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NEW PUBLICATION

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The Arab Medical Association Against Cancer (AMAAC) is a medical body that was established in 2001 as part of the Arab Medical Association where its main office is located in Cairo - Egypt, and it is also a continuation of the Arab Council Against Cancer that was founded in 1995. The Executive Committee of (AMAAC) is represented by two members who are named officially by the Oncology Society of each Arab Country.

The Arab Medical Association Against Cancer aims at strengthening relationships between members in different Arab Countries to raise the level of cooperation in the field of oncology on both scientific and practical aspects. Exchanging information and researches between members through Regional and Arab Conferences and Publications. Holding Public Awareness Campaigns in the field of oncology that are organized by Arab Countries. Participating in scientific activities with International Oncology Societies. Finally, encouraging researchers and doctors to meet and exchange experiences together with finding training opportunities in the field of oncology inside and outside the Arab World.

Pan Arab Publishing Company
P. O. Box: 2509
Amman 11953 - Jordan
Beer Al Sabe' St
Shocair Medical Complex
2nd Fl, office No. 201
Phone + 962 6 566 78 53
Fax + 962 6 562 38 53
www.e-pamj.com

Dr Marwan Ghosn

Dr Marwan Ghosn is currently the Head of Hematology & Oncology division at Clemenceau Medical Center, affiliated with Johns Hopkins International, in Beirut - Lebanon. He has previously served for more than 15 years as Head of the Hematology-Oncology Department at Hotel-Dieu de France University Hospital in Beirut. He is Professor and Program Director of the Hematology Oncology Department at Saint-Joseph University School of Medicine. He served as President of the Lebanese Society of Medical Oncology. He is an active member of several national & international scientific organizations and societies.
He is author and co-author for more than 60 peer-reviewed articles. He contributed in the redaction of several chapters in books in the field of medical oncology and pharmacology. He is the Editor-in-Chief of the "Cancer Letter" edited by the Lebanese Cancer Society. Dr Ghosn has special interests in multiple areas including leadership in conducting research and clinical trials for new drugs and/or new combinations in solid tumors, and an expertise in the management of breast cancer, urologic cancers, gastrointestinal tumors and in the geriatric oncology domain. He recently acquired an expertise in the health care management and hospital management, and especially in Patient Safety issues.

Dr Sami Khatib

Dr. Sami Khatib earned his MD (1978) and the Spanish Board in Clinical Oncology (1982) from Autonomous University of Barcelona – Spain. He is a Senior Consultant in Clinical Oncology and Early Detection, and has a Diploma in Hospital Management.
Dr. Sami's areas of professional interest are in Radiation Oncology (breast and lung), Screening, and Early Detection. He is a member of Barcelona Medical Association, Barcelona Radiation Oncology Association, Spanish Oncology Association, Jordan Medical Association, American Society of Clinical Oncology, European Society for Therapeutic Radiology and Oncology, and a member of the American Society for Therapeutic Radiology and Oncology.
Dr. Khatib is the Co-Author of the WHO – Pan American Health Organization Book entitled «Organization, Development, Quality Assurance and Radiation Protection in Radiology Services: Imaging and Radiation Therapy».
Dr. Khatib was the Associate Director for Patients and Community Affairs at King Hussein Cancer Center (KHCC). Recently, He is the Senior Assistant Director General and the Director, Office of Cancer Planning and Public Outreach Programs at King Hussein Institute for Biotechnology and Cancer (KHIBC). Moreover, he is the Secretary General of the Arab Medical Association Against Cancer (AMAAC).

Dr Khaled Al-Saleh

Dr Khaled Al-Saleh is currently Consultant and Head of Radiation Oncology Department at Kuwait Cancer Control Center in Kuwait. He obtained his degree of M.B.B & Ch. from Alexandria, Egypt in February 1980. He obtained his Board Certificate in Radiotherapy and Oncology from Madame Curie Institute, Warsaw, Poland on November 1992. He served as Registrar at the National Cancer Centre, Tokyo, Japan in 1985 and the Middle Sex Hospital, London, from1986 to1989.

He served as General Secretary of the Gulf Federation for Cancer Control (GFCC), since 2002. He is an Associate General Secretary of the Arab Medical Association Against Cancer (AMAAC) and Head of Kuwait Society of Oncology since 2001.

He is currently the Editor-in-Chief of the Gulf Journal of Oncology and an Associate Editor of the Pan Arab Journal of Oncology (PAJO). He is an active member of the American Association of Clinical Oncology and the International Union Against Cancer (UICC). Dr Al-Saleh is member of the Kuwait Writer Association and the Kuwait Press Association. He has published four short stories in Arabic language, has weekly articles in Al-Watan daily news paper and translated brief of oncology book in Arabic. He was also a writer of Palliative Medicine in Arabic in 2002.

Dr Jamal Khader

Dr Jamal Khader is a Consultant Radiation Oncologist at King Hussein Cancer Center (KHCC) in Amman, Jordan. He is currently the Director of the Radiation Oncology Residency Program and the Head of the Section of Thoracic Cancers and Genitourinary in the Radiation Oncology Department at KHCC. He is also acting as Director of the International Extramural Affairs Office of the Center. He is an Examiner Member of the Radiation Oncology Committee-Jordan Medical Council.

Dr Khader is an active member of the American Society of Therapeutic Radiation Oncology (ASTRO), the European Society of Therapeutic Radiation (ESTRO), the Association of UICC fellows (AUF), the American Brachytherapy Society (ABS), the Jordan Oncology Society (JOS), the Jordan Medical Association (JMA), the Arab Medical Association Against Cancer (AMAAC), the Jordanian Chapter of the Mediterranean Task Force for Cancer Control (MTCC). He was nominated as General Secretary of the Jordan Oncology Society (JOS) from 2003-2006.

Dr Hussein Khaled

Professor of Medical Oncology and is currently Dean of the National Cancer Institute – Cairo University Since 2002. He has many national and international activities. Professional membership includes: European Society of Medical Oncology (ESMO), American Society of Clinical Oncology (ASCO), European Organization for Research and Treatment of Cancer (EORTC) - Lymphoma Group, Egyptian Foundation for Cancer Research (Secretary General), INCTR (President of Egyptian Branch), Egyptian Cancer Society, NIH Alumni Association (Secretary General of Egyptian), President of South and East Mediterranean College of Oncology, Egyptian Academy of Science (Health Sector), Specialized National Council (Health Sector). He is Editor-in-Chief of the NCI journal and he is member of the Editorial Board of the Annuals of Oncology since 2 years. He is also the Head of the Scientific Council of the East Mediterranean region non governmental online against cancer.

Dr Nazar Makki

Dr Nazar Makki is graduated from Alex University in 1959. He obtained his diploma in 1961 and pursued his fellowship (Ed) in UK where he obtained his diploma in May 1965. He worked as house officer and registrar in surgery in Alex. University, Saint James Hospital (London) and Surbiton General Hospital (Surrey, UK). He was appointed as clinical demonstrator in surgery and lecturer in surgery in 1965 and as assistant Professor of Surgery in 1970 at Mosul Medical College, University of Mosul, Iraq. He was appointed as Head of the department of surgery in Mosul 1979 and Head of the department of surgery at Al-Nahrain Medical College, Al-Nahrain University (Formerly Saddam College of Medicine Saddam University 1989-1994, Baghdad).

He served as Supervisor of the Arab Board of Surgery at Mosul Medical College and Saddam College of Medicine from 1981 to 2007. He joined Erbil Medical College in Iraq for the last one year. He is currently member of examinations committee for undergraduate and post graduate study and member and Chief Editor of Mosul Medical College Journal and the Iraqi Medical Association Journal in Baghdad.

INTERNATIONAL ADVISORY BOARD ◄

Patient Safety: It's all about quality!

Donald Berwick, President and Chief Executive Officer of the Institute of Healthcare Improvement (IHI), wrote in Newsweek: "When I climb Mount Rainier, I face less risk of death than I will face in the operating room table".

The Institute of Medicine reported a quiet epidemic of patient injury resulting in perhaps as many as one million serious medication errors and 100,000 preventable deaths annually and at least one death every day in the United States. Preventable Adverse drug events increase in length stay of 4.6 days at a cost of $ 4,685 each.

The total amount of death per year related to the Healthcare is dangerous (>1/1000) compared to those related to mountain climb, charter flights, regular air flight, chemical industry and bungy-jump.

Medication errors have economic and, sometimes, fatal consequences. It affects the moral and scientific aspects (image de marque) of an institution. A study done to evaluate the cost of medication related problems at a university hospital showed a high cost of these events to the institution, with the cost varying with clinical outcome. Multiple studies showed that:

- Medical errors result in injury cost $17 to $29 Billion each year.
- Nosocomial bloodstream infections prolong a patient's hospitalization by a mean of 7 days; the cost per bloodstream infection ranges $ 3,700 and $ 29,000.
- The length of stay for patients with ICU-acquired Blood Stream Infection (BSI) compared to patients without ICU-acquired BSI is 15.5 days (8d - 26d) vs. 12 days (7 d -18.5 d) with significant p-value (p=0.003). The median costs of Hospital Care for patients with ICU-acquired BSI compared to patients without ICU-acquired BSI is $ 85,137 ($45,740 - $131,412) vs. $ 67,879 ($35,043 - $115,915) with significant p-value (p=0.02).

The National Coordinating Council for Medication Error Reporting and Prevention defines the medication error as «any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems, including: prescribing, order communication, product labeling, packaging, and nomenclature, compounding, dispensing, distribution, administration, education, monitoring, and use.»

The American Hospital Association lists the following as some common types of medication errors:

- Incomplete patient information (not knowing about patients' allergies, other medicines they are taking, previous diagnoses, and lab results, for example);
- Unavailable drug information (such as lack of up-to-date warnings);
- Miscommunication of drug orders (verbal orders), which can involve poor or illegible handwriting, confusion between drugs with similar names, misuse of zeroes and decimal points, confusion of metric and other dosing units, and inappropriate abbreviations.
- Lack of appropriate labeling as a drug is prepared and repackaged into smaller units;
- Environmental factors, such as lighting, heat, noise and interruptions, that can distract health professionals from their medical tasks

In the oncology area, the prescription, manipulation and administration of cytotoxic drugs include a multitude of risks. Side-effects of anti-cancer drugs lead to fatal and life-threatening complications. This is critical for drugs where the maximum tolerated dose is close to the usual dose, the route of administration is vital (confusion between intravenous and intrathecal administration of vincristine), the existence of multiple routes of administration (simultaneous intake of oral and transdermal morphine which may lead to respiratory depression).

There are multiple strategies to reduce medication related problems and to increase patient security and safety. Each procedure should be adapted and reviewed on regular basis to ensure its proper implementation.

Quality Improvement is our objective by doing the right thing right for every patient every time (Evidence-based Medicine, Equality and Consistency). To achieve our goal, we have to live the Culture of Patient Safety every time.

Marwan GHOSN, MD

Gefitinib (Iressa) in Non-Small Cell Lung Cancer: A Retrospective Analysis

Karim Rashid[1], Zaher Otrock[1], Ahmad Husari[1], Marwan Ghosn[2], Joseph Kattan[2], Nagi S. El-Saghir[1], Nizar Bitar[3], Ghazi Nsouli[4], Walid Moukaddem[5], Georges Chahine[2], Ziad Salem[1], Ali Shamseddine[1].

(1) American University of Beirut Medical Center, Beirut, Lebanon; (2) Hotel-Dieu de France, University Hospital, Beirut, Lebanon; (3) Sahel Hospital, Beirut, Lebanon; (4) Makassed Hospital, Beirut, Lebanon; (5) Islamic Hospital, Tripoli, Lebanon

✉ *Corresponding Author: Ali Shamseddine, MD, Division of Hematology/Oncology, Department of Internal Medicine, American University of Beirut-Medical Center, P.O. Box:1136044-, Beirut 1107 2802, Lebanon; E-mail: as04@aub.edu.lb*

Key words: non-small cell lung cancer, gefitinib, response, performance status, retrospective.

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Abstract

Background This study is a retrospective review of 50 non-small cell lung cancer (NSCLC) patients who received 250 mg/day gefitinib (Iressa) as third-line monotherapy.

Patients and Methods 50 patients were included in this study. The data were collected from five tertiary care centers in Lebanon.

Results The mean age of patients was 61 (median 64); 72% were male and 28% female. All 50 patients received 250 mg oral gefitinib as monotherapy for a mean duration of 3.9 months (range 1-19 months). One-year and three-year survival was 73% and 21% respectively. Patients with Eastern Cooperative Oncology Group (ECOG) status 0-1 as compared to patients with ECOG status 2-4 enjoyed significantly better survival and response rates.

Conclusion From the data it appears that patients may benefit from earlier administration of gefitinib.

