IY, Tsai CH. Successful treatment of acute promyelocytic leukemia in a pregnant Jehovah's Witness with all-trans retinoic acid, rhG-CSF, and erythropoietin. Am J Hematol 1996 Mar; 51(3):251-2.

121. Sackmann Massa F, Pavlovsky S. Myelodysplastic syndrome and pregnancy: case report. Leuk Res 2009 Mar; 33(3):e23-5.

122. Djokanovic N, Klieger-Grossmann C, Koren G. Does treatment with bisphosphonates endanger the human pregnancy? J Obstet Gynaecol Can 2008 Dec; 30(12):1146-8.

123. Levy S, Fayez I, Taguchi N, Han JY, Aiello J, Matsui D, et al. Pregnancy outcome following in utero exposure to bisphosphonates. Bone 2009 Mar; 44(3):428-30.

124. Berkovitch M, Mazzota P, Greenberg R, Elbirt D, Addis A, Schuler-Faccini L, et al. Metoclopramide for nausea and vomiting of pregnancy: a prospective multicenter international study. Am J Perinatol 2002 Aug; 19(6):311-6.

125. Einarson A, Maltepe C, Navioz Y, Kennedy D, Tan MP, Koren G. The safety of ondansetron for nausea and vomiting of pregnancy: a prospective comparative study. BJOG 2004 Sep; 111(9):940-3.

126. Pavlidis N, Pentheroudakis G. The pregnant mother with breast cancer: diagnostic and therapeutic management. Cancer Treat Rev 2005 Oct; 31(6):439-47.

127. Azim HA, Jr., Santoro L, Pavlidis N, Gelber S, Kroman N, Azim H, et al. Safety of pregnancy following breast cancer diagnosis: a meta-analysis of 14 studies. Eur J Cancer 2011 Jan; 47(1):74-83.

128. Van Calsteren K, Berteloot P, Hanssens M, Vergote I, Amant F, Ganame J, et al. In utero exposure to chemotherapy: effect on cardiac and neurologic outcome. J Clin Oncol 2006 Apr 20; 24(12):e16-7.

129. Aviles A, Neri N. Hematological malignancies and pregnancy: a final report of 84 children who received chemotherapy in utero. Clin Lymphoma 2001 Dec; 2(3):173-7.

130. Amant F. Chemotherapy during pregnancy does not seem to cause developmental problems in children. 2011 European Multidisciplinary Cancer Congress (EMCC): Abstract 12LBA 2011.

131. Aviles A, Neri N, Nambo MJ. Long-term evaluation of cardiac function in children who received anthracyclines during pregnancy. Ann Oncol 2006 Feb; 17(2):286-8.

Consensus on the better diagnosis, treatment and management of non-infectious pneumonitis

Elias Athanassiadis[1], Vassilis Georgoulias[2], Charalampos Kalophonos[3], Paris Kosmidis[4], Aristotelis Bamias[5], Vassilios Barbounis[6], Ioannis Boukovinas[7], Dimitrios Pectasides[6], Epameinondas Samantas[8], Dimosthenis Skarlos[9]; On behalf of non-infectious pneumonitis study group

[1]"Mitera" Hospital, Hygeia-Polis, Athens, Greece
[2]Department of Medical Oncology, University General Hospital of Heraklion, Crete, Greece
[3]General University Hospital of Patras - Rio, Ahaia, Greece
[4]"Hygeia" Hospital, Athens, Greece
[5]University General Hospital of Athens "Alexandra", Athens, Greece
[6]"Hippokration" Hospital, Athens, Greece
[7]Theageneio Anticancer Hospital, Thessaloniki, Greece
[8]"Agioi Anargyroi" General Oncology Hospital of Kifissia, Athens, Greece
[9]Metropolitan Hospital, Athens, Greece

ABSTRACT

There are several chemotherapeutic agents, affecting pulmonary parenchyma developing drug-induced pneumonitis. Patients develop drug-induced pneumonitis at a rate lower than 10%; non-infectious pneumonitis in patients treated with everolimus is not a rare adverse event. The frequency of this entity varies between 6% and 14%, while only 2%-4% of them present with Grade 3 pneumonitis, and 0.3% present with Grade 4 pneumonitis. In most cases, reducing the dose and/or interrupting the chemotherapeutic agent, in combination with symptomatic treatment, has positive results. The purpose of this paper is to provide the steps that should be followed for diagnosing pneumonitis, the treatment to be provided and the management to be designed for this non-infectious pneumonitis which is considered as a class-effect adverse event for all mTOR inhibitors. The same pneumonitis management rules apply in all cases, regardless of the agent that caused it. In the Greek clinical practice, non-infectious pneumonitis cases occurring in patients who receive treatment with everolimus for metastatic renal cancer are extremely rare. However, clinical safety surveillance protocols are in order so as to study and accumulate experience on this specific toxicity.

Key words: non-infectious pneumonitis; everolimus-induced pneumonitis; RECORD-1; REACT; metastatic renal cancer.

INTRODUCTION

The term "interstitial lung disease" or "interstitial disease" is used to describe diseases that affect the epithelium, endothelium and interstitial pulmonary tissue; these diseases are characterized by lymphocyte, macrophage and neutrophil invasion in the interstitial alveolar space. As the interstitial disease progresses, depending on its cause, the endothelium in the affected area is destroyed, the number of capillaries is reduced, and both fibroblasts and collagen increase in an attempt to repair the damage. Intra-alveolar interstitial space expands and fibroblastic nodules and alveolar exudate is formed. In many cases, the lungs are depicted in chest X-ray in a cystic "honeycombing" pattern, which is also the case for many other diseases, such as Chronic Pulmonary Obstructive Disease. Lesion distribution is usually segmental; pleura and interlobar spaces (interlobar fissures) may also be affected and it is possible to develop pleural effusion.

Interstitial diseases include idiopathic pulmonary fibrosis; sarcoidosis; histiocytosis X; pneumoconiosis; miliary tuberculosis; interstitial pneumonias; allergic alveolitis; as well as non-infectious pneumonitis, either drug-induced or due to hypersensitivity.

There are several drugs besides chemotherapeutic agents (e.g. bleomycin, azathioprine and methotrexate, nitrosoureas, gemcitabine, taxanes, cyclophosphamide) affecting pulmonary parenchyma such as several antibiotics of the nitrofurantoin and sulfasalazine class; amiodarone (common heart medicine); anti-inflammatory drugs, such as aspirin and penicillamine; gold compound drugs; oxygen; isoniazid (well known antituberculosis drug); and others. Thus, drug-induced pneumonitis is a common phenomenon.

CLINICAL IMAGE

The clinical image of pneumonitis is atypical. Its main symptoms include exertional dyspnea, non-chill fever and dry cough without sputum. At auscultation, the patient may present with crackles whereas in radiological examination a mere 10% may have a normal

Table 1.
Pneumonitis following everolimus administration in patients with metastatic renal cancer [1, 2]

n (%)	N	All grades	Grade 3	Grade 4
RECORD-1 [1]	274	37 (14)	10 (4)	0
REACT [2]	1367	83 (6)	33 (2)	4 (0.3)

X-ray. Lesions may initially begin to appear in one lobe and then diffuse. Also, in severe pneumonitis, i.e. Grade 3 and 4, hypoxemia and type 1 respiratory failure may co-exist, i.e. low oxygen levels with normal dioxide levels. Radiographic lesions observed in the X-ray together with pathology image (e.g. granulomas) in case a biopsy is feasible, provide substantial evidence of possible pneumonitis.

Patients develop drug-induced pneumonitis (from cancer-targeting agents or other kinds of drugs) at a rate lower than 10%; Grade 3 and 4 pneumonitis (pneumonitis with radiological lesions affecting patient everyday activities that may cause hypoxemia and are life-threatening or resulting in permanent disability) occur at a far smaller rate of <1%.