Introduction

Lung cancer is the leading cause of cancer-related mortality in the world accounting for 32% of all cancer-related deaths among males and 25% among females and accounts for 13% of all cancers in males and 12% in females [1]. In Lebanon, the incidence of lung cancer in males is 14.1%, but is only 4.3% among women [2]. Despite advances in diagnostic and therapeutic interventions, the prognosis of patients with advanced stage non-small cell lung cancer (NSCLC) remains dismal [3]. For patients who fail to respond to first-line therapy, response rates to second-line therapeutics range from 7 to 27% [4]. Currently, there is no approved treatment for patients who fail 2 different chemotherapy regimens.

The current standard of care for patients diagnosed with advanced lung cancer is 4-6 cycles of platinum-based chemotherapy. From the evidence it appears that platinum-based chemotherapy offers a 2-month survival advantage compared to best supportive care alone. Because treatment for advanced lung cancer is only palliative, clinicians must weigh any possible survival advantage, symptom control and quality of life improvements against the toxicities of chemotherapy. Treatments with targeted agents such as gefitinib are considerably less toxic than systemic chemotherapies.

Gefitinib (Iressa) is an epidermal growth factor receptor inhibitor belonging to the anilinoquinazoline class of compounds [5]. Epidermal growth factor receptor (EGFR) is a transmembrane receptor identified as the cellular homologue of the viral oncogene v-erb. Many solid tumors of epithelial origin over-express EGFR and overexpression is associated with poor prognosis. Therefore, EGFR inhibition is a rational anticancer strategy.

Preliminary studies with gefitinib on human tumor xenografts in experimental mice showed a dose-dependent inhibition of growth of different tumors including breast, lung and prostate. Tumor growth was completely inhibited at doses above 200 mg/kg/d. Although the inhibition was sustained for the duration of the treatment, tumor growth resumed with treatment cessation [5].

Data from phase II studies of third-line gefitinib indicate that about 43% of patients experience symptom improvement and 12% have a radiographic partial response. In one study, one-year survival was 25% [4]. Unfortunately, phase III studies of concurrent treatment with carboplatin-paclitaxel plus gefitinib failed to support the survival trends noted in phase II gefitinib monotherapy trials [6-8].

Survey Data

Patient data was obtained from treating oncologists in 5 tertiary care centers and included smoking history, pathology, treatment and follow-up.

Statistical analysis

Comparison of continuous variables between various sub-groups was performed using a two-tailed t-test. The relationship between continuous and non continuous variables was evaluated using a Spearman correlation coefficient. Chi-square analysis was used to compare discrete variables between various sub-groups. The

analyses were performed using SPSS software version 13.0 (SPSS, Chicago, Illinois). Statistical significance was set at $p<0.05$.

Patients

Patients were treated until disease progression. The clinical characteristics of all patients are shown in *Table 1*. The mean age of patients was 61 years (median 64); 72% were male and 28% female. 78% of patients had received platinum-based chemotherapy and 92% had received non-platinum chemotherapy. 41% of the patients had received first-line chemotherapy prior to starting gefitinib, 41% had received second-line chemotherapy and 18% had received third-line treatment. Radiation therapy was administered to 54% of the patients, while 24% had prior surgery. As for histological type, 44.1% had adenocarcinoma, 35.3% had squamous cell carcinoma, 5.9%, 8.8% and 5.9% had non-small cell lung carcinoma, large cell, and epidermoid types respectively.

Results

Overall response rate to gefitinib was 12%; 2 patients (4%) had a complete response and 4 (8%) had a partial response. Data was missing on 3 patients with overall clinical benefit and disease control in 36%. 24% of the patients had stable disease, while 58% exhibited continued disease progression. When stratified by histology type, 14 patients had adenocarcinoma *(Figure 1)*. Of those 1 had a complete response, 2 had stable disease and 11 had progressive disease while on gefitinib. Of the 11 patients who had a squamous cell carcinoma, 2 had partial response, 2 had stable disease and 7 had progressive disease. 7 patients had other histological subtypes, 2 had partial response and 2 had stable disease, with progressive disease in 3 patients. It is worth noting that the only patient with complete response and histology data available had adenocarcinoma subtype. Female patients tended to have poorer prognosis as 11 out of 13 (84.6%) had progressive disease on gefitinib versus 18 out of 34 males (52.9%), however the difference was not significant ($p=0.91$).

Of the 25 patients who had Eastern Cooperative Oncology Group (ECOG) performance status (PS) scores 0-1, 11 (44%) had disease progression versus 12 of the 15 patients (80%) who had ECOG performance status of 2 or more. ($p = 0.046$). Survival at 1 year was 73%, and 21% at 3 years. Patients with ECOG PS 0 or 1 had a 31% chance of 3-year survival whereas ECOG PS 2 and 3 was associated with a 3-year survival probability of 17%. Mean survival was 40 and 20 months for the ECOG subgroups respectively ($p= 0.044$) *(Figure 2)*. No grade 3 to 4 toxicities were observed.

Discussion

Gefitinib is an oral agent that inhibits EGFR tyrosine kinase, resulting in antitumor activity among patients with previously treated NSCLC [9]. This retrospective analysis of 50 Lebanese patients with NSCLC who did not respond to prior treatment and were treated with oral gefitinib (<Iressa>, ZD1839; AstraZeneca) 250 mg/day. Although the response rate to gefitinib is rather low, in the order of 12%, the drug can induce full remission in a selected subset of patients. Two patients out of fifty (4%) in the present analysis experienced disease remission.

Data obtained in this analysis is comparable with published data from the phase II IDEAL 1 and 2 studies [10, 11]. In these studies, administration of second or third-line gefitinib provided disease control in 42–54% of patients with advanced or metastatic NSCLC who were previously treated with platinum-based chemotherapy. Overall survival was 35% and 25% in IDEAL 1 and 2 respectively. In our study, disease control was experienced by 36% of patients (4% had CR, 8% had PR, and 24% had SD). One-year and three-year survival was 73% and 21% respectively.

Although large-scale phase III trials such as INTACT 1 and 2 failed to show any benefit from the addition of gefitinib to standard chemotherapy regimens, the disappointing result might be attributed to inadequate patient selection. Subsequent to publication of INTACT 1 and 2, an EGFR mutation which confers sensitivity to gefitinib was identified in 2004 [12]. In addition, multiple studies have confirmed that patients most likely to respond to gefitinib are never-smoking females of Asian ethnicity with adenocarcinoma or bronchioalveloar histology [5]. In the present analysis, patients were selected for third-line gefitinib treatment based solely on failure of previous trials of chemotherapy rather than demographic or disease characteristics now known to be associated with superior response. In addition, it should be noted that gefitinib can provide durable disease remissions to patients who do not have any established characteristics of response.

Recently, a placebo-controlled phase III study (the ISEL study) investigated the effect of gefitinib on survival [13]. At a median follow-up of 7.2 months, median survival did not differ significantly between groups in the overall population. However, subgroup analyses showed significantly longer survival for never-smokers and those of Asian origin who received gefitinib compared to placebo. Never smokers had a median survival of 8.9 vs 6.1 months ($p=0.012$). Asians had a median survival 9.5 vs 5.5 months $p=0.01$).

In addition, our analysis confirmed that patients with a lower ECOG PS (0-1) have better response rates and better survival. This implies that gefitinib treatment may be more effective if initiated early. However, because gefitinib is associated with considerably less toxicity than traditional chemotherapies, it is worth considering as a treatment option for poor PS patients as well.

Conclusion

Gefitinib has been approved by the Food and Drug Administration (FDA) as the first molecularly targeted monotherapy for patients who are refractory to both platinum-based and docetaxel chemotherapies [10, 11].

Our data indicates that the response rate to gefitinib is better for patients with good PS, so starting it earlier for a selected subset of patients may produce better response rates and survival. Additional studies on selection of target populations for gefitinib are warranted.

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TABLES

Table 1. Main characteristics of the patients

Age	61 ± 9.9
Mean Duration of Iressa Rx	3.9 ± 3.6
Gender	72% male, 28% female
Prior Surgery	24% Yes, 74% No, 2% Missing
Prior Radiation	54% Yes, 26% No, 20% Missing
ECOG Status	0 8%, 1 44%, 2 28%, 3 4%, Missing 16%
Staging (stage-%)	IIB-6%, IIIA-14%, IIIB-18%, IV-48%, Missing-14%
Cisplatin Containing Chemo-Rx	70% Yes, 20% No, 10% Missing

Rx: therapy

FIGURES

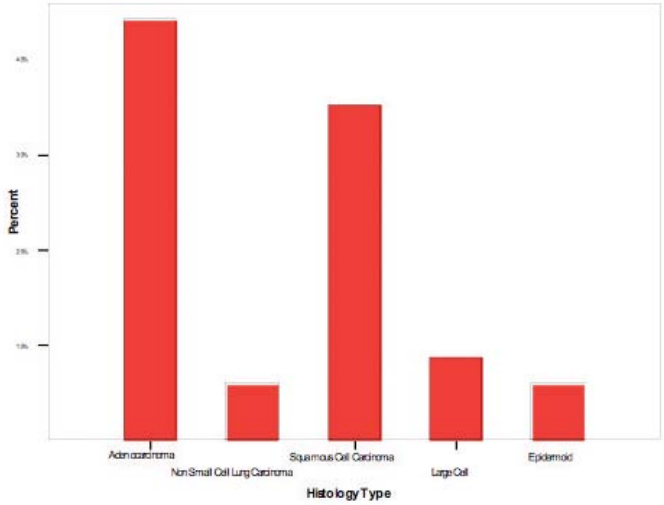

Figure 1. Cases stratified by Histological type

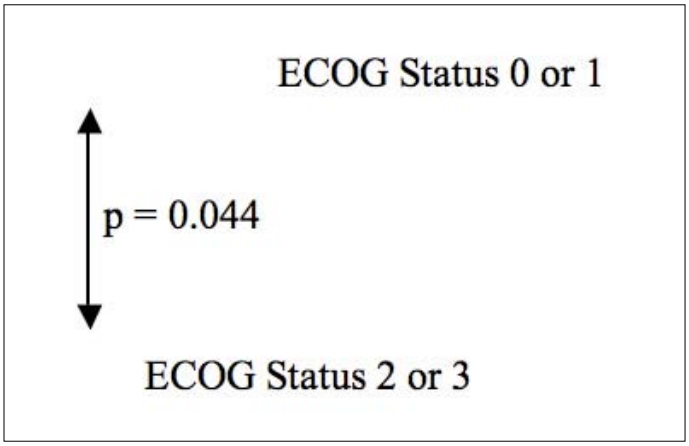

Figure 2. Survival Stratified by ECOG Performance Status

Present and future of radiation oncology

Anne Laprie[1], Gregory Hangard[1], Laure Vieillevigne[1], Carole Massabeau[1], Elizabeth Cohen-Jonathan Moyal[1] and Jean-Marc Bachaud[1].

(1) Institut Claudius Regaud, Department of Radiation Oncology - Toulouse, France

✉ *Corresponding Author : Anne Laprie, MD PhD, Institut Claudius Regaud, Department of Radiation Oncology - 24 rue du pont st Pierre; Toulouse F-31052 , France; Email: Laprie.Anne@claudiusregaud.fr*

Key words: radiotherapy, proton, Magnetic Resonance Spectroscopy, Intensity-Modulated Radiotherapy, Image guided radiotherapy, Positron-Emission Tomography.

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Abstract

Modern advances in computers have allowed parallel advances in imaging technologies. The improvements in imaging have in turn resulted in a higher level of complexity being incorporated into radiotherapy treatment planning systems. As a result of these changes, the delivery of radiotherapy evolved from therapy designed on two dimensional x-ray images and hand calculations to three-dimensional x-ray based images from computerized tomography (CT), incorporating increasingly complex computer algorithms reaching to intensity modulated radiation therapy (IMRT). The incorporation of multimodality imaging (MRI, MR spectroscopy, PET....) is increasingly used for radiotherapy planning. In addition, greater awareness of the challenges to the accuracy of the treatment planning process, such as problems with set-up error and organ movement, have begun to be systematically addressed, ushering in an era of so-called Four-Dimensional Radiotherapy. In this review, we will detail these advances, how they have changed the way cancers are treated now and will be treated in the near future.

Introduction

The greatest challenge for radiation therapy or any cancer therapy is to attain the highest probability of cure with the least morbidity. The simplest way in theory to increase this therapeutic ratio with radiation is to encompass all cancer cells with sufficient doses of radiation during each fraction, while simultaneously sparing surrounding normal tissues. In practice, however, we have been hampered by our abilities to both identify the cancer cells and target them with radiation. The technology of radiotherapy planning and delivery have undergone rapid changes in the last decade due mainly to computer and imaging advances. In this review, we highlight how these new technologies are being used now and are likely to be used in the near future.

Radiotherapy Techniques

The planning of radiotherapy treatment has been revolutionized by the ability to delineate tumors and adjacent normal structures in three dimensions using specialized CT scanners and planning softwares[1].
Two-dimensional (2D) radiotherapy consisted of a single beam from one to four directions. Beam setups were usually quite simple; plans frequently consisted of opposed lateral fields or four-field "boxes". The introduction of three-dimensional (3D) conformal radiotherapy and intensity-modulated radiotherapy (IMRT) has allowed more accurate placement of radiation beams than is possible using conventional X-rays, where soft-tissue structures are often difficult to assess and normal tissues difficult to protect.
Traditionally, the irradiated volume encompasses the gross tumour volume (GTV) and the area at risk for microscopic spread : the clinical target volume (CTV). To assure a proper coverage of the CTV, a margin is added to compensate for daily positioning errors and internal motion of organs, resulting in the planning target volume (PTV), to which the radiation dose is prescribed.

> 3D CRT and IMRT

An enhancement of virtual simulation is 3-Dimensional Conformal Radiotherapy (3DCRT), in which the profile of each radiation beam is shaped to fit the profile of the target from a beam's eye view (BEV) using a multileaf collimator (MLC) and a variable number of beams. When the treatment volume conforms to the shape of the tumour, the relative toxicity of radiation to the surrounding normal tissues is reduced, allowing a higher dose of radiation to be delivered to the tumor than conventional techniques would allow.
Intensity-Modulated Radiation Therapy (IMRT) is an advanced type of high-precision radiation that is the next generation of 3DCRT [2;3] Computer-controlled x-ray accelerators distribute precise radiation doses to malignant tumors or specific areas within the tumor. The pattern of radiation delivery is determined using highly-tailored computing applications to perform optimization and treatment simulation. The radiation dose is consistent with the 3-D shape of the tumor by controlling, or modulating, the radiation beam's intensity. IMRT also improves the ability to conform the treatment volume to concave tumor shapes, for example when the tumor is wrapped around a vulnerable structure such as the spinal cord or a major organ or blood vessel or salivary glands. The

radiation dose intensity is elevated into the gross tumor volume while radiation dose among the neighboring normal tissue is decreased or avoided completely. The customized radiation dose is intended to maximize tumor dose while simultaneously protecting the surrounding normal tissue.

3DCRT is still used extensively for many body sites but the use of IMRT is growing in more complicated body sites such as brain, head and neck, prostate, breast and lung. Unfortunately, IMRT is limited by its need for additional time from experienced medical personnel. This is because physicians must manually delineate not only the tumors on one CT image at a time through the entire disease site but also absolutely all organs at risk which can take much longer than 3DCRT preparation. Then, medical physicists and dosimetrists must be engaged to create a viable treatment plan. And before starting treatment, quality control on the accelerators is much more complex than with 3D CRT. Also, the IMRT technology has only been used commercially since the late 1990s even at the most advanced cancer centers, so radiation oncologists who did not learn it as part of their residency program must find additional sources of education before implementing IMRT.

Proof of improved survival benefit from either of these two techniques over conventional radiotherapy (2DXRT) is growing for many tumor sites, but the ability to reduce toxicity is generally accepted. Both techniques enable dose escalation, potentially increasing usefulness. There has been some concern, particularly with 3DCRT, about increased exposure of normal tissue to radiation and the consequent potential for secondary malignancy. Overconfidence in the accuracy of imaging may increase the chance of missing lesions that are invisible on the planning scans (and therefore not included in the treatment plan) or that move between or during a treatment (for example, due to respiration or inadequate patient immobilization). New techniques are being developed to better control this uncertainty—for example, real-time imaging combined with real-time adjustment of the therapeutic beams. This new technology is called image-guided radiation therapy (IGRT) or four-dimensional radiotherapy – see paragraph 4.

The first works on IMRT were aimed at irradiating patients with head and neck cancer particularly nasopharynx cancer who have a high rate of cure but, due to salivary glands irradiation, were enduring definitive dry mouth, a reduction in taste, and poor dental health. Before IMRT we were unable to reduce these side effects without risking a compromise in cure. The IMRT technique allowed to avoid salivary glands while delivering the same dose to the clinical target volume. Figure 1 displays the previsional dosimetry for a patient with head and neck cancer; figure 1a displays the usual conformationnal treatement, the parotid glands (in purple and blue) receive most of the total dose; on figure 1b, with IMRT, the parotid glands receive a media dose inferior to 26 Gy that keeps them functioning. On figure 1C, the different fields for IMRT are displayed, they are composed by the addition of several subsegments, therefore each beam has a modulated intensity.
IMRT indications are now broadened to all other types of cancer, but mainly to cancers where there is a need for concave tumor shapes of irradiation and steep doses, therefore it is used for
- prostate tumors in order to protect the rectum and increase dose
- in brain tumors when fragile structures as the optic pathways are close to the target volume
- in paediatric tumors when IMRT can avoid late neurological or musculo-squelettal sequelaes
- in mesotheliomas, as it is the only way of irradiating the whole pleura and avoiding lung.

IMRT can be performed either
- on a new generation linear accelerator (Elekta®, Varian® or Siemens®) equipped with multi-leaf collimators and an IMRT software.
- on a special device dedicated only to IMRT : the TomoTherapy® Hi·Art® treatment system The treatment is based on the concept of slice therapy. By mounting the linear accelerator (linac) on a ring gantry, tomotherapy allows a 360° fan-beam delivery of IMRT and fully-integrated, megavoltage CT imaging. This device is equipying around 100 cancer centers worldwide, among them four centers in France, of the federation of comprehensive cancer centers (federation national des centres de lutte contre le cancer FNCLCC) : Bordeaux, Nantes, Paris and Toulouse.
The possibility to acquire rapid daily in-room CT imaging (CBCT) allows adaptive dose guided radiotherapy as shown in figure 2.

> High precision radiotherapy
High precision radiotherapy has to be delivered when the dose needed for a small tumour control exceeds the limiting tolerated dose of the surrounding tissues.
Its technical application requires a stereotactic coordinate system, highly accurate patient repositioning (usually fixed), and multiple convergent beams of photon radiation. Radiosurgery provides no benefit for infiltrative tumors. Moreover the hypofractionation or the use of single dose is more harmful for the surrounding tissue, therefore its use is very limited.
Radiosurgery can be delivered
- with a Gamma Knife® device, but exclusively for brain radiosurgery, and contrarly to all radiotherapy devices now that are linear accelerators using X rays, this device has permanent radioactive sources of Cobalt-60. These 201 sources of radioactive cobalt direct gamma radiation to the center of a helmet, where the patient's head is inserted.
- with a new generation linear accelerator equipped with on-board imaging and a micro-multileaf collimator, for any type of tumor.
- with a CyberKnife®, which is a compact linear accelerator mounted on a robotic arm. For small lung cancer : it allows

to deliver precisely an ablative radiation dose with surgical precision when surgery is not possible. As the robotic arm of the accelerator can follow breathing movements through implanted markers or through markers placed on the surface of the thorax[4]. For example, it can be used too for prostate cancer, small intracerebral tumors, or irradiation at high dose around the spine (initial treatment or reirradiation).

Hadrontherapy: protontherapy and light ions therapy

The particle or hadron beams deployed in radiotherapy (protons and light ions as carbon) have physical and radiobiological characteristics which differ from those of conventional radiotherapy beams (photons) and which offer a number of theoretical advantages over conventional radiotherapy. They deposit their maximum energy density in the Bragg peak at the end of their range, where they can produce severe damages to the cells while sparing both traversed and deeper located healthy tissues.

> Protontherapy

A beam of protons allows highly conformal treatment of deep-seated tumours with millimetre accuracy, giving minimal doses to the surrounding tissues. The result is a smaller treatment volume and therefore a lower incidence and frequency of treatment-related morbidity. Moreover, the reduction in treatment volume permits a higher dose to the tumor. This means an improved local control probability and lower normal tissue complications. The indications for protontherapy are pediatric tumors[5;6], uveal melanomas, base of skull/spinal chordomas and chondrosarcomas and prostate tumors[7]. Although the construction and running costs of hadrontherapy units are considerably greater than those of conventional facilities, a comprehensive analysis that considers all the costs, particularly those resulting from the failure of less effective conventional radiotherapy and the late sequelae induced, might indicate that hadrontherapy could be cost effective. To date, there are only 32 protontherapy centers in operation in the world, and at least 20 others centers proposed. The growing interest in this form of treatment seems to be fully justified by the results obtained to date, although more cost-effectiveness, efficacy and dosing studies are required.[8-10]

> Light ions beams

Other charged particles therapy with carbon ions for example are under evaluation and used for the moment in only a handful of centers around the world.

Quality assurance

Great technical and tools advances in external radiotherapy oblige consequently centers to perform a complete quality control and security control. Methods and appropriate procedures are either imposed by legislation[11] or registered by learned societies or reference organisms[12].

The first step of quality assurance consists in proving the constant performances of linear accelerators and software during acceptance tests or major changes (breakdown, fault, new software version etc). The second step of quality assurance controls the dose applied to the patients (pre-therapeutic measurements with water phantom and ionization chamber, in vivo dosimetry[13] etc...) in order to detect possible systematic or unpredictable errors in process.

Besides, beyond standard and conformational radiotherapy, innovative particular techniques such as intensity modulated radiotherapy, radiosurgery or Tomotherapy® amplified the necessity of more specific total quality control[14] due to the potential greater danger linked to their wrong uses.

Finally, it is important to stress the fact that beyond any control, human error remains the first reason of undesirable events in external radiotherapy[15] and that the human factors (trainings, communication, etc) cannot be excluded from these steps.

Image guided radiotherapy (IGRT)

These radiotherapy techniques have shown to reduce normal tissue toxicity and to allow radiation dose escalation, thus increasing tumor control probability[1;16-18]. On the other hand, the dose distributions delivered to the site of interest can be highly conformal with steep dose gradients. Any variation in organ volume or position during treatment may significantly alter the actual dose delivered to both the target and surrounding normal tissue. This argues for image-guided radiation therapy. Namely, image-guided radiation therapy uses :

- the incorporation of multimodality imaging for treatment planning in order to delineate accurately the target volumes
- then the use of in-room imaging for patient repositioning maximum accuracy.

Image registration is now becoming central to every step of the radiotherapy planning and delivery process. It can improve the ease and accuracy with which multimodality images can be incorporated into a single model of the patient[19], by resolving the geometric discrepancies that exist between the images.

> Multimodality imaging for radiotherapy planning

> CT and MRI

As all patients undergo a CT scanner with their immobilization device on, a good quality CT is helpful to delineate tumors. But the registration of MRI scan data sets with the treatment-planning CT scan is essential for accurate definition of tumor and surrounding organs at risk, in case of brain tumors[20] and prostate tumors[21].

> Metabolic and functional imaging for radiotherapy planning

Integrating additional metabolic and functional imaging studies that reflect the biologic characteristics of tumors is an area of active research.

> Positon Emission Tomography (PET)

2-[18F]fluoro-2-deoxyglucose (FDG) – PET imaging is useful, not only in characterizing disease extent in many tumors of which particularly Lung, Head & Neck and Hodgkin tumors but also in helping target volume definition. It will not be of similar utility across all tumor sites.
It has been now proved that nodal involvement can not be only predicted on the size of the node on the CT[22]. Therefore the addition of PET for planning allows to improve the coverage of nodal extent in lung and head and neck tumors, by either increasing or diminishing the nodal target volume.
For primary lung tumors, recent papers have shown that the use of the registration of PET images on the planning CT diminishes significantly the interobserver variability of tumor delineation when the tumor is close to large vessels, mediastinum of when there is a part of atelectasia[23-25].

For Head and neck tumors[26], the definition of the tumor contours depends on the display windowing that strongly influences the visual rendering of the tumor leading to intra and interobserver variability. Research is still focusing on a reliable segmentation method. As an example, Paulino et al showed that tumor delineated with FDG-PET were larger than those delineated with a CT in 25% of the cases[27].As a whole, PET-FDG is useful for nodal determination[26;28] and is promising for primary tumor definition but it remains a challenging task and an incompletely resolved issue.

Other types of markers are subjects to research too for radiotherapy planning: F-Misodinazole (F-Miso), 11C-methionine (MET) and O-2-18F-fluoroethyl-L-tyrosine (FET).

> Functional Magnetic resonance (MR) imaging

MR spectroscopy, the example of glioblastoma
Proton MR spectroscopy is a technique which is able to characterize biochemical, metabolic, and pathologic changes of tissues, it has been extensively used to date for prostate and brain tumors[29-33]. It was recently suggested that MRSI would be a valuable diagnostic tool for defining the sites of metabolically active tumor[34;35] among and outside MRI abnormalities[36] and for the assessment of residual disease after surgical resection in high-grade gliomas (HGG)[37].
It is, as well, a helpful modality in characterizing suspicious MRI lesions in irradiated gliomas[38-41].