CLINICAL TRIALS

Following everolimus administration (see Table 1), 14% and 6% of the patients with metastatic renal cancer presented with various grades of pneumonitis according to two everolimus-investigating clinical trials. One trial (RECORD-1) included 274 patients, 4% of which presented with Grade 3 pneumonitis, whereas in another trial (REACT) that included 1,367 patients, only 2% presented with Grade 3 pneumonitis and 0.3% presented with Grade 4 pneumonitis.

DIAGNOSIS OF PNEUMONITIS

Pneumonitis is mostly diagnosed through a chest X-ray, regardless of the symptoms. Patient clinical status evaluation, medical history, chest X-ray, high-definition CT as well as DL_{CO} (Diffusing capacity of the lung for carbon monoxide) testing are crucial in fully establishing a pneumonitis diagnosis. In case of a suspected respiratory failure, performing a blood gas study at rest is suggested. In order to exclude opportunistic infections or depending on the treating physician's clinical judgment, the patient may be referred to a pulmonologist for bronchoscopy and transbronchial biopsy.

According to a recent publication by Porta *et al.* in the 2011 European Journal of Cancer [3], patients with metastatic renal cancer showed all grades of pneumonitis at a rate of 14%. The use of drugs may cause interstitial pneumonitis, pulmonary fibrosis, pulmonary eosinophilia, organizing pneumonia, pulmonary edema, pleural effusion, pulmonary hypertension as well as alveolar hemorrhage.

Table 2 describes the therapeutic protocol suggested by White *et al.* (AJRCCM, 2010) for the management of non-infectious pneumonitis.

Table 2.
Therapeutic algorithm for non-infectious pneumonitis [4]
*Cortisone therapeutic dose (full dose) in non-infectious pneumonitis is 50-60mg.

Grade	Intervention	Investigations	Everolimus Dose Adjustment
1	No specific therapy required	CT scan and PFTs.* Repeat chest X-ray/CT scan every two cycles until return to baseline	No change
2	Symptomatic only. Prescribe corticosteroids if cough is troublesome	CT scan and PFTs.* Repeat each cycle until return to baseline. Consider bronchoscopy	Reduce dose until improvement to grade ≤1; consider interruption if symptoms are troublesome. Discontinue treatment if recovery to grade ≤1 is not evident within 3 weeks
3	Prescribe corticosteroids if infectious etiology is ruled out. Taper as clinically indicated	CT scan and PFTs.* Repeat each cycle until return to baseline. Bronchoscopy required	Interrupt treatment until improvement to grade ≤1. Restart therapy within 2 weeks at a reduced dose if clinical benefit is evident
4	Prescribe corticosteroids if infectious etiology is ruled out. Taper as clinically indicated	CT scan and PFTs.* Repeat each cycle until return to baseline. Bronchoscopy required	Discontinue treatment

Abbreviations: Abbreviations: CT, computed tomography; PFT, pulmonary function test.
*PFTs include spirometry diffusion capacity of carbon monoxide and room air oxygen saturation at rest tests.

Table 3.
Non-infectious pneumonitis evaluation criteria (CTCAE v3.0)

GRADE	SIGNS
Grade 1	Asymptomatic, with radiological findings
Grade 2	Symptomatic, not affecting everyday activities
Grade 3	Symptomatic, affecting everyday activities or requiring oxygen therapy
Grade 4	Life-threatening or requiring oxygen therapy

TREATMENT AND MANAGEMENT

In general, when oxygen is administered for the management of pneumonitis, drug toxicity may worsen, as for example in the case of bleomycin. For this reason, a differential diagnosis that will exclude other infections or lymphangitic spread from the underlying disease must be established in advance. The mechanism relating everolimus to non-infectious pneumonitis remains unknown. Based on clinical study results in patients with metastatic renal cancer, everolimus-induced non-infectious pneumonitis may occur following a median of 4 months (1-9 months) after treatment initiation.

The suggested instructions for a patient under everolimus treatment are as follows: Perform a chest X-ray and blood gas study in visit 1, and then follow-up by the treating physician on a monthly basis. Depending on the findings of the first chest X-ray, proper follow-up is advised. Also, DL_{CO} (Diffusing capacity of the lung for carbon monoxide) testing is considered a reliable technique. Based on CTCAE v3.0 (Common Terminology Criteria for Adverse Events v3.0, see Table 3), the treating physician may evaluate the severity of pneumonitis and then decide on treatment. The everolimus indication-based clinical trial in metastatic renal cancer [4] showed that a proportion of patients diagnosed with pneumonitis were also diagnosed with pleural effusion and chronic obstructive pulmonary disease (COPD), whereas for 55% of these patients lymph node involvement was confirmed. The main symptoms of these patients were cough, dyspnea or both in various grades, whereas most patients had positive radiological findings regardless of their symptoms. Grade 2, 3 and 4 patients were treated with corticosteroids. The administered everolimus dose was reduced in the majority of patients and/or was interrupted in a small number of patients. Out of a total of 37 pneumonitis patients, 20 showed complete symptom and disease resolution following treatment adjustment.

In summary, non-infectious pneumonitis is a common side-effect of anti-cancer agents. It is rare and considered as a class-effect adverse event for all mTOR inhibitors. Special caution is recommended when combining palliative radiation therapy and anti-cancer therapy administration. In metastatic renal cancer, despite the fact that the kidney neoplasm is considered as a radiation-resistant neoplasm, everolimus and concomitant radiation therapy is not recommended and the experience in such cases is still quite limited. It is important to note that micromolecules and antibodies, such as EGFR inhibitors, bevacizumab, trastuzumab, gefitinib, etc. very often cause non-infectious pneumonitis; this is not the case with everolimus, for which pneumonitis is far more rare. The same pneumonitis management rules apply in all cases regardless of causing agent. It is important for the treating physician to have the differential diagnosis history prior to performing a high-resolution CT. It is suggested that, before initiating everolimus treatment, treating physicians should prepare their patients by suggesting that they stop smoking and asking to immediately contact them in case of fever, cough or dyspnea.

In the Greek clinical practice, non-infectious pneumonitis cases are extremely rare. However, clinical safety surveillance protocols are in order so as to study and accumulate experience on this specific toxicity.

REFERENCES

1. Motzer RJ, Escudier B, Oudard S, Hutson TE, Porta C, Bracarda S, Grünwald V, Thompson JA, Figlin RA, Hollaender N, Kay A, Ravaud A; RECORD 1 Study Group. Phase 3 trial of everolimus for metastatic renal cell carcinoma: final results and analysis of prognostic factors. Cancer 2010; 116:4256-65.
2. Grünwald V, Karakiewicz PI, Bavbek SE, Miller K, Machiels JP, Lee SH, Larkin J, Bono P, Rha SY, Castellano D, Blank CU, Knox JJ, Hawkins R, Anak O, Rosamilia M, Booth J, Pirotta N, Bodrogi I; on behalf of the REACT Study Group. An international expanded-access programme of everolimus: Addressing safety and efficacy in patients with metastatic renal cell carcinoma who progress after initial vascular endothelial growth factor receptor-tyrosine kinase inhibitor therapy. Eur J Cancer 2011 Jul 29 [Epub ahead of print].
3. Porta C, Osanto S, Ravaud A, Climent MA, Vaishampayan U, White DA, Creel P, Dickow B, Fischer P, Gornell SS, Meloni F, Motzer RJ. Management of adverse events associated with the use of everolimus in patients with advanced renal cell carcinoma. European Journal of Cancer 2011; 47:1287-98.
4. White D, Camus P, Endo M, Escudier B, Calvo E, Akaza H, Uemura H, Kpamegan E, Kay A, Robson M, Ravaud A, Motzer RJ. Noninfectious pneumonitis after everolimus therapy for advanced renal cell carcinoma. American Journal of Respiratory and Critical Care Medicine 2010; 182:396-403.

Leprosy reactivation and lepromatous gangrene associated with chemotherapy for advanced gastric cancer: a case report and review of the literature

Michalis Liontos[1], Giannis Mountzios[1], Stergios Karapsias[2], Christos Tsironis[3] and Nikolaos Kentepozidis[1]

[1]Department of Medical Oncology, 251 Air Force General Hospital, Athens, Greece
[2]Department of Microbiology, 251 Air Force General Hospital, Athens, Greece
[3]Department of Plastic Surgery, 251 Air Force General Hospital, Athens, Greece

Correspondence:
Dr Giannis Mountzios,
Department of Medical Oncology,
251 Air Force General Hospital,
Athens, Greece,
e-mail: gmountzios@med.uoa.gr

ABSTRACT

Immunity suppression is frequent among cancer patients and further exacerbated by antineoplastic chemotherapy. It is usually complicated by opportunistic viral, microbial or fungal infections and less frequently involves reactivation of chronic infections. Herein we present a rare case of leprosy reactivation in a patient with advanced gastric cancer who had received first-line chemotherapy. Lepromatous lesion reactivation was complicated with thrombotic angiopathy that led to lepromatous gangrene and subsequent amputation of the left hand. The pathophysiology of this rare entity is discussed and the potent role of immense immune reactions, including the anti-phospholipid syndrome and its subsequent thrombotic complications is also addressed.

Key words: leprosy; lepromatous gangrene; gastric cancer; anti-phospholipid antibodies; taxane chemotherapy.

INTRODUCTION

Immunity disorders including anosoparesis, hypogammaglobulinemia and immune evasion are paraneoplastic features that are associated with a wide variety of human malignancies. Immunosuppression as a result of antineoplastic chemotherapy is also frequently observed in cancer patients, rendering them susceptible to infectious complications. Chemotherapy-induced neutropenia and lymphopenia and impairment of cellular immunity further increase the risk for new opportunistic infections or reactivation of chronic ones. Herein, we present a case of leprosy reactivation that led to the rare complication of lepromatous gangrene and subsequent amputation in a male patient with adenocarcinoma of the stomach that was subjected to first-line chemotherapy.

CASE PRESENTATION

A 76-year old man was admitted in our hospital with fatigue of recent onset and microcytic anemia (Hct: 25%), while the rest of the laboratory tests were unremarkable. His medical history included lepromatous leprosy that was diagnosed at the age of 12 and successfully treated with dapsone. He was a social drinker and smoker. The patient underwent upper gastrointestinal tract endoscopy that revealed an extensive ulcerative lesion at the major arch of the stomach. Pathological examination of the biopsies established the diagnosis of an infiltrative mucinous adenocarcinoma of the stomach with signet-ring cell morphology. Imaging studies of the abdomen and thorax revealed peritoneal implantations and liver metastases. The patient received first-line chemotherapy with six cycles of docetaxel (75 mg/m^2 on Day 1), carboplatin (area under the curve 5, on Day 1) and capecitabine (2000 mg/m^2 on Days 1 to 5) every three weeks. Primary prevention for neutropenia with filgrastim was administered from the first cycle. However, grade III neutropenia at the third cycle led to 10% decrease in docetaxel and carboplatin doses. Subsequent imaging studies showed partial remission of the disease, according to the RECIST criteria and the patient was referred to the outpatient Oncology clinic for periodical follow-up. He experienced no other substantial toxicity during chemotherapy.

Two months after completion of first-line chemotherapy, the patient presented with reddish skin lesions in the interdigital area of his right hand (Figure 1) and his nose (Figure

2). Biopsy of the hand lesion was compatible with chronic granulomatous disease. Due to the patient's medical history nasal smear was examined with Ziehl-Nielsen staining and was found positive for acid-fast bacilli (Figure 3). The combination of clinical signs and nasal smear findings suggested the diagnosis of leprosy relapse. Similar lesions in his left hand expanded rapidly and became necrotic (Figure 4) despite oral broad spectrum multi-drug treatment (MDT), including rifampicin, ciprofloxacin and doxycycline. Doppler sonography of the hand disclosed severe thrombo-tic angiopathy of the small branches of the left radial and ulnar arteries with critically reduced blood perfusion and the patient was referred to the plastic surgery department for amputation at the carpal level. After surgery, the patient continued antibiotic treatment for *Mycobacterium leprae* infection and thalidomide, as an immunomodulator, was added to the regimen. One month after amputation, the patient was free of symptoms, experiencing no signs or clinical evidence of active infection. Unfortunately, two months after the amputation the patient experienced disease progression in the abdomen and despite second-line chemotherapy died from metastatic disease in August 2011.

DISCUSSION

Immunoevasion is an emerging hallmark of cancer cells [1]. Due to genomic instability (a hallmark of transforming cells [2]) and selective pressure from host immunity mechanisms [3], transforming cells adopt phenotypical characteristics that allow their unrestrictive proliferation [1, 3]. These mechanisms include: the avoidance of cytotoxic lymphocyte stimulation by attenuation of human leukocyte antigen class (HLA) molecules and the suppression of tumor-infiltrating immune cells activity by molecular and cellular factors [4]. In addition, cancer cells excrete immune suppressive factors (including vascular endothelial growth factor or VEGF, IL-10, and PGE2) that exert systemic effects on immune cell function [5, 6], thus compromising the host's native and adaptive immunity. In this setting, immune suppression is clearly observed in cancer patients.

The function of the immune system in cancer patients is further impaired by the applied treatment modalities. Both radiotherapy and the majority of chemotherapeutic agents inhibit proliferation and maturation of the myeloid lineage in the bone marrow resulting in increased risk for neutropenia and subsequent bacterial or fungal infections [7]. Moreover, certain chemotherapeutic agents cause lymphopenia [8], or affect lymphocytic function, directly inhibiting both humoral and cellular immunity [9]. Finally, corticosteroids that are frequently used during chemotherapy have similar adverse effects on T- and B-cell activation [10].

The integrity of cellular immunity is indispensable for the prevention from opportunistic infections, including pneumocystis jiroveci pneumonia (PCP) or the reactivation of mycobacterial infections [11]. Malignant disease and chemotherapy have long been recognized as risk factors for the development of tuberculosis [12]. Despite the higher incidence of mycobacterium tuberculosis infections in patients with malignant lymphomas, certain solid tumors, such as lung, head and neck and stomach carcinomas have also been associated with the development of tuberculosis [13]. To the best of our knowledge, this is the first case of relapse of *M. leprae* infection in a cancer patient receiving chemotherapy reported in the literature. Diagnosis of leprosy is based mainly on the combination of its characteristic clinical signs and detection of acid-fast mycobacteria in liquid smears or skin biopsies of the patient. Paucity of data may surely be attributed to disease "elimination" (reduction in prevalence in less than 1 per 10,000 population) in most parts of the world with the exception of endemic areas (e.g. India, Brazil). Furthermore, in the era of

Figure 1.

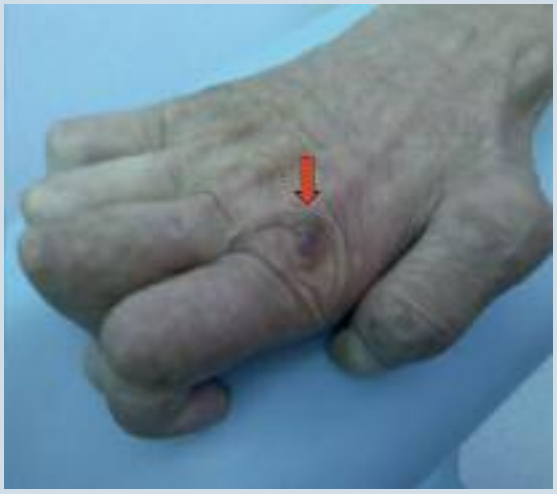


Figure 2.

multi-drug therapy (MDT) of leprosy, patients receiving adequate treatment should be considered as "cured" since the incidence of relapse is below 1% in 9 years after completion of MDT [14]. However, older patients who were treated with dapsone as monotherapy –like our case– are declared as "disease arrested" and present 10 times greater risk for disease relapse than patients receiving MDT [14].