For example, the patients with Glioblastoma Multiforme (GBM) have a poor prognosis and although adjuvant RT increases overall survival, the predominant pattern of failure continues to be within the irradiated volumes[42-44]. As a result, there is a growing interest in increasing the dose to certain portions of the tumor while sparing normal tissue with new technologies such as Radiosurgery (RS)[45] and intensity-modulated radiation therapy (IMRT)[46-48]. T1-weighted images (T1WI) with gadolinium show a heterogeneous, irregular, contrast-enhancing lesion that usually underestimate tumor volumes, as contrast enhancement is more a reflection of blood-brain barrier disruption than actual tumor extent. Conversely, T2-weighted images tend to overestimate tumor volumes due to the high signal intensity resulting from surrounding edema as well as microscopic tumor extension[49]. Since diagnosis and planning for surgical, chemotherapy and radiotherapy treatment utilize MR methods, increased information describing tumor extent and functional regions within the heterogeneous environment would be useful. We reasoned that MRSI might be a valuable tool for helping target definition for radiotherapy.

We recently published the results of a prospective longitudinal study[50] that found a strong predictive value of metabolically abnormal region seen on MR spectroscopy imaging (MRSI) before RT for the site of onset of progression or recurrence. In our study, all patients were included in a prospective phase I clinical trial associating a farnesyltransferase Inhibitor with radiotherapy[51] and underwent MRI/MRSI before RT and every two months thereafter. Among the 23 MRS studied and 1207 voxels analyzed, we observed that metabolically abnormal regions represented a small percentage of MRI lesions before RT, and that without MRSI data; the imaging abnormalities do not predict the site of relapse. We showed that MRSI either alone or associated with T1 and T2 weighted images has a highly statistically significant predictive value for the site of relapse. Our opinion it that the incorporation of MRSI data in the definition of radiotherapy target volumes may be a promising avenue leading to increased local control of glioblastoma. Figure 3 is an example of our results[50].

> Other MR functional imaging
- Prostate MR spectroscopy: the addition of MR spectroscopy to MRI improves the sensitivity and specificity for identifying sites of predominant intraprostatic lesion and therefore has been used for targeting radiotherapy boosts, particularly with IMRT or with brachytherapy[52]. MR prostate diffusion is under evaluation.
- Brain MR perfusion and diffusion: these modalities may give additional information on the localization of radio-resistant areas and are under evaluation in prospective clinical trials

> In room imaging for patient repositioning accuracy
To account for geometric uncertainties during radiotherapy, safety margins are applied. In many cases, these margins overlap organs at risk, thereby limiting dose escalation. The aim of image-guided radiotherapy is to improve the accuracy by imaging tumors and critical structures on the machine just before irradiation. The availability of high-quality imaging systems and automatic image registration

on the machine leads to many new clinical applications, such as high-precision hypofractionated treatments of brain metastases and solitary lung tumors with online tumor position corrections. IGRT makes use of many different imaging techniques, using modalities ranging from planar imaging to fluoroscopy to cone-beam CT, and following procedures as simple as using a single set-up image or as complex as intra-fraction tumor tracking. Figure 4 and 5 display the examples of use of in-room imaging.

Respiratory gating

Respiration-gated radiotherapy improves significantly the irradiation of tumor sites affected by respiratory motion such as lung, breast and liver tumors. Reduction of respiratory motion can be achieved by using either breath-hold techniques or respiration synchronized gating techniques. Breath-hold techniques can be achieved with active techniques, in which airflow of the patient is temporarily blocked by a valve, or passive techniques, in which the patient voluntarily holds his/her breath. Synchronized gating techniques use external devices to predict the phase of the respiration cycle while the patient breathes freely[53].

Summary

In summary, there have been recently many exciting advances in radiation therapy including IMRT, functional imaging for RT, and in-room imaging. These modalities are more commonly finding their way into clinical practice and early data are emerging on their effectiveness. The next decade is likely to yield more advances regarding the role of radiotherapy in an increasingly multidisciplinary oncology environment.

FIGURES

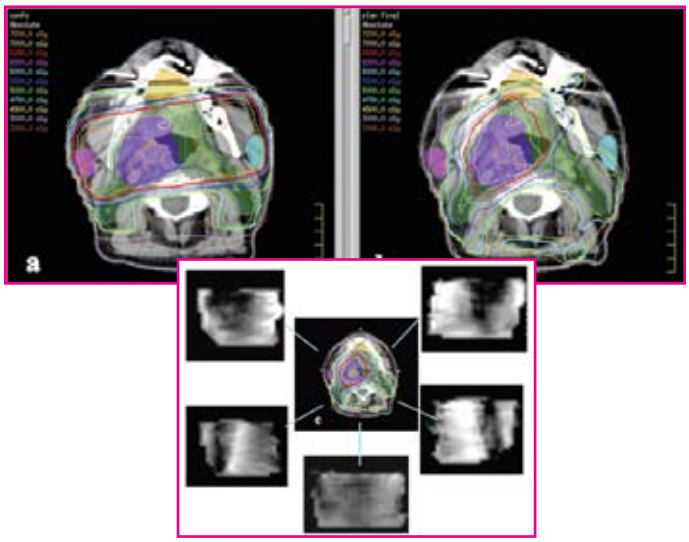

Figure 1 displays the previsional dosimetry for a patient with head and neck cancer; figure 1a displays the usual conformational treatment, the parotid glands (in purple and blue) receive most of the total dose. Dose delivered to tumor is 70 Gy, to nodal areas is 50 Gy and the dose that stops parotid glands from functionning is 26 Gy, the dose received with conformal treatment is superior to 65 Gy; on figure 1b, with IMRT, tumor receives a more conformal dose of 70 Gy, nodal areas receive 50 Gy and the parotid glands receive a much lower median dose that keeps them functioning. On figure 1C, the different fields for IMRT are displayed, they are composed by the addition of several subsegments, therefore each beam has a modulated intensity.

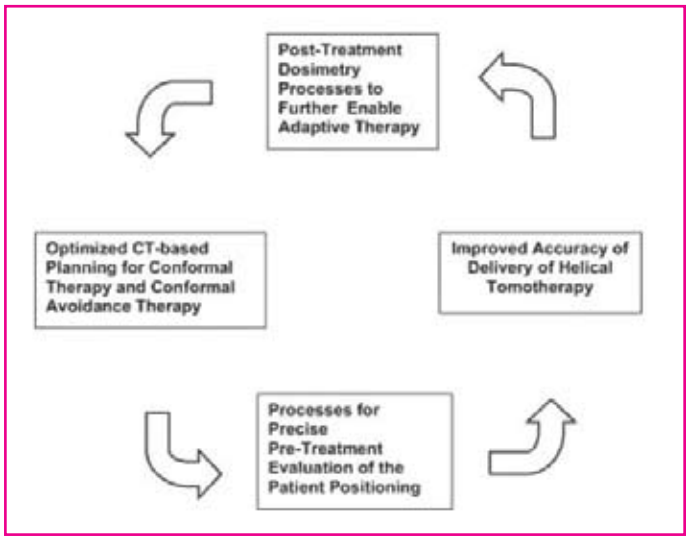

Figure 2 The possibility to acquire rapid daily in-room CT imaging (CBCT) allows adaptive dose guided radiotherapy.

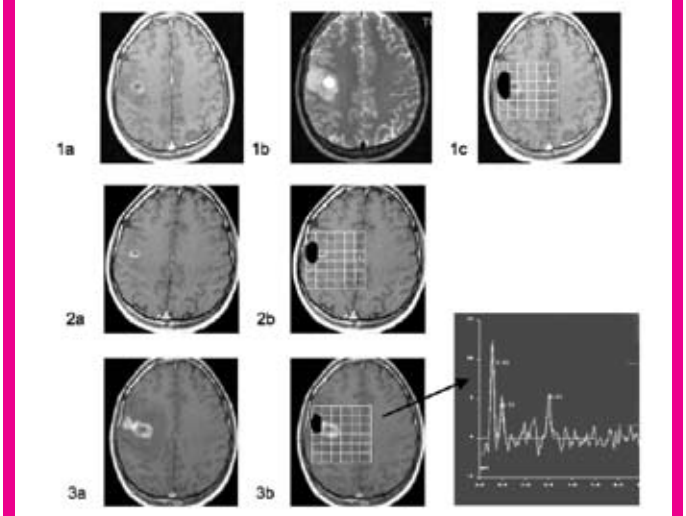

Figure 3 MR spectroscopic follow-up of a 31 years old patient with an unresecable glioblastoma
1- before radiotherapy:
Axial T1WI post contrast
Axial T2WI
MRSI volume, the black region is metabollicaly active and was situated on the T2 hyperintensity (HyperT2), outside contrast enhancement (CE) on T1 weighted sequences (T1).
At 4 months: HyperT2 regions outside CE on T1 kept metabolically active despite lesion regression.
At 6 months:. The initial lesion was growing and a new CE appeared exactly on the site of the initial and persistent metabolically active region. The choline on NAA ratio of this voxel was greater than 2.0 suggesting it was recurrent tumor rather than radiation necrosis. The patient died one month after the six-month scan.

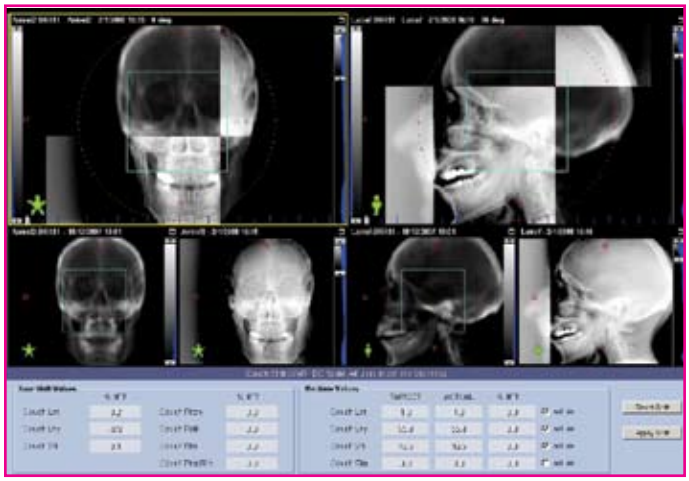

Figure 4 Combined kilovoltage orthogonal images : exemple of an overlay of digitally reconstructed radiographs (from the planning CT scanner) and daily kilovoltage imaging after adjustement. The necessary adjustements required for registration of both imaging sets yield information on the corrections that are required for patient set-up.

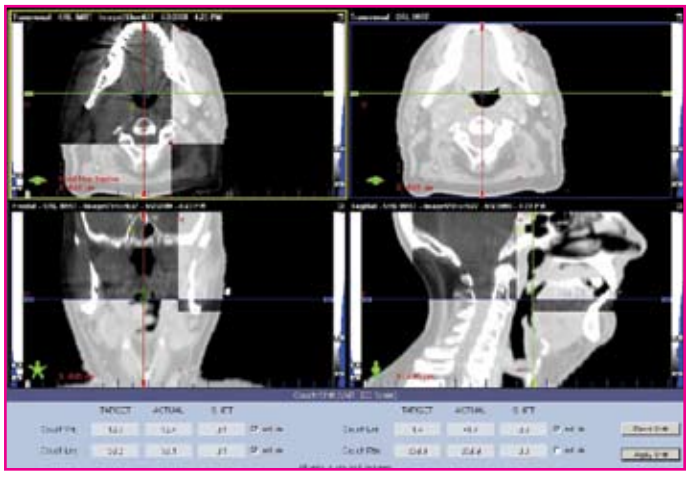

Figure 5 combined computed tomography and daily MVCT image data. Example of an overlay (axial and sagittal cross-sections are shown) of planning computed tomography data and daily Megavolt computed tomography (MVCT) data, after adjustment. The necessary adjustments required for registration of both imaging sets yield information on the corrections that are required for patient set-up.

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Une révolution dans l'approche du cancer du sein basée sur les progrès de la biologie moléculaire

Ahmad Awada[1] and Martine Piccart[1].
(1) Department of Medicine, Medical Oncology Clinic, Jules Bordet Institute, Brussels, Belgium

✉ *Corresponding author: Ahmad Awada, MD, Head of Medical Oncology Clinic, Jules Bordet Institute, University Libre of Brussels, Brussels, Belgium; Email: ahmad.awada@bordet.be*

>> The management of breast cancer has known a major improvement in the last decade. This is made possible through the advances in molecular biology leading to a better understanding of the breast cancer pathophysiology, creating new targets for treatment and individualizing the patient's approach. Fields of improvements are detailed by Dr Ahmad Awada & Dr Martine Piccart from Jules Bordet Institute, Brussels.