In the present case, the patient received a docetaxel-based combination as first-line therapy for his non-operable gastric adenocarcinoma. Docetaxel is known to reduce the number of peripheral blood lymphocytes [8, 15-17] and also suppress major histocompatibility-unrestricted cytotoxicity of T-lymphocytes [16]. Furthermore, docetaxel inhibits Toll-like receptor 4 (TLR-4) signaling [18], that is implicated along with TLR-2 in the initiation of the immune response against mycobacteria [19, 20]. However, the significance of this mechanism in the role of docetaxel in inducing leprosy relapse should be further examined, since recent data correlates dysfunctional TLR-4 single nucleotide polymorphisms with protection against *M. leprae* [19].

Lepromatous gangrene is a rare complication of lepromatous leprosy that is usually attributed to thrombotic micro-angiopathy and involves mainly the extremities. However, recent evidence suggests an important role of the anti-phospholipid antibodies in the lepromatous gangrene pathophysiology [21]. Anti-phospholipid antibodies (APLA) have been originally described in the anti-phospholipid syndrome that can occur either in its primary form or secondarily in association with other autoimmune disorders or various infections, including syphilis, HIV, HCV disease, tuberculosis and cytomegalovirus infection. Of note, increased APLA levels were reported in 29% among 112 leprosy patients in one study [22]. It is thus probable that infection-induced increased APLA are associated with the thrombotic manifestations of the anti-phospholipid syndrome that complicated leprosy reactivation in our case. However, anti-cardiolipin antibodies (ACLA), APLA and lupus anticoagulant were negative in our patient and tests for other hypercoagulable states (protein C, protein S, antithrombin III, homocysteine and factor V Leiden) were within normal limits. Moreover, histopathological findings of the lesion biopsy in our patient showed microvascular thrombosis in the absence of inflammatory infiltration of the vessel wall, a situation which is frequently described as Lucio's phenomenon [23]. Therefore, a clear etiopathological association between APLA and lepromatous gangrene could not be established in our case, as it was in a similar one recently reported in the literature [21]. Nevertheless, the beneficial effect of thalidomide –an agent with well-defined immunomodulatory properties in autoimmune disorders– in our patient suggests a potent role of immune reactions in thrombotic complications associated with leprosy reactivation [24, 25].

CONCLUSION

Leprosy reactivation is a rare chemotherapy complication due to low prevalence of the disease and the current use of multi-drug therapy (MDT) for its treatment. The attenuation of cellular immunity though caused by the neoplasia itself and the commonly used chemotherapeutic agents increase the risk for mycobacterial and opportunistic infections in cancer patients. In this setting, new reddish patches with loss of sensation or thickened peripheral nerves should raise high clinical suspicion for leprosy relapse in a patient with previously treated Hansen's disease. Moreover, thrombotic complications, including the rare entity of lepromatous gangrene, should always be anticipated and aggressively treated simultaneously with the infection. The potent role of overt immune reactions in thrombotic disease justifies the use of immunomodulatory agents, such as thalidomide, along with anticoagulants, for the treatment of this serious complication.

Figure 3.

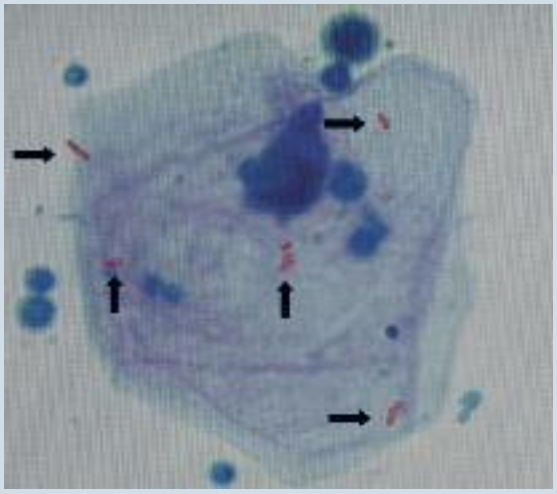
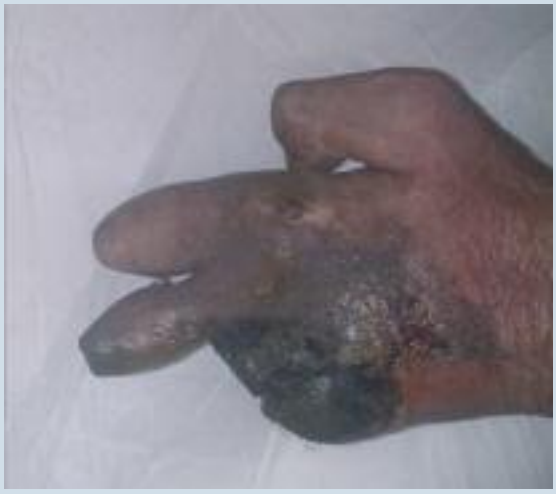


Figure 4.



REFERENCES

1. Hanahan D, and Weinberg RA. Hallmarks of cancer: the next generation. Cell 2011; 144:646-674.
2. Negrini S, Gorgoulis VG, and Halazonetis TD. Genomic instability - an evolving hallmark of cancer. Nat Rev Mol Cell Biol 2010; 11:220-228.
3. Vivier E, Raulet DH, Moretta A, Caligiuri MA, Zitvogel L, Lanier LL, Yokoyama WM, and Ugolini S. Innate or Adaptive Immunity? The Example of Natural Killer Cells. Science 2011; 331:44-49.
4. Du C, and Wang Y. The immunoregulatory mechanisms of carcinoma for its survival and development. J Exp Clin Cancer Res 2011; 30:12.
5. Yang L, and Carbone DP. Tumor-Host Immune Interactions and Dendritic Cell Dysfunction. Advances in Cancer Research (Academic Press) 2004; 92:13-27.
6. Zou W. Immunosuppressive networks in the tumour environment and their therapeutic relevance. Nat Rev Cancer 2005; 5:263-274.
7. Vento S, Cainelli F, and Temesgen Z. Lung infections after cancer chemotherapy. The Lancet Oncology 2008; 9:982-992.
8. Kotsakis A, Sarra E, Peraki M, Koukourakis M, Apostolaki S, Souglakos J, Mavromanomakis E, Vlachonikolis J, and Georgoulias V. Docetaxel-induced lymphopenia in patients with solid tumors: a prospective phenotypic analysis. Cancer 2000; 89:1380-1386.
9. Su YB, Sohn S, Krown SE, Livingston PO, Wolchok JD, Quinn C, Williams L, Foster T, Sepkowitz KA, and Chapman PB. Selective CD4+ Lymphopenia in Melanoma Patients Treated with Temozolomide: A Toxicity with Therapeutic Implications. Journal of Clinical Oncology 2004; 22:610-616.
10. Craddock CG. Corticosteroid-induced lymphopenia, immunosuppression, and body defense. Ann Intern Med 1978; 88:564-566.
11. Collins FM. Mycobacterial disease, immunosuppression, and acquired immunodeficiency syndrome. Clin Microbiol Rev 1989; 2:360-377.
12. Karnak D, Kayacan O, and Beder S. Reactivation of pulmonary tuberculosis in malignancy. Tumori 2002; 88:251-254.
13. Kim DK, Lee SW, Yoo C-G, Kim YW, Han SK, Shim Y-S, and Yim J-J. Clinical Characteristics and Treatment Responses of Tuberculosis in Patients with Malignancy Receiving Anticancer Chemotherapy. Chest 2005; 128:2218-2222.
14. Jakeman P. Risk of relapse in multibacillary leprosy. Lancet 1995; 345:4-5.
15. Brunsvig PF, Hatlevoll R, Berg R, Lauvvang G, Øwre K, Wang M, and Aamdal S. Weekly docetaxel with concurrent radiotherapy in locally advanced non-small cell lung cancer: A Phase I/II study with 5 years' follow-up. Lung Cancer 2005; 50:97-105.
16. Munkarah A, Chuang L, Lotzová E, Cook K, Morris M, and Wharton JT. Comparative Studies of Taxol and Taxotere on Tumor Growth and Lymphocyte Functions. Gynecologic Oncology 1994; 55:211-216.
17. Souglakos J, Kotsakis A, Kouroussis C, Kakolyris S, Mavroudis D, Kalbakis K, Agelaki S, Vlachonikolis J, Georgoulias V, and Samonis G. Non-neutropenic febrile episodes associated with docetaxel-based chemotherapy in patients with solid tumors. Cancer 2002; 95:1326-1333.
18. Resman N, Gradisar H, Vasl J, Keber MM, Pristovsek P, and Jerala R. Taxanes inhibit human TLR4 signaling by binding to MD-2. FEBS Letters 2008; 582:3929-3934.
19. Bochud P-Y, Sinsimer D, Aderem A, Siddiqui M, Saunderson P, Britton S, Abraham I, Tadesse Argaw A, Janer M, Hawn T, and Kaplan G. Polymorphisms in Toll-like receptor 4 (TLR4) are associated with protection against leprosy. European Journal of Clinical Microbiology and Infectious Diseases 2009; 28(9):1055-1065.
20. Kleinnijenhuis J, Oosting M, Joosten LA, Netea MG, and Van Crevel R. Innate immune recognition of Mycobacterium tuberculosis. Clin Dev Immunol 2011; 2011:405310.
21. Akerkar SM, Bichile LS. Leprosy & gangrene: A rare association; role of anti phospholipid antibodies. BMC Infect Dis 2005; 5:74.
22. Loizou S, Singh S, Wypkema E, Asherson RA. Anticardiolipin, anti-beta(2)-glycoprotein I and antiprothrombin antibodies in black South African patients with infectious disease. Ann Rheum Dis 2003; 62(11):1106-11.
23. Bakos L, Correa CC, Bergmann L, Bonamigo RR, Muller LF. Antiphospholipid antibodies thrombotic syndrome misdiagnosed as Lucio's phenomenon. Int J Lepr Other Mycobact Dis 1996; 64(3):320-3.
24. de Larrañaga GF, Forastiero RR, Martinuzzo ME, Carreras LO, Tsariktsian G, Sturno MM, Alonso BS. High prevalence of antiphospholipid antibodies in leprosy: evaluation of antigen reactivity. Lupus 2000; 9(8):594-600.
25. Panunto-Castelo A, Almeida IC, Rosa JC, Greene LJ, Roque-Barreira M. The Rubino test for leprosy is a beta2-glycoprotein 1-dependent antiphospholipid reaction. Immunology 2000; 101(1):147-53.

Recurrent multi-loculated symptomatic malignant pleural effusion after talc pleurodesis: drain and re-drain improve quality of life and patient survival

Anna Tsiara[1], Lampriani Tsali[1], Antonis Valachis[1,2], Andreas Nearchou[1,2], Aggelos Panagopoulos[1], Dimitrios Koutsianas[1], Emmanouil Manos[1], Davide Mauri[1]

[1]Department of Medical Oncology, Radiology and Respiratory Medicine, General Hospital of Lamia, Lamia, Greece
[2]Onkologkliniken Sörmland, Mälarsjukhuset, Eskilstuna, Sweden

Correspondence:
Davide Mauri,
Department of Medical Oncology,
General Hospital of Lamia,
Kerasountos 7, Eleftherio Neo Kordelio,
56334 Thessaloniki, Greece,
e-mail: dvd.mauri@gmail.com

ABSTRACT

Medical oncology is a high-cost and challenging medical specialization, however sometimes low-cost interventions combined with appropriate pharmacological treatments might provide more benefits to the patient than drug delivery alone.

We report the case of a patient with recurrent multi-loculated pleural effusion, who would otherwise be condemned to 24-hour use of oxygen mask and inhalers.

Key words: recurrent loculated malignant pleural effusion; pleurodesis; quality of life.

INTRODUCTION

Medical oncology is a challenging medical specialization characterized by breakthrough research, human touch and high-cost challenging biological drugs.

Due to the distinctiveness of oncology patients, health care providers around the world deliver high-cost drugs amounting to tens of thousands of euros/year/patient to attain less than one month of overall survival benefit [1] or even no benefit at all [2-4]. However, sometimes, low-cost interventions might provide more benefits to the patient than would high-cost drug delivery alone, especially if such interventions are associated with proper treatment of the primary disease.

We report the case of a patient who would otherwise be condemned to 24-hour use of oxygen mask and inhalers.

CASE PRESENTATION

Male patient aged 68, was referred for palliative care treatment to a Greek regional hospital on November 2010 because of poor performance status (PS=3) and severe dyspnea, due to recurrent multi-loculated pleural effusion secondary to metastatic clear cell renal carcinoma. **Medical History:** In 2006, the patient underwent a right nephrectomy for a GII pT1b, N0, M0, stage I clear cell renal carcinoma. In August 2010, he was hospitalized in a tertiary care central hospital for respiratory disease because of dyspnea and chest pain due to malignant left lung pleural effusion. Thoracentesis and talc pleurodesis were performed. Computed tomography (CT) restaging evidenced complete pleural effusion evacuation and total lung re-expansion; no evidence of metastatic disease in organs other then pleura was noted; and bone scan was negative for bone secondarisms. Patient was placed in observation follow-up without further treatment by his physicians. In November 2010, respiratory symptoms reappeared, chest CT imaging documented pleural effusion relapse in the same pleura, with multi-loculated pattern of pleural fluids, trapped by pleural adhesions. Recurrence and patient general condition (PS 3) were scrutinized in an oncology and respiratory disease consultation. Re-thoracentesis with re-pleurodesis was deemed of no value. Due to the severity of dyspnea symptoms, β2 agonists and corticosteroid inhalers as well as 24-hour oxygen mask were prescribed to the patient together with oral sunitinib 50 mg/day for four weeks, 2 weeks rest and recycling every 6 weeks [9].

Palliative care management: β2 agonists and corticosteroid inhalers are of little value in managing dyspnea of pleural effusion origin. Considering the severity of respiratory distress

Figure 1.
Chest X-Ray before the 3rd thoracentesis

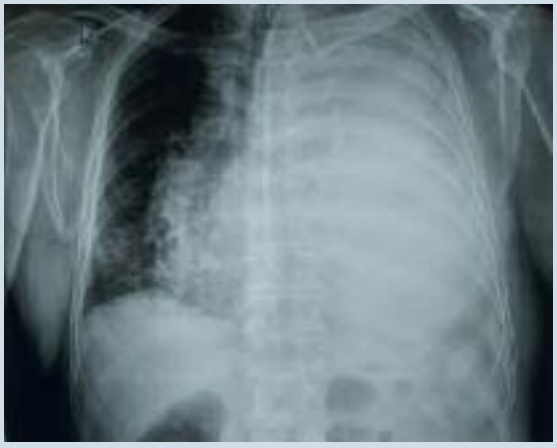
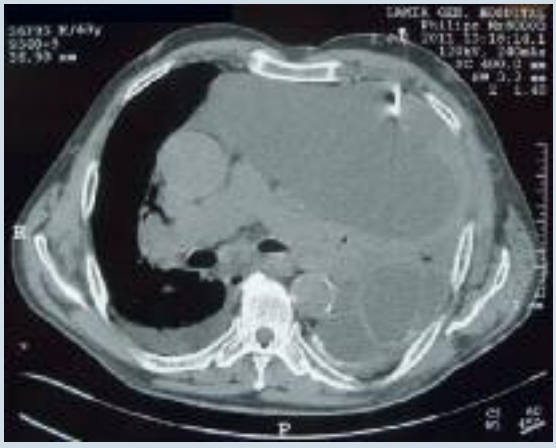


Figure 2.
CT at 3rd thoracentesis



and that the 24-hour oxygen mask was not enough to palliate the patient's respiratory discomfort, overall patient indications were re-scrutinized in our secondary care department. Taking into consideration that multi-loculated patterns of pleural effusion trapped by pleural adhesions do not seem to communicate anatomically in classical imaging, yet these effusions frequently communicate functionally with each other (despite the imaging picture) [6], we decided to re-drain the pleural effusion under US guidance and to re-perform talc pleurodesis after fluid evacuation. In view of the minimally interventional thoracic procedure, due to the potential risk for hemorrhage, sunitinib treatment was discontinued. After 5 days, all of the patient's left hemithorax trapped pleural fluid effusions were screened with ultrasound for potential drainage. Chest seldinger tube 12ch was positioned using US guidance and remained for 4 days; a total of 2.5 liters of malignant pleural effusion was removed with satisfactory lung expansion and with notable reduction in number and size of the multi-loculated effusions. Re-talc pleurodesis was then performed with slurry talc powder.