Les cliniciens savent depuis toujours que le cancer du sein est une maladie très hétérogène, son pronostic est hasardeux et son évolution est jusqu'à un certain niveau imprévisible.

Des progrès ont été réalisés dans la prise en charge de cette maladie mais malheureusement, ces progrès ont été lents.
On connait peu sur l'origine de cette maladie au moins dans sa forme non-héréditaire. Des virus et des facteurs environnementaux et hormonaux ont été impliqués ainsi que des modifications épigénétiques.

Moins de 50% des cancers du sein héréditaires ont été élucidés par la découverte d'une mutation soit au niveau du gène BRCA1 ou BRCA2 et ont amené à des approches préventives (mastectomie bilatérale, ovariectomie) ou diagnostiques (RMN des seins). Au niveau chirurgical, la tumorectomie a remplacé, quand c'est possible, la mastectomie et la technique du ganglion sentinelle a remplacé dans des conditions précises l'évidement axillaire avec sa morbidité physique et fonctionnelle. Finalement, la radiothérapie a fait aussi des progrès avec comme conséquence une diminution de la cardiotoxicité.

Les progrès récents en biotechnologie ont eu comme conséquence une avancée tangible dans la compréhension de la biologie moléculaire de cette maladie complexe. Des progrès en biostatistique et bioinformatique ont permis d'intégrer des milliers d'informations en relation avec des modifications géniques et protéiques au sein de la tumeur.

Ces progrès sont à la base de la découverte de cibles pour des thérapies biologiques non chimiothérapeutiques. Au-delà de l'histologie classique, la biologie moléculaire commence à mieux définir le pronostic de quelques groupes de patientes et prochainement, espérons-le un progrès dans la prédiction de la réponse ou encore mieux la résistance à un traitement prescrit. Le but de ces avancées est l'individualisation des traitements avec l'espoir d'avoir une meilleure efficacité dans la prise en charge des malades, d'éviter des effets secondaires inutiles et finalement d'améliorer le coût/bénéfice des traitements anticancéreux.

Au niveau pronostic, les facteurs historiques classiques restent d'actualité. La taille, le grade, le nombre de ganglions envahis gardent une valeur pronostique importante mais imparfaite. L'analyse des milliers de gènes dans une tumeur est à la base de la découverte de signatures dites géniques de bon ou de mauvais pronostics. Ces signatures sont en cours d'évaluation pour leur utilité clinique dans des études à grande échelle. Le grade 2 histologique s'est avéré génétiquement être soit un grade 1 ou un grade 3 et non une entité à part. Cela conduira sans aucun doute à une meilleure définition du risque chez la patiente atteinte d'un cancer du sein.

Les gènes impliqués dans la prolifération cellulaire ont émergé comme étant à la base des signatures géniques de mauvais pronostique. Les patientes qui portent ces tumeurs bénéficieront probablement le plus de la chimiothérapie cytotoxique et de schémas thérapeutiques avec intensification de la dose. Les études cliniques sont en cours dans ce domaine.

Les récepteurs hormonaux ont été considérés pendant longtemps comme des factures pronostiques. La méta-analyse avec un suivi de 15 ans a permis de constater que leur valeur pronostique est limitée : ces cancers avec récepteurs hormonaux négatifs récidivent surtout tôt après le diagnostic tandis ceux avec récepteurs hormonaux positifs récidivent plus tard, de sorte que les probabilités de survie ne diffèrent pas fondamentalement à 10-15 ans après le diagnostic. L'implication thérapeutique de cette constatation est qu'il est probablement important de continuer l'hormonothérapie au-delà de 5 ans et que les tumeurs récepteurs hormonaux négatifs nécessitent un traitement le plus efficace possible immédiatement après le diagnostic.

Le gène HER-2/neu a émergé comme un facteur de mauvais pronostic et surtout comme un facteur prédictif de réponse à l'anticorps monoclonal appelé trastuzumab. Son efficacité en monothérapie et surtout en combinaison

avec la chimiothérapie a été bien documentée tant en situation métastatique qu'adjuvante, avec une excellente tolérance à part la dysfonction myocardique qui reste peu fréquente et est observée surtout quand le trastuzumab est associé avec les anthracyclines.

Un progrès important de la biologie moléculaire a été la classification des cancers du sein en au moins quatre groupes de tumeurs distinctes : le groupe des tumeurs exprimant le récepteur, HER-2/neu, le groupe des tumeurs «triple négatif » avec absence d'expression des récepteurs hormonaux et du récepteur neu, le groupe « luminal A » avec une forte expression des récepteurs hormonaux (et probablement une bonne réponse au traitement hormonal) et sans autres facteurs d'agressivité tumorale et finalement le groupe « luminal B » dont la sensibilité aux traitements hormonaux est imparfaite et qui présente souvent d'autres facteurs de risque (tel qu'une prolifération importante).
L'implication clinique de cette subdivision est qu'il est essentiel que les patients de chaque groupe soient englobés dans des études cliniques séparées comportant les thérapies les plus adaptées à la carcinogénèse de leurs tumeurs.

Les anthracyclines, les taxanes, les agents akylants, les antimétabolites sont à la base de la chimiothérapie anticancéreuse du cancer du sein. Les antioestrogènes et les inhibiteurs d'aromatase sont la base du traitement hormonal et finalement le trastuzumab est le premier traitement anti HER-2/neu.

Plus récemment, des nouvelles formulations de taxanes (par exemple l'abraxane), des antimicrotubules actifs en cas de résistance aux taxanes (ex. ixabepilone) et une nouvelle génération d'antimicrotubules (ex. E7389, un analogue de l'halochondrine B) ont vu le jour.
Au-delà du trastuzumab, le lapatinib, administré oralement est apparu actif dans les tumeurs HER-2-/neu prétraitées ou non par trastuzumab et il a l'avantage de passer la barrière hémato-encéphalique et de prévenir ou traiter les métastases cérébrales dont l'incidence est de 30 à 40 % dans ce groupe de patientes avec tumeurs surexprimant HER-2/neu.

Au niveau de la thérapie hormonale, il n'y a pas eu de percées thérapeutiques récentes. Des inhibiteurs d'enzymes appelés sulfatases impliqués dans le métabolisme des oestrogènes sont en cours d'investigation et pourraient représenter une nouvelle «famille » d'agents hormonaux.

La pharmacogénétique, par l'analyse des variants de cytochromes a permis de subdiviser les patientes traitées par tamoxifene en situation adjuvante en bons et mauvais métaboliseurs du tamoxifène.
Les bons métaboliseurs avaient un meilleur pronostic mais avaient aussi plus de bouffées de chaleur et un risque majoré d'arrêt du traitement. Les médicaments interférant avec le métabolisme du tamoxifène en dérivés actifs comme quelques psychotropes sont à proscrire.

Il n'y a pas pour le moment de médicaments qui ont montré clairement une bonne activité dans les tumeurs « triple négative » ou « basal-like ». Les antiangiogénèses (ex. bevacizumab), les anti-EGFR (ex. cetuximab), les dérivés du platine, les inhibiteurs de la topoisomérase et les inhibiteurs de l'enzyme PARP (molécule impliqués dans la réparation de l'ADN) sont en cours d'investigation particulièrement dans ce groupe de tumeurs.

Un nombre considérable de nouvelles thérapies ciblées sont en cours d'investigation dans le cancer du sein. Citons à titre d'exemple, les inhibiteurs de l'IGF(R) et les anti Ras/Raf/MAPKPi3K/Akt. Les premiers résultats des vaccins anti HER-2/neu sont prometteurs.

En conclusion, l'approche du cancer du sein connait une évolution remarquable basée sur les progrès de la biologie moléculaire. Les tumeurs sont mieux classifiées, le pronostic est mieux défini et des thérapies biologiques ont vu le jour. Il est urgent de rapidement valider les outils moléculaires diagnostiques et pronostiques afin de les implémenter en pratique clinique. De plus, il est heureux de constater l'apparition de thérapies moins empiriques qui portent en elles l'espoir de mieux individualiser les traitements et d'améliorer l'index thérapeutique.

Practical management of advanced prostate cancer

Fadi El Karak[1-2], Jean-Pierre Droz[2].

(1) Massachusetts General Hospital, 55 Fruit street- Boston- MA02114; Email:colodine@hotmail.com
(2) Léon Bérard Cancer Centre, 28 Rue Laennec, 69008- Lyon- France; Email:droz@lyon.fnclcc.fr

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Abstract

Prostate cancer is the most common cancer in men and the second leading cause of cancer death in this population. Androgen deprivation is the basis of first line treatment for advanced prostate cancer providing disease control in over 80 percent for a median duration of 18 months. This can be achieved by either bilateral orchiectomy or LH-RH agonist administration. Complete androgen blockade provides similar survival benefit when compared to LH-RH agonist alone, however with a higher incidence of side effects and thus it is not recommended as a standard first line treatment for advanced disease. Early hormonal suppression is mandatory since it reduces the risk of progression and cancer related complications. Continuous hormonal suppression is the most acceptable mode of LH-RH agonist administration. Second line hormonal manipulation has generally low response rate. It includes the addition of anti-androgen, estrogens, aromatase inhibitors or ketoconazole. LH-RH agonists must be continued during the second line hormonal treatment and the hormone refractory phase. Two chemotherapeutic agents have been approved in hormone refractory prostate cancer (HRPC): mitoxantrone and docetaxel. Three- weekly Docetaxel and prednisone is currently the standard of care chemotherapy treatment for first line HRPC. The adjunction of Zoledronic acid should be considered for metastatic bone disease.

Introduction

Prostate cancer is the most common malignancy in men [1]. The incidence of prostate cancer increased dramatically in the early 1990s and surpassed that of lung cancer [1]. These changes resulted from prostate-specific antigen (PSA) screening that detected many early-stage prostate cancers [2-3].

Advanced prostate cancer is an incurable disease and treatment objective is only palliation. The major observation is that prostate cancer is a hormone-sensitive tumor. Median duration of hormone sensitivity is 18 months. Progression of prostate cancer from the hormone sensitive to the hormone resistance status occurs in all patients with advanced disease. This article is focused on the practical hormonal and chemotherapeutic options for patients with advanced prostate cancer.

Hormone- sensitive stage

Mechanism of action of anti androgen therapeutics.

Prostate normal and malignant cells are sensitive to androgens. There are two major sources of androgens: testicles which produce testosterone (95% of all androgens) and adrenal glands (dehydroandrosterone, dehydroandrosterone sulfate and androstenedione). Testicles and, to a lower extent, adrenal glands are under the control of the anterior lobe of the pituitary. Luteinuzing hormone (LH) stimulates testosterone production by testicles. LH secretion is under the control of hypothalamic LH-RH (LH-releasing hormone). Production of LH-RH is pulsatile. It is reduced as a function of the serum testosterone level (feed-back mechanism).

There are specific androgen receptors on normal and malignant prostate cells which allow the internalisation of testosterone. Testosterone is then transformed into dihydrotestosterone (DHT), the active form of the hormone, which is translated into the nuclear and induces cell proliferation [4] (figure 1).

Huggins and Hodges were the first to demonstrate that castration and oestrogen injection had therapeutic activity in men with metastatic prostate cancer [5-6]. Hormonal suppression options include orchiectomy, the most simple androgen suppressor, LH-RH antagonists, steroidal and non steroidal androgen blockers and estrogens (figure1). The different mechanisms of action for hormone manipulation drugs are listed in table 1. The major side effects of hormone suppression are loss of potency. Other toxicities are shown in table 1. A particular side effect of LH-RH agonists is the flare syndrome which must be prevented [7]. At the beginning of treatment with LH-RH agonists, a surge of LH, and a secondary increase of serum testosterone level is observed. This may induce pain increase and, more importantly, tumor growth with bladder retention, and spinal medulla compression. It can be prevented by anti-androgens administrated 15 days before the first injection of LH-RH agonist [8-10]. Long-term hormone suppression results in osteoporosis. This phenomenon has been well demonstrated in patients who receive hormone suppression for local-stage prostate cancer without bone metastasis. These patients have elevated markers of osteoporosis: osteocalcin pro-collagen, C-terminal propeptide, and collagen C-telopeptides and their estimated risk of fracture is 5% [11].