Five days after thoracentesis, recurrent daily 37.5 mg sunitinib treatment was initiated [7, 8] and the patient was discharged from the hospital. The patient's overall condition re-flourished and he returned to his daily life without oxygen mask or inhalers and with an ECOG PS=0. Due to the lack of a cytology department in our small hospital (many regional secondary care hospitals lack cytology departments) no pleural effusion cytology was obtained. However, considering that the patient was completely assessed and referred to our regional hospital for terminal care from a university department of medical oncology in a tertiary care (central) hospital, no major reason to re-perform cytology was imperative in this setting (terminal care).

In March 2011, pleural effusions began to deteriorate slowly but the patient continued to be asymptomatic. No visceral metastases developed in vital organs (lung parenchyma vs. liver vs. brain etc). Pleural effusion was the only manifestation of recurrence and the pleural effusion relapse was nicely delayed in time with a low incremental rhythm. A watchful waiting policy was thus preferred over an early drug switch. Two months later, in May 2011, the patient's condition deteriorated (PS=2) and dyspnea reappeared. US-guided screening of trapped effusion was performed but thoracentesis was difficult, due to the effusion location and dimensions. No chest tube was located and only 100 ml could be removed on-site. A chest CT was thus programmed, while the patient's dyspnea, back ache and PS (=3) continue to worsen (Figures 1, 2). During CT restaging, CT-guided parasternal chest seldinger 12ch was located and 3.5 liters of pleural effusions were removed in three days with satisfactory lung expansion, notable reduction in number and size of the multi-loculated effusions (Figures 3, 4). Re-talc pleurodesis was then performed with slurry talc powder and the patient was discharged from the hospital on the following day under everolimus [10] treatment (10 mg once daily) and with an ECOG PS=1. In September 2011, pleural effusions deteriorated further, CT-guided thoracentesis was performed and 3rd line treatment with oral sorafenib 400 mg twice a day was initiated [11].

More than a year after palliative care referral the patient continues to live without an oxygen mask.

DISCUSSION

Medical oncology is an exciting medical specialization, characterized by challenging, cutting-edge research; educational and trial breakthrough opportunities; intense human contact in taking care of patients; and availability of high-cost, fashionable biological drugs [12]. In this convulsive and full of

Figure 3.
Chest X-Ray after the 3rd thoracentesis

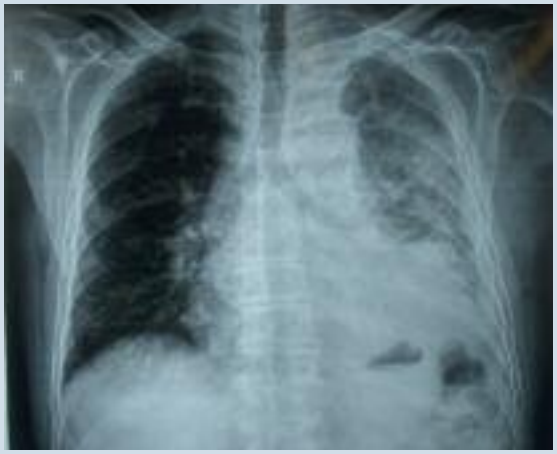
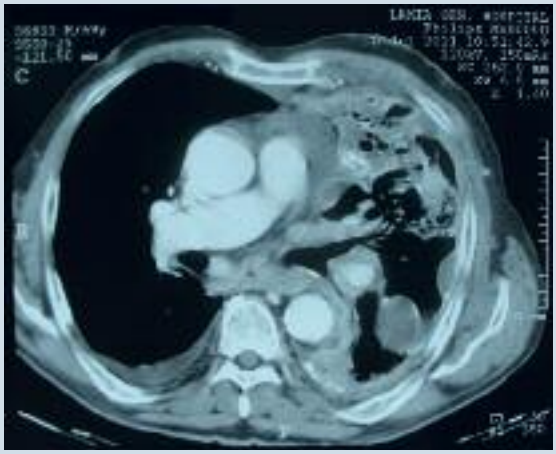


Figure 4.
CT after the 3rd thoracentesis



attractions life, sometimes the propensity for and facility in prescribing drugs may replace a comprehensive patient approach. Occasionally, however, low-cost interventions may provide notable benefits in quality of life and survival, especially if such interventions are associated with proper treatment of the underlying disease.

In this case, a multi-loculated pleural effusion, recurrent after a single course of talc pleurodesis, was condemning the patient's health to serious and extremely undesirable conditions (poor performance status, mandatory continuous use of oxygen mask and inhaler, potential negative effects resulting from compulsory sedentary life such as decubitus ulcers; infections and PE; continued deterioration of dyspnea and pain; and probably life expectancy reduction).

Recurrent loculated malignant pleural effusions are common after the use of sclerosant pleural agents such as talc, bleomycin, tetracycline and doxycycline [5]. However, despite the fact that multiple loculated effusions sometimes do not seem to communicate in classical imaging, these effusions communicate functionally with one another; for these reasons further re-drainage and re-management is indicated, either with re-use of sclerosant pleural agents, or with the use of tunneled pleural catheters [6].

Consequently, management of recurrent malignant pleural effusions is an important issue in the supportive care of cancer patients. Due to the procedure's low cost and considering its potential benefit for patients' quality of life, management of recurrent loculated effusions should be guaranteed to all patients who need it. Indeed, these low-cost interventions combined with appropriate treatments of the underlying disease might provide more patient benefits than would drug delivery alone.

REFERENCES

1. Moore MJ, Goldstein D, Hamm J, Figer A, Hecht JR, Gallinger S, et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 2007 May 20; 25(15):1960-6.
2. Valachis A, Polyzos NP, Patsopoulos NA, Georgoulias V, Mavroudis D, Mauri D. Bevacizumab in metastatic breast cancer: a meta-analysis of randomized controlled trials. Breast Cancer Res Treat 2010 Jul; 122(1):1-7.
3. Mauri D, Valachis A, Polyzos NP, Tsali L, Mavroudis D, Georgoulias V, Casazza G. Does adjuvant bisphosphonate in early breast cancer modify the natural course of the disease? A meta-analysis of randomized controlled trials. J Natl Compr Canc Netw 2010 Mar; 8(3):279-86.
4. Valachis A, Polyzos NP, Georgoulias V, Mavroudis D, Mauri D. Lack of evidence for fracture prevention in early breast cancer bisphosphonate trials: a meta-analysis. Gynecol Oncol 2010 Apr; 117(1):139-45.
5. Shaw P, Agarwal R. Pleurodesis for malignant pleural effusions. Cochrane Database Syst Rev 2004; (1):CD002916.
6. Thornton RH, Miller Z, Covey AM, Brody L, Sofocleous CT, Solomon SB, Getrajdman GI. Tunneled pleural catheters for treatment of recurrent malignant pleural effusion following failed pleurodesis. J Vasc Interv Radiol 2010 May; 21(5):696-700.
7. Escudier B, Roigas J, Gillessen S, et al. Phase II study of sunitinib administered in a continuous once-daily dosing regimen in patients with cytokine-refractory metastatic renal cell carcinoma. J Clin Oncol 2009 Sep 1; 27(25):4068-75. Epub 2009 Aug 3. PubMed PMID: 19652072.
8. Motzer RJ, Hutson TE, Olsen MR, Hudes GR, Burke JM, Edenfield WJ, Wilding G, Martell B, Hariharan S, Figlin RA. Randomized phase II multicenter study of the efficacy and safety of sunitinib on the 4/2 versus continuous dosing schedule as first-line therapy of metastatic renal cell carcinoma: Renal EFFECT Trial. J Clin Oncol 29: 2011 (suppl 7; abstr LBA308).
9. Motzer RJ, Hutson TE, Tomczak P, et al. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. J Clin Oncol 2009; 27(22):3584-90.