First-line hormone suppression: principles.
The basis of first-line hormone suppression is castration by either bilateral orchiectomy or LH-RH agonist administration [12]. Three questions are important at this stage: what is the role of complete anti-androgen blockade (CAB)? What is the optimal timing of hormonal suppression? And what is the optimal duration of treatment?
As for the first question, different trials were designed to study the impact of anti-androgen addition to castration or LH-RH agonist [13- 23]. Only several trials included a sufficient number of patients. One American Intergroup trial, which compared leuprolide with and without flutamide, demonstrated a significantly longer progression-free survival and median overall survival in the group of patients who received CAB [14]. However, further large-scale trials failed to demonstrate such a significant difference even when trials were designed to study good-prognosis patients [23]. Meta-analysis published in Lancet included 8275 patients from 27 randomized trials, 88 % of patients had metastatic and 12 % locally advanced disease; the median age was 70 years and the median follow-up was 5 years. A 1.8 % 5-year survival gain was observed with CAB but failed to reach statistical significance. Patient on CAB present more significant side effects [24]. Consequently, CAB cannot be recommended as standard treatment of metastatic prostatic cancer.
To respond to the second question, a Bristish randomised trial has demonstrated a slight impact of immediate versus deferred hormone suppression in advanced prostate cancer [25]. The majority of patients had non metastatic but locally advanced disease (55%) at the time of randomisation. Patients of the deferred treatment group were treated when clinically significant progression occurred. All events occurred more rapidly in the deferred treatment group: progression from Mo to M1 disease, development of pain, need for transuretheral resection for local progression, pathological fractures, spinal cord compression, ureteric obstruction, and development of visceral metastases [25]. These data represent clear evidence that early androgen suppression is a must in patients with metastatic prostate cancer or locally advanced disease who have failed local treatment.
Androgen blockade must be continued indefinitely. Intermittent treatment consists of stopping the hormonal treatment when PSA reach its nadir level (6 to 9 months). Reintroduction of hormonal blockade could be done when symptoms reappear or when PSA reach 10 to 20 ng/ml. The aim of this intermittent treatment is to delay the occurrence of androgen-refractoriness and to decrease adverse events of hormone suppression [26]. Different phase II trials have been published [27- 34]; phase III trials are on-going [35-36]. This treatment option could be considered for patients with metastatic asymptomatic disease who have cancer responsive to hormonal treatment, aged more than 70 years with lower tumour volume or aged less than 70 years with Gleasson score less than 6. This type of treatment is not still standard [37].

Second line hormone-therapy.
Second line hormonal manipulation has generally low response rate ranging from 10 to 20%. The most frequently used further hormone therapy lines are: addition of anti-androgens, inhibitors of aromatase, estrogens, or Ketokonazole. Estramustine phosphate must be considered as a chemotherapeutic agent, even it is partly composed of estrogen molecule, because it acts as an inhibitor of microtubules and it is more active when combined to other cytotoxic drugs. If patients are treated with CAB, the anti-androgen agent must be stopped [38-39].
The observation of the development of gynecomastia in patients treated by ketoconazole for fungal infection set the stage for a totally new application for this drug. Oral Ketoconazole reduces serum testosterone to the castrate level range. In addition, the adrenal androgens androstenedione and dihydroepiandrosterone are dramatically reduced. The effect is due to an interaction with cytochrome P450-dependent enzymes active in the sex steroid-synthesizing organs [40-41]. The CALGB 9583 phase III study randomized 260 patients at the time of progression on combined androgen blockade to undergo either antiandrogen withdrawal (AAWD) simultaneous with ketoconazole or AAWD followed by ketoconazole at the time of PSA progression. The PSA response proportion to those undergoing antiandrogen withdrawal alone was 13% compared with 30% in the combination arm ($P < 001$). Fourteen percent of patients treated with ketoconazole/AAWD experienced objective responses. Overall survival in the two arms was not different approximatively 16 months, however this study allowed cross over and 108 (82%) of 132 of patients who were randomly assigned to AAWD eventually did receive ketoconazole. These data confirmed that ketoconazole is an active drug and may be considered an acceptable secondary hormonal therapy [42].

Hormone-resistant stage

Progression of prostate cancer to the hormone refractory status is a universal phenomenon which is not well understood. It may result of altered structure or expression of androgen receptors, altered androgen receptor signalling and interactions with other signal transduction pathways which possibly involve growth factor receptors [43]. Occurrence of hormone refractoriness is the major event during metastatic prostate cancer evolution.

Hormone resistance is clinically expressed in different situations: serum PSA level increase, progression of metastases, progression of pain and other symptoms while hormone deprivation is continued. Physicians must not forget that LH-RH antagonists must be continued during hormone refractory stage.

Chemotherapy

Chemotherapy was studied very early, in the 70s-80s, particularly in the setting of the National Prostate Cancer Project (NPCP) group [44]. Actually, only two cytotoxic agents are approved by the United States Food and Drug Administration for palliative treatment of HRPC. These are mitoxantrone and docetaxel.

Two corner-stone studies for mitoxantrone have been performed [45-46]. Both studies compared prednisone alone versus prednisone plus mitoxantrone. The trial designs were different: the Canadian study was designed to demonstrate a palliative advantage of mitoxantrone [45], the American CALGB study was armed to demonstrate a survival advantage [46]. Both studies failed to demonstrate any survival advantage. CALGB study randomly assigned 242 men with HRPC (65 percent of whom were taking analgesics for bone pain) to mitoxantrone (14 mg/m2 IV every three weeks) plus hydrocortisone (40 mg daily) or the same dose of hydrocortisone alone. Median survival was similar (approximately 12 months in both groups), and pain control was significantly better with combination therapy. Although the greater PSA response with combined therapy (38 versus 22 percent) achieved statistical significance, it was quantitatively similar to the earlier study, and the median time to disease progression was short in both groups (3.7 and 2.3 months, respectively) [46]. Another confirmatory study in asymptomatic patients showed a significantly prolonged PFS in the mitoxantrone arm but failed to prolong survival, its primary objective [47]. These study set mitoxantrone as standard first line treatment for hormone refractory metastatic prostate cancer.

Multiple phase II trials have tested the efficacy and toxicity of docetaxel in HRPC with weekly or three weekly regimen [48-54]. The TAX 327 trial published by Tannock in 2004 was the basis for the shifting of standard from mitoxantrone to docetaxel [55]. In this study, 1006 men with chemotherapy-naive metastatic HRPC were randomly assigned to docetaxel 75 mg/m2 every three weeks (D/P), or docetaxel 30 mg/m2 weekly
(WD/P)or mitoxantrone 12 mg/m2 every three weeks (M/P), with all patients receiving prednisone 5 mg orally twice daily. The primary endpoint was overall survival. At a median follow-up of 21 month, patients receiving every three week had a significantly longer median survival 18.9 when compared to the weekly docetaxel arm 17.4 months or the mitoxantrone arm 16.5 months. Moreover, three weekly docetaxel had a higher pain response rate (35 versus 31 versus 22 percent). As expected, grade 3 or 4 neutropenia during therapy was most common with D/P (32 versus 1.5 and 22 percent with wD/P, and M/P, respectively), although rates of neutropenic infection were low (3 versus 0 and 2 percent, respectively), and few patients discontinued therapy because of adverse effects (11, 16, and 10 percent with D/P, wD/P, and M/P, respectively). With longer follow-up, the survival benefit of every three week docetaxel has persisted (median survival 19.3 versus 16.3 months for mitoxantrone/prednisone). The corresponding three year survival rates were 18 versus 14 percent [56].
Another trial compared the combination of docetaxel and estramustin to mitoxantrone and prednisone and similarly showed a mild but significantly survival benefit of the docetaxel/estramustin arm [57]. This treatment arm was also associated with significantly more grade 3 or 4 gastrointestinal, cardiovascular, metabolic, and neurologic toxicity. Although these results confirm the superiority of docetaxel/Estramustin over mitoxantrone/prednisone, it is difficult to endorse the continued use of Estramustin in view of the similar survival benefit and better tolerability of docetaxel plus prednisone compared to mitoxantrone/prednisone in the TAX-327 study, and the elevated risk of venous and arterial thromboembolism in patients receiving Estramustin.
Vinorelbine was also evaluated in a phase III trial [58]. Patients with metastatic prostate cancer, progressive after primary hormonal therapy, were randomised to receive intravenous vinorelbine (VRL) 30 mg/m2 on days 1 and 8 every 3 weeks, and hydrocortisone (HT) 40 mg/day or hydrocortisone alone until disease progression. Second line hormonal manipulation was allowed for all patients. PFS was significantly prolonged in the VRL plus HT arm compared with the HT alone arm (p= 0.055). Clinical benefit, defined as a decrease in pain intensity or analgesic consumption or an improvement of Karnofsky PS for at least 9 weeks, and at least stable assessment in the other two, was also more frequently observed in patients who received VRL plus HT versus HT alone (30.6% and 19.2%; P = 0.008). There was no statistical difference in overall survival. This therapeutic gain is similar to that previously reported with mitoxantrone in combination with low-dose corticosteroids. The authors concluded that the combination Vinorelbine/HT is well tolerated in this elderly group of patients, who often present cardiac co-morbidities, and therefore offers an active and safe therapeutic option for patients with hormone-refractory prostate cancer.

One particular problem is the evolution of hormone-refractory prostate cancer through neuro-endocrine components. Patients with such evolution generally have visceral metastases, low serum PSA level, increase of neuro-endocrine markers (neurone-specific-enolase, chromogramin A). Specific protocols based on platin analogues, etoposide and taxanes have been developed [59]. Response rate is 30-40%. However no trial has demonstrated any impact of chemotherapy on patients survival.

Biphosphonates treatment

Bisphosphonates are pyrophosphate analogs that inhibit bone resorption. Zoledronic acid (Zometa, Novartis Oncology) is a highly potent intravenous bisphosphonate that is

approved for the treatment of patients with documented bone metastases from solid tumors, in conjunction with standard antineoplastic therapy. Patients with prostate cancer are at high risk of bone complications since the most frequent site of metastasis in prostate cancer is bone and since ADT is associated with osteoporotic effects. Preventing the adverse skeletal effects in prostate cancer is increasingly important, because these patients have relatively long life expectancies.

Zoledronic acid was compared with placebo in prostate cancer patients with a history of metastatic bone disease who had a rising serum PSA level despite treatment with ADT in a randomized, double-blind clinical trial [60]. Zoledronic acid demonstrated a 25% reduction in the proportion of patients with a skeletal-related event (P = .021). The time to the first skeletal-related event was at least 100 days later in patients receiving zoledronic acid compared with patients receiving placebo (P =.01). These improvements with zoledronic acid are clinically significant and offer a new therapeutic strategy in prostate cancer patients with skeletal metastases.

Conclusion

Advanced prostate cancer is an incurable disease and treatment must be focused on palliation of symptoms. In the hormone sensitive stage, castration by either bilateral orchiectomy or LH-RH agonist administration is the cornerstone of treatment. CAB is an option but does not have a survival benefit comparing to LH-RH agonists alone. Early continuous androgen suppression is the most acceptable mode of LH-RH agonists administration however future trials evaluating intermittent treatment are awaiting to completely answer this question. In the hormone refractory stage, three weekly docetaxel and prednisone is the standard of care. Biphosphonate must be added to the arsenal treatment especially in this category of patients at high risk of bone related complications.

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TABLES

Table 1. Hormone treatments in prostate cancer: mechanisms of action and side effects.

Drug	Mechanism of action	Side effects
	LH-RH agonists	
Leuprorelin Goserelin Buserelin Triptorelin	- negative feed-back of pulsatile secretion of LH - initial LH surge	- flare-up syndrom - loss of potency - hot flushes
	Non steroidal antiandrogens	
Flutamide Bicalutamide nilutamide	- competitive blockade of DHT to receptors	- diarrhea - hepatotoxicity - flushing reactions - hemeralopy - pulmonary fibrosis
	Steroidal antiandrogen	
Cyproterone acetate	- inhibition of LH release - competitive blockade of DHT to receptors	
	Oestrogens	
Diethyl-stilbestrol Fosfestrol	- inhibition of LH release - inhibition of 5 ∝ reductase activity - direct cytotoxic effect	- loss of potenty - gynecomastia - thromboembolism

FIGURES

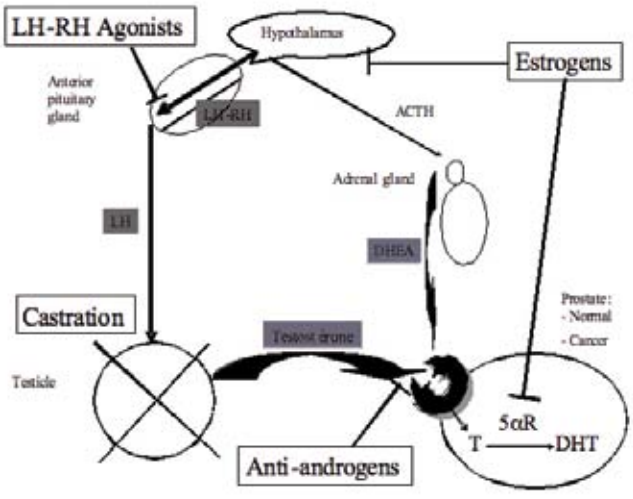

Figure 1

A cost-minimization analysis of first line polychemotherapy regimens in the treatment of advanced non small cell lung cancer

Robert Launois[1-2], Katell Le Lay[1], Nicolas Chemali[3], Alain Vergnenegre[4]

(1) REES France (Réseau d'Evaluation en Economie de la Santé); (2) Université de Paris XIII, France; (3) Eli-Lilly France ; (4) Service d'Information Médicale, CHU de Limoges, France.

✉ *Corresponding author : Robert Launois, MD; REES France, 28 rue d'Assas, 75006 PARIS, France; Email: reesfrance@wanadoo.fr*

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PAJO is glad to publish this valuable study aiming to determine, using the example of metastatic non small cell carcinoma of the lung, which case management minimizes costs for the French Health Care System while ensuring patient safety.

The American Society of Clinical Oncology (ASCO) announced on March 26, 2008, that they are preparing guidelines for physicians on discussing cost-of-treatment options with patients. In fact, the cost of oncology care is an important topic that is often ignored, but with the explosion of costs of emerging therapeutics and patients living longer, and therefore needing longer periods of treatment, the cost of treating cancer is rising by 15% annually.

In another hand, it is important to note that recently new and expensive drugs are approved even with as low as 3% response rates that improve survival by 2 to 6 weeks.

Unfortunately, we don't have in our countries cost-effectiveness thresholds followed for treatments' decisions. Those put by the National Institute of Health and Clinical Excellence (NICE) in the UK to accept or reject drugs should also be revised and adapted to each Healthcare system in the light of this cost explosion.

Abstract

Objectives

Five polychemotherapy regimens, one of which may be given by two different administration schedules: gemcitabine-cisplatin (GC), vinorelbine-cisplatin (VC), docetaxel-cisplatin (DC), paclitaxel-cisplatin (PC) and paclitaxel-carboplatin (PCa), are commonly used in first-line treatment of advanced non-small cell lung cancer. Whereas taxans have to be administered within a conventional day-hospitalisation setting, gemcitabine and vinorelbine can be administrated in a domiciliary care setting. The purpose of the study is to determine which case management minimises costs for the French Health care system while ensuring patient safety.

Methods

A Markov model was constructed in order to estimate the cost consequences of domiciliary administrations for gemcitabine and vinorelbine chemotherapies without cisplatin, compared to taxans administrated only at hospital. Transition probabilities are based on the Scagliotti (2002), Fossela (2002), Smit (2003), published randomised trials. No differences in efficacy were found between any of the regimens. A cost-minimisation analysis was performed. The costs of treatments were calculated by adding DRG costs, high cost drugs reimbursed beyond the DRGs, and travel expenses. Costs of severe toxicities, diagnosis and palliative care are included.

Results

With the conservative hypothesis that the treatments do not differ in efficacy and with no more than two domiciliary administrations per cycle, GC and VC emerge as the least expensive regimens with a follow-up costs of 7,315 € [95% CI: 7,064-7,570] and 7,686 € [95% CI: 7,378-7,997]. Administrated within a conventional day-hospitalisation, their follow-up costs are 8,109 [95% CI: 7 799 – 8 419] and 8,943 €, [95% CI: 8 554 – 9 338] respectively. Taxans DC, PC and PCa at hospital have a follow-up costs of 8,778 € [95% CI: 8,185-9,108], 9,068 € [95% CI: 8,367-9,446], and 10,140 € [95% CI: 9,436-10,510]. To obtain the same overall costs for GC and DC, the acquisition cost of gemcitabine has to be increased by 50%.

Conclusion

Following the national guidelines on chemotherapy domiciliary care infusion, out of hospital treatment is more efficient in the context of equivalent efficacy from the French health care system perspective.

Introduction

Lung cancer is mostly attributed to smoking and is the leading cause of death in men and the fourth leading cause of death in women in Europe, with 1,000,000 new cases and 921,000 deaths each year throughout the world[1]. Non-small cell lung cancer (NSCLC) is the commonest form, diagnosed in 80% of cases. Only 25% of these patients have an operable tumour, and have a 5 year survival rate of 30-40%. Patients presenting with locally advanced cancer (stage III) or metastatic cancer (stage IV) are treated by chemotherapy and/or radiotherapy or receive palliative care. Their 5 year survival rate is no more than 4-8%, or even less than 1% for stage IV patients. Four phase III trials have demonstrated the survival benefits of treatments associating "classical" platinum salts and third generation drugs[2-19]: gemcitabine, vinorelbine and taxans, compared to cisplatin alone[2,3] or to the older double or triple therapy regimens with cisplatine[4-6] such as vindesin-cisplatin, etoposide-cisplatin or mitomycin-ifosfamide-cisplatin. Six of these protocols are now widely used for the first line treatment in the indication: gemcitabine-cisplatin (GC) which may be administered over three or four weeks, vinorelbine-cisplatin (VC), docetaxel-cisplatin (DC), paclitaxel-cisplatin (PC) and paclitaxel-carboplatin (PCa). The first two associations may be administered alternately at home. The other, taxan-based associations must be used in hospital. The aim of this study is to identify the type of management which optimises expenditure for the health care system, at the same time offering patients the greatest safety.

Methods

Comparators and Administration Regimens

No trials compare the six protocols head to head. The Schiller[7] (2002) trial allows results obtained with the associations gemcitabine-cisplatin (GC 4 week), paclitaxel 135 mg/m2-cisplatin (PC 135 mg/m2), paclitaxel-carboplatin (Pca) and docetaxel-cisplatin (DC) to be compared although the protocol used for gemcitabine 1000 mg/m2 D1, D8 , D15 followed by a one week washout has now become obsolete because of its toxicity and the dosage used for paclitaxel is different to the dosage for which the drug was granted its European MA (175 mg/m2). Scagliotti[9] (2002) examined the treatment benefits and toxicities of gemcitabine-cisplatin over 3 weeks at the recommended dose of 1250 mg/m2 (GC 3 weeks), vinorelbine-cisplatin and paclitaxel-carboplatin. In the Fossela trial[10] (2003), vinorelbine-cisplatin was the comparator which was used to assess the merits of two possible associations of docetaxel with carboplatin(DCa) or cisplatin(DC) although no combination containing gemcitabine or paclitaxel was studied in this trial. Smit's trial [11] (2003) shows the reverse approach and directly compared the three week gemcitabine-cisplatin protocol with the associations paclitaxel-carboplatin(PCa) and paclitaxel 175 mg/m2-cisplatin (PC) although this trial did not contain either a vinorelbine-cisplatin arm or the docetaxel-cisplatin association.

The 3 protocols in the Scagliotti trial were compared indirectly with the other three associations currently available to clinicians using the 4 week gemcitabine-cisplatin arm from the Schiller 2002 trial[7], the docetaxel-cisplatin arm from the Fossella trial[10] (2003) and the paclitaxel-cisplatin arm from the last trial conducted by EORTC in this indication, which used doses of paclitaxel of 175 mg/m2, consistent with the MA doses permitted in France (Smit 2003[11])

The different administration regimens and type of management are shown in figure 1.

Scagliotti[9] describes a mean treatment period of 4 cycles, i.e. 12 weeks for gemcitabine-cisplastin and 3.2 and 4.2 cycles, i.e. 12.8 and 12.6 weeks respectively for vinorelbine-cisplatin and paclitaxel-carboplatin (rounded off to 13 weeks of treatment in the model). The other trials described duration of treatment by the median number of cycles. The median treatment periods were 5 cycles, i.e. 15 weeks for both docetaxel-cisplatin and for paclitaxel-cisplatin in Fossela[10] and Smit[11].

Modelling

Each of the types of management was analysed by a cyclical Markov tree process[25-26] in which a cohort of patients goes repetitively into a defined number of mutually exclusive states of health. Thirteen states were distinguished from purely clinical criteria: treatment induction (T100), treatment drop-out (DO), remission at the end of the tumour staging assessment (REM) or treatment escape (Progressive Disease - PD) and death (D). Three severe toxicities were identified: febrile neutropaenia (FN1, FN2), thrombocytopaenia requiring blood transfusion (TP1, TP2) and severe nausea and vomiting, (NV1, NV2). Two specific states were associated with reducing doses by 25 or 50% (T75 and T50) after these toxicities had occurred. As the length of chemotherapy cycles in weeks differs between cytotoxic agents, the lowest common time denominator was used to define the pace of the model, which was constructed on the basis of weekly cycles with a modelling time of 52 weeks.

The tree begins with a decision node (figure 2). The six branches coming from this node represent the competing treatment options. The Markov node represented by a circle containing the letter M indicates application of a Markov process. Each branch leading from the node represents a state. The patients' status at the beginning of cycle 2 is influenced by the probabilities of each of the states onto which they branch. At each course, treatment is stopped for patients who die, enter progressive disease or drop out of treatment whereas those in remission or without a dose reduction receive a further course of the same chemotherapy until disease progression.

Each clinical state the patient may pass through is associated with a disease management cost and a binary result value of 1 for survivors or survivors without relapse and 0 for

death or progressive disease. At the end of the model the follow up costs per patient of the six treatment options can be calculated and compared from their cumulative costs.

Transition Probabilities

The number of patients moving from one clinical state to another and from one cycle to another was quantified using a set of transition probabilities calculated from published data.

The likelihood of death or relapse per week were obtained using the DEALE method[27-29] from the median global survival (GS) and time to progression (TTP). Median global survival is the time during which 50% of patients have not died because of an event since starting chemotherapy. The mortality rate per cycle μ is therefore equal to -(Ln 0.5) / GS. The proportion of patients who survive at the end of a cycle is expressed as $\exp^{-\mu * 1}$, and the probability of dying during the cycle (pDeath) is equal to $1 - \exp^{-\mu * 1}$. The probability of surviving during the cycle (pSurvival) is obtained by calculating its compliment $1 - (1 - \exp^{-\mu * 1})$. In the same way, the median time to progression is the time after which 50% of patients do not have progressive disease or did not die because of cancer or an adverse event occurring since starting the chemotherapy. The progressive disease or death rate per cycle (μ) is therefore equal to -(Ln 0.5) / TTP. The probability of not continuing treatment during the cycle because of progressive disease or death is equal to $(1 - \exp^{-\mu * 1})$. In order to calculate the probability of developing progressive disease (pD) over the same time period we subtracted the specific probability of dying from a cancer from the probability of not being able to continue treatment. The probability of relapse alone per cycle is therefore equal to p(Relapse or Death) – pDeath or pD = $(1 - \exp^{-(\text{Ln } 0.5/\ \text{TTP}) * 1})$ – pDeath.

Adverse events and drop-outs during trials are usually described by their cumulative incidence P(to, t) between the beginning and end of chemotherapy. The probability of a patient developing an adverse event or stopping treatment in each of the weeks following administration was estimated using a simplified form of the actuarial method[27] for calculating cumulative probabilities. Assuming the frequency at which toxicities to be constant over time, the cumulative incidence observed during the treatment period can be converted to a weekly incidence using the equation $Pi = 1-[1-P(to, t)]^{1/j}$ where to and t are the start and end of treatment, and j is the number of calendar periods (weeks) contained within the treatment follow up period for the trials published.

Efficacy Data

The parameters needed to model the clinical course of a patient on treatment (response rate; global survival and disease free survival) were extracted from four landmark trials: Schiller [7] (2002), Scagliotti[9] (2002), Fossela 2003[10], Smit 2003[11], (table 1).

No difference in efficacy in terms of survival was found in the Scagliotti trial[9] (2002) which compared gemcitabine-cisplatin 3 weeks, vinorelbine-cisplatin and paclitaxel-carboplatin or in the Schiller trial[7] (2002), in which the gemcitabine-cisplatin 4 weeks, docetaxel-cisplatin, paclitaxel-cisplatin, and paclitaxel-carboplatin all produced the same results. In the article by Fossela[10], docetaxel cisplatin had a higher global survival than vinorelbine-cisplatin (49 weeks versus 44 weeks, p=0.044). Smit's trial directly compared the gemcitabine-cisplatin three week protocol with the associations paclitaxel-carboplatin and paclitaxel-cisplatin and found no significant difference in survival between the three arms.

The median time to progression (TTP) may be a more relevant criterion of efficacy for treatments that are ultimately not curative. Published figures vary little between the drugs: Scagliotti's trial[12] showed no difference in terms of disease free survival. Schiller[7] found a significant difference for this criterion between gemcitabine-cisplatin and paclitaxel-cisplatin (18 and 15 weeks, p<0.001) but no difference compared to the other two comparators docetaxel-cisplatin and paclitaxel-carboplatin. The confidence interval for this end point overlaps with those of the three comparators in the Fossela trial. Smit's trial showed a significant difference for this parameter between paclitaxel-carboplatin and paclitaxel-cisplatin, but none between gemcitabine-cisplatin or paclitaxel-cisplatin.