10. Motzer RJ, Escudier B, Oudard S, et al. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. Lancet 2008; 372(9637):449-56.

11. Escudier B, Eisen T, Stadler WM, Szczylik C, Oudard S, Siebels M, Negrier S, Chevreau C, Solska E, Desai AA, Rolland F, Demkow T, Hutson TE, Gore M, Freeman S, Schwartz B, Shan M, Simantov R, Bukowski RM; TARGET Study Group. Sorafenib in advanced clear-cell renal-cell carcinoma. N Engl J Med 2007 Jan 11; 356(2):125-34. Erratum in: N Engl J Med 2007 Jul 12; 357(2):203.

12. Nearchou AD, Valachis A, Polyzos NP, Mauri D, Lind PA. Conflict of interest in economic analyses of targeted therapies in oncology. J Clin Oncol 29: 2011 (suppl; abstr 6120).

Pancreatic metastasis from prostate cancer

Georgia Milaki[1], Maria Georgiadou[1], Efthimia Manassaki[1], Ioannis Drositis[1], Georgios Georgiou[2], Evangelia Sfakianaki[3], Nikolaos Androulakis[1]

[1]Department of Medical Oncology, "Venizeleio-Pananeio" General Hospital of Heraklion, Greece
[2]Department of Pathology, "Venizeleio-Pananeio" General Hospital of Heraklion, Greece
[3]Department of Radiology, "Venizeleio-Pananeio" General Hospital of Heraklion, Greece

ABSTRACT

The pancreas is an unusual location for metastases from other primary cancers. Disparity in prognosis and management between primary and secondary pancreatic tumours makes recognition of metastases to the pancreas an important goal. We report an exceptional case of pancreatic metastasis from prostate cancer. In such cases, a high degree of suspicion can lead to early detection and potentially effective treatment.

Key words: prostate cancer; pancreatic metastasis.

Correspondence:
Nikolaos Androulakis,
Medical Oncology Department,
General Hospital of Heraklion
"Venizeleio-Pananeio",
Knossou Avenue, 71409 Heraklion,
Crete, Greece,
e-mail: nandroulakis@yahoo.gr

INTRODUCTION

The pancreas is an uncommon location for metastases from other primary cancers [1]. These tumours are usually asymptomatic or present with vague symptoms that can delay metastatic disease diagnosis. When they become clinically evident, their most common manifestations are that of obstructive jaundice and/or acute pancreatitis. Such cases usually involve patients with widespread, disseminated disease, so therapeutic management is mostly palliative and symptomatic.

Nonetheless, there have been a few sporadic reports of radical surgical interventions in selected patients.

In this report, we present the case of a 70-year-old patient with prostate cancer who presented with metachronous pancreatic metastases that became clinically evident with obstructive jaundice.

CASE REPORT

A 70-year-old Caucasian male patient was diagnosed in 1999 with high-grade prostate adenocarcinoma. The patient underwent radical prostatectomy with no further treatment. Ten years after the initial diagnosis the disease had progressed with mediastinal lymph node involvement, malignant pleural effusion and bone metastases. He then received androgen deprivation therapy for 18 months until his PSA became elevated.

On August 2010, a routine follow-up abdomen CT revealed multiple liver metastases and a borderline enlargement of periaortic, paraaortic and hilar lymph nodes. Twenty days later, the patient was admitted to the hospital with high fever, rigor, recurrent vomiting resulting in incapability to eat, right upper quadrant abdominal pain and jaundice. Biological analysis revealed a significant elevation of bilirubin (Tot Bil: 8.7mg/dl, conjugated Bil: 6.14mg/dl), alkaline phosphatase (3N) and gamma-glutamyl transferase (12N). Serum prostatic specific antigen (PSA) remained unchanged (106ng/ml). Radiological examination of the abdomen with both an ultrasound and a computed tomography revealed cholelithiasis and a highly suspicious, well-circumscribed lesion of the pancreatic head, with both cystic and solid elements, resulting in distension of both intra- and extra-hepatic biliary tree and causing pyloric stenosis. A distorted Vater ampulla with adenomatoid appearance, as well as distension of the intra- and extra-hepatic biliary tree, secondary to stenosis of the distal common bile duct was revealed on a subsequent ERCP. Endoscopic sphincterectomy was performed and a metallic stent was placed in the common bile duct. Tru-cut biopsy of the pancreatic head lesion under US guidance revealed a low-grade adenocarcinoma, with positive immunohistochemical staining for PSA (Figure 1), supporting the diagnosis of pancreatic metastasis from prostate adenocarcinoma.

The liver function tests normalized and the patient started 1st line chemotherapy with docetaxel/prednisone every 3 weeks. After 6 cycles of chemotherapy, imaging studies showed an excellent partial response with 50% shrinkage of the pancreatic mass. The serum levels of PSA were normalized.

The patient is still alive and in excellent general condition (PS=0). He completed 10 cycles of Docetaxel/Prezolon on May 2011 and since then is followed regularly without clinical or radiological evidence of disease progression, despite a recent increase in PSA value (from nadir 3.14ng/ml to 6.36ng/ml).

DISCUSSION

Pancreatic cancer is one of the leading causes of cancer death, ranking 4th in the US and 6th in Europe [1]. The vast majority of pancreatic carcinomas are primary and, among these, over 90% are of ductal origin [2]. However, a variety of extrapancreatic tumours may involve the pancreas secondarily and may manifest different clinicopathological characteristics and outcomes [3, 4]. The route of metastases is lymphatic (28%); vascular (27%); lymphatic-vascular (19%); and by direct invasion (18%). Such lesions usually appear in patients between 60-70 years of age. The most common manifestation is that of a solitary mass, located in the head of the pancreas [5]. Primary and metastatic tumours are often indistinguishable by imaging studies since both may show a single mass in the pancreas and have regional lymphadenopathy [6].

Symptoms caused by metastatic pancreatic lesions are variable and most patients are free of organ-specific complaints. Metastatic disease is usually incidentally detected on abdominal CT scan during the follow-up period. Those patients that do have clinical manifestations may present with abdominal or back pain, nausea, weight loss, jaundice, gastrointestinal haemorrhage or intestinal obstruction [8]. Moreover, whenever the pancreatic metastatic lesion directly invades the pancreatic duct epithelium, it may clinically mimic primary pancreatic adenocarcinoma or, less commonly, induce acute pancreatitis [8, 9].

The diagnosis is usually confirmed by percutaneous fine needle aspiration of the pancreatic lesion under CT guidance; or endoscopic ultrasound (EUS); or by cytological examination of brushing specimens obtained during endoscopic retrograde cholangiopancreatography (ERCP) [9, 10].

The incidence of pancreatic metastases in autopsy series performed in patients with malignant neoplasms range from 1.6-11%. Renal cell carcinoma is the most common primary tumour, followed by lung cancer, breast cancer, and more rarely, melanoma, carcinoma of gastrointestinal origin (including gastric cancer, colon cancer and GIST), ovarian cancer and soft-tissue sarcoma. Solitary pancreatic masses can be classified as secondary tumours to the pancreas in only 2% of the cases, and they are frequently misdiagnosed as primary pancreatic cancers [3-7].