Prudence and reality lead us to assume that in this context all of the drugs are similar in efficacy. In conducting this cost minimisation study we have used the same efficacy data for all treatment options: those published for gemcitabine-cisplatin three weeks in the landmark trial by Scagliotti 2002[9].

Toxicity Data

The incidence of febrile neutropaenia, thrombocytopaenia requiring blood transfusion and severe nausea and vomiting used in the model to describe the severe toxicities associated with the gemcitabine-cisplatin 3 weeks, vinorelbine-cisplatin, and paclitaxel-carboplatin protocols were obtained from the Scagliotti[9] trial. The toxicity rates for the other three associations: gemcitabine-cisplatin 4 weeks, paclitaxel-cisplatin and docetaxel-cisplatin were taken from the corresponding arms for each of these protocols in the Schiller[7], Fossela[10] and Smit[11] trials. For each of these treatment options we used the severe toxicity rates reported in the published trials (Schiller's[7] data for the gemcitabine-cisplatin 4 week administration regimen, toxicity incidence from Fossela[10] for docetaxel-cisplatin, and from Smit[11] for the paclitaxel-cisplatin arm).

These side effects lead to treatments being stopped or reduced/doses being omitted. The drop-out rate on vinorelbine-cisplatin is higher than for gemcitabine-cisplatin (23% vs 13% from Scagliotti[9], p< 0.02) and the incidence of dose reduction/omission is higher than is seen

with gemcitabine-cisplatin (17% / 19% vs 12 % / 6%) or found in the paclitaxel-carboplatin and paclitaxel-carboplatin arms (13% / 0%).

Evaluation of Costs

Chemotherapy administration costs in hospital or at home and the costs of any complications were estimated from the perspective of the French health care system in 2004. Resources used in hospital for each course of chemotherapy were calculated using a PMSI approach by summating the DRG tariff "chemotherapy for less than 48 hours" from classification v9.0 and the price of high cost compounds paid additionally in the context of the T2A (tariff based activity)[31-32]. The costs of chemotherapy in domiciliary care were estimated using the hospitalisation at home (HAH) tariff model [33]. Direct and indirect non-medical costs were excluded from the scope of the analysis.The most appropriate DRG was sought in order to calculate the costs of managing the 3 groups of severe toxicities studied, incorporating the cost of tumour diagnosis and palliative care in cases of progressive disease into the model [34]. Patient transport costs between home and hospital were also included.

Acquisition Cost for High Cost Substances

The five compounds studied appear on the "high cost drug list" published with their reimbursement rates by UCD in the Official Journal on 31 December 2004 [37-39]. These tariffs are the same as the sales price stated by the pharmaceutical companies and form the basis of a calculation set by the Health Products Economic Committee (CEPS), where applicable, and should be increased by 2.1% for VAT. Vinorelbine and gemcitabine can also be dispensed to a private domiciliary care organisation for home administration 38 by an in-house pharmacist (IHP) authorised by hospitals. A clinician margin of 15% per prescription is then added[39].

Injectable cytotoxic drugs, either ready to use or for reconstitution, require individualised dose adaptation for each patient. For centralised preparations[40], the packaging units are fractionated and the amounts to be administered calculated in milligrams and dispensed as bags. The amounts of each cytotoxic agent and corresponding acquisition costs were therefore calculated in milligrams from the recommended dosages, using a mean body surface area of 1.75m2.

The cost of the substances used in day hospitalisation were 133 € for vinorelbine administered at a dose of 25 mg/m2, and 357 € and 447 € for gemcitabine depending on whether the 1000 mg/m2 or 1250 mg/m2 doses are used, in the day hospital. The acquisition costs for docetaxel 75 mg/m2, paclitaxel 175 mg/m2 and paclitaxel 225 mg/m2 are 1,179 €, 1,329 € and 1,709 € respectively.

For public hospitals having a domiciliary care organisation (HH), the acquisition costs for vinorelbine, gemcitabine 1000 mg/m2 and gemcitabine 1250 mg/m2 were 133€, 357 € and 447 € respectively in 2005. When administered in private HH their prices increased to take account of commission are 157 €, 411 €, 514 €. In order to obtain a mean tariff for all establishments combined we applied the distribution of public and private domiciliary care observed in the IRDES study of 42.8% and 57.2% to each of the public and private home hospitalisation (HH) tariffs. All types of establishment combined, the weighted acquisition costs of the chemotherapies were 144 €, 388 € and 485 € per administration.

Acquisition Cost for High Cost Substances

The DRG "Chemotherapy for less than 48 hours" is valued in the T2A 2005[32] list of hospital stay, services and care at 421.74 € (DRG 8300 "Chemotherapy session"). The cost of travel between home and hospital is added to the chemotherapy administration cost for each course. Taking account of the different methods of transport used: sanitary transport vehicle, ambulance, taxi and own vehicle, the respective proportions in which these vehicles are used: 20, 25, 26 and 29% [31-32] the regional charges applicable to health transport, the mean price per km for the different vehicles used and the 6-7 CV kilometre charge (2004) paid for the use of private vehicles, the average return cost of all transportation methods was estimated to be 82.97 € based on an average estimated distance of 30 km between home and hospital.

Once the return transport costs, additional payments and the hospital stay cost are added, the cost of the chemotherapy course was 640 € for vinorelbine 25mg/m2, and 782 € and 871 € for gemcitabine 1000 and 1250 mg/m2. The costs of docetaxel 75 mg/m2, paclitaxel 175 and 225 mg/m2 were 1,603 €, 1,753 € and 2,133 € respectively.

Cost of Chemotherapies in Domiciliary Care

The tariffs for organisations and establishments providing domiciliary care have recently been defined in the regulatory and legislative activity based tariff structure[33]. The sums for the 31 daily stay and care payments called Tariff Reference Groups is obtained from the weightings attached to the approved five variable combinations: main type of management, where applicable an additional method of management, level of dependency measured by the Karnofsky index, length of hospital stay and status of the establishment. The daily tariff for a domiciliary care visit with chemotherapy and pain treatment for a typical patient with mild dependency (Karnofsky index 70-80%), managed for less than 5 days was 198.1 € in 2004 in a public establishment and 197.83 € in a private profit-making establishment. The weighted daily tariff all types of the establishment combined in 2004 was 197.94 €.

The total cost of home chemotherapy to the health care system after adding the cost of the cytotoxic agents[37], the cost of domiciliary care and that of the initial consultation with the general practitioners (20 €) is 362 € for vinorelbine, 606 € for gemcitabine 1000 mg/m2 and 703 € for gemcitabine 1250 mg/m2.

Costs of Severe Toxicities

DRGs 6152, 8306 and 2104 are the groups most closely equivalent to the management required for febrile neutropaenia, haematological disorders requiring blood transfusion and severe gastro-intestinal disorders. A return home-hospital transport cost has been added to each of the tariffs. These "cost bundles" are used each time a patient passes into the given state of health for each adverse event occurring in the model.

At the beginning of the model, a diagnostic cost of 3,793.28 € for non-small cell lung cancer was applied to the entire cohort as DRG 1112 "Respiratory system tumours" added to which were home-hospital transport costs of 82.97 €. Hospital palliative care costs were also added for patients leaving the model for progressive disease, using DRG 7986 equivalent to a tariff of 6,464.8 € and home- hospital ambulance transport cost of 193 €.

Ranking of Strategies

In the absence of a statistically significant difference between the major efficacy criteria, the six treatment options were firstly compared and ranked for equivalent efficacy using the follow up cost of a patient treated exclusively in hospital as the major end point. The cost minimisation study was conducted by allocating the same clinical results as those seen for gemcitabine-cisplatin in the Scagliotti[9] trial (GS: 42 weeks, TTP: 23 weeks, treatment drop-out: 13%), to each of the associations, retaining the severe toxicity rates reported for each of the arms of the trials examined indirectly for each treatment option and each administration regimen: Scagliotti[9] frequencies were used for toxicity due to gemcitabine-cisplatin 3-weeks, vinorelbine-cisplatin and paclitaxel-carboplatin. We used the toxicity data from Schiller[7] for gemcitabine-cisplatin 4 weeks, those of Fossela[10] for docetaxel-cisplatin, and those of Smit[11] for paclitaxel-cisplatin. Vinorelbine and gemcitabine can be administered as domiciliary care when they are not associated with cisplatin, unlike the taxans which are reserved for hospital use. Two administration regimens with a reduced hospital management frequency were considered for these 2 drugs, involving either a day hospitalisation on alternate weeks or hospitalisation only at the start of the cycle. The six treatment options were ranked for the three possible modalities using the respective cost of each protocol to the health care system as the major end point.

Determinist Sensitivity Analysis

The toxicities of the gemcitabine-cisplatin arm in the Smit trial[11], the vinorelbine-cisplatin arm in the Fossella trial and the taxan arms in the Schiller[7] trial, which were not used in the general comparison of the six protocols, were re-introduced into the sensitivity analysis. The aim was to confirm that differences in costs in the central model based on the Scagliotti[9] results and on an indirect reconciliation of the arms extracted from the three different trials would re-emerge when the toxicity data obtained from the direct comparisons: vinorelbine-cisplatin and docetaxel-cisplatin (Fossella[10] 2002) or gemcitabine-cisplatin 3 weeks and paclitaxel-cisplatin (Smit 2002) were re-introduced into the analysis. The treatment drop-out rate of 23% seen by Scagliotti for vinorelbine-cisplatin was used alone and in combination with the Smit toxicity data[11] for gemcitabine-cisplatin and paclitaxel-cisplatin and Fossela's data[10] for vinorelbine-cisplatin. These represent the upper limits of the values reported in the literature.

The corresponding weekly probabilities introduced into the model during the first six or eight weeks of treatment before the first tumour staging assessment were calculated from the simplified actuarial method equation[27-28] (table 7). The costs associated with chemotherapy treatment and those of toxicities were distinguished for each of these assumptions. Finally, the least and most favourable assumptions for gemcitabine-cisplatin were regrouped into two scenarios (upper assumption and lower assumption). An analysis was performed excluding the costs of transport added to each course of chemotherapy.

Treatment costs were modified using multiplication coefficients in order to identify increases or falls in cost liable to change the ranking of the treatment options, for equivalent efficacy. We sought to determine the price of Gemzar® at which the follow up costs for a patient treated with gemcitabine-cisplatin would be the same as that of patient treatment with vinorelbine-cisplatin or the association docetaxel-cisplatin.

Probabilitic Sensitivity Analysis

Nine variables in the model have a value which is subject to uncertainty. The other variables of the model either relate to the choices made when it was constructed (for example number of Markov cycles) or to fixed tariff (for example the cost of a day hospitalisation for chemotherapy), or depend on other variables (for example the acquisition costs of vinorelbine which depends on mean patient body surface area and the price of the drug). In order to take these uncertainties into account[41,42] simultaneously, each of these variables was treated as a normal distribution A 5,000 point Monte-Carlo simulation allowed us to determine a confidence interval for each of our results.

In the cost minimisation study we used the same efficacy data for all of the treatment options: the Median Global Survival and Median Time to Progression published in the Scagliotti trial 2002 for gemcitabine-cisplatin. These were 9.8 months [95% CI: 8.6 – 11.2] and 5.3 months [95% CI: 4.4 – 6.3] respectively, i.e. 42.4 weeks [95% CI: 37.2 – 48.5] and 22.95 weeks [95% CI: 19 – 27.3]. Given that the median is the best estimator of mean in large sample sizes43, we can deduce the median values and confidence intervals two standard deviations from the mean as being 3.11 and 2.19 respectively and describe these two efficacy criteria, survival and time to progression, by two parametric distributions (table 6): Distribution (42.4; 3.1122) and Distribution (22.95; 2.1938).

The treatment drop-out probabilities were described by Beta distributions (table 6). The Body Surface area was represented by a parametric distribution of mean 1.75 in which 99% of values were located at ± 20 % from the mean. The IRDES database contains 3,228 domiciliary care organisations of which private institutions make up 1,847 organisations and 1,381 are public organisations. The proportion of domiciliary care organisations in the public sector was described by a beta distribution (3228; 1847).

Transport costs depend on two factors: the distance in kilometres and the type of transport used. The 1997 IRDES report[36] provides a mean distance of between 15 and 45 kilometres. Considering an initial normal distribution around a central value of 30 km and Dirichlet's law stating that the sum of the proportions of the type of transport used is always equal to 1, the cost of transport follows a normal distribution of mean 82.97 € and standard deviation of 12.53 € in a parametric bootstrap analysis.

The probability distributions for the Scagliotti drop-outs and severe toxicities from Scagliotti, Fossela and Smit were used initially to isolate the impact of place of management on costs (table 7). The Beta distributions associated with the various severe toxicity rates seen in the trials were then combined, based on a simple composition rule, the weighted frequency with which they occurred in the population of combined trials population. In Scagliotti for example, 1 out of the 205 patients who received gemcitabine-cisplatin developed febrile