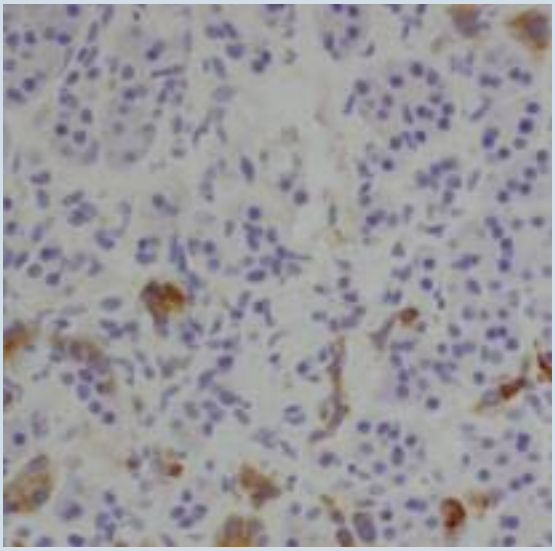
The main site of metastasis in prostatic adenocarcinoma is the bone. Most atypical prostate carcinoma metastases are well-defined in the presence of known advanced disease [11]. To our knowledge, only three cases of pancreatic metastasis from prostate cancer have been previously reported [4, 5, 12].

The time interval between primary carcinoma initial diagnosis and the detection of pancreatic metastasis varies widely. Diagnosis is frequently simultaneous (within 1 year) or intermediate (within 3 years). Only in rare cases is pancreatic metastasis the first sign of malignant disease. Metastasis to the pancreas has been described up to 17 years following primary diagnosis in renal cell carcinoma [16].

This suggests that pancreatic tumours in patients with a history of non-pancreatic malignancy should always be considered as a potential metastatic lesion at an unusual site. If feasible, pathological confirmation should be obtained, as pancreatic metastases may clinically or radiologically mimic a pancreatic primary tumour. Although the differential diagnosis between a primary pancreatic cancer and metastases of other adenocarcinomas may be complex, using common pathological and immunohistochemical techniques may provide relevant information.

There have been several papers suggesting that pancreatectomy for metastatic lesions may result in improved survival rates and disease free intervals [13-16]. In highly selected cases, a radical surgical approach may be considered for the treatment of metastasis to the pancreas. This is especially true in cases with a long disease-free interval between resection of the primary carcinoma and discovery of the pancreatic metastasis and when no detectable metastases in other organs exist. For example, up to 80% of patients with pancreatic metastasis from renal cell carcinoma will have no other sites of metastatic disease [17]. In this setting, prolonged survival may be achieved with successful surgical resection.

Figure 1.
Positive PSA staining in the biopsy specimen



CONCLUSION

Symptomatic metastatic lesions of the pancreas from prostate cancer are extremely rare. Biopsy of the suspicious lesion is fundamental in order to achieve differential diagnosis from other primary pancreatic tumours.

Detection and characterization of pancreatic metastases may significantly influence patient management. Knowledge of unusual locations for metastatic spread will reduce diagnostic delay and lead to a timely delivery of an appropriate treatment.

REFERENCES

1. Michaud DS. Epidemiology of pancreatic cancer. Minerva Chir 2004; 59:99-111.
2. Smith HJ. Extrahepatic bile duct obstruction in primary carcinoma of the lung: incidence, diagnosis, and non-operative treatment. J Natl Med Assoc 1980; 72:215-220.
3. Merkle EM, Boaz T, Kolokythas O, Haaga JR, Lewin JS, Brambs HJ. Metastases to the pancreas, British Journal of Radiology 1998; 71:1208-1214.
4. Volmar KE, Jones CK, Xie HB. Metastases in the pancreas from nonhematologic neoplasms: report of 20 cases evaluated by fine-needle aspiration. Diagnostic Cytopathology 2004; 31:216-220.
5. Minni F, Casadei R, Perenze B, et al. Pancreatic metastases: observations of three cases and review of the literature. Pancreatology 2004; 4:509-520.
6. Nakamura E, Shimizu M, Itoh T, Manabe T. Secondary tumors of the pancreas: clinicopathological study of 103 autopsy cases of Japanese patients. Pathol Int 2001; 51:686-690.
7. Abrams HL, Spiro R, Golstein N. Metastases in carcinoma: analysis of 1000 autopsied cases. Cancer 1950; 3:74-85.
8. Mitry E, Hammel P, Chaussade S, et al. Pancreatic metastases: a multicentric study of 22 patients. Gastroenterol Clin Bio 2004; 28:872-876.
9. Boudghune FP, Deslandes PM, LeBlanche AF, Bigot JM. US and CT imaging features of intrapancreatic metastases. J Comput Assist Tomogr 1994; 18:905-910.
10. Rumancik WM, Megibow AJ, Bosniak MA, Hilton S. Metastatic disease to the pancreas: evaluation by computed tomography. J Comput Assist Tomogr 1984; 8:829-834.
11. Long MA and Husband JES. Features of unusual metastases from prostate cancer. British Journal of Radiology 1999; 72:933-941.
12. Jacob J, Chargari C, Bauduceau O, Fayolle M, Ceccaldi B. "Pancreatic Metastasis from Prostate Cancer". Case Reports in Medicine 2010; 2010:826273.
13. Le Borgne J, Partensky C, Glemain P, Dupas B, de Kerviller B. Pancreaticoduodenectomy for metastatic ampullary and pancreatic tumors. Hepatogastroenterology 2000; 47:540-544.
14. Hiotis SP, Klimstra DS, Conlon KC, Brennan MF. Results after pancreatic resection for metastatic lesions. Ann Surg Oncol 2002; 9:675-679.
15. Zgraggen K, Fernandez-del Castillo C, Rattner DW, Sigala H, Warshaw AL. Metastases to the pancreas and their surgical extirpation. Archives of Surgery 1998; 133:413-417.
16. Stankard CE, Karl RC. The treatment of isolated pancreatic metastasis from renal cell carcinoma: a surgical review. Am J Gastroenterol 1992; 87:1658-1660.
17. Hashimoto M, Watanabe G, Matsuda M, Dohi T, Tsurumaru M. Management of the pancreatic metastases from renal cell carcinoma: report of four resected cases. Hepatogastroenterology 1998; 45:1150-1154.

Θεραπευτικές επιλογές στην ογκολογία...

Μέγιστη σχέση ποιότητας κόστους

Pataxel®
paclitaxel
30mg/5ml VIAL & 100mg/16.7ml VIAL

Gemnil®
gemcitabine
200mg/VIAL & 1000mg/VIAL

Carboplan®
carboplatin
150mg/15ml VIAL & 450mg/45ml VIAL

Iritec®
irinotecan
40mg/2ml & 100mg/5ml

Viastrol®
anastrozole 1mg/Tab

Linol®
letrozole Tabs 2.5mg

BLEOCIN®
Bleomycin

MITOMYCIN-C®
Mitomycin

ELITYRAN® DPS
LEUPRORELIN ACETATE Depot inj. 3,75mg-11,25mg

Πριν τη συνταγογράφηση παρακαλούμε συμβουλευθείτε την περίληψη χαρακτηριστικών των προϊόντων.

προϊόντα ογκολογίας

ΒΙΑΝΕΞ Α.Ε. ΒΙΟΜΗΧΑΝΙΑ ΦΑΡΜΑΚΩΝ
Γραφεία Επιστημονικής Ενημέρωσης ΑΘΗΝΑ: Οδός Τατοΐου 146 71 Ν. Ερυθραία, Τηλ.: 210 8009111 • **E-Mail:** mailbox@vianex.gr
• **INTERNET:** http://www.vianex.gr **ΘΕΣΣΑΛΟΝΙΚΗ:** Β.Ολγας 2, Τηλ: 2310 840440

VE11044ONCOV1-3/2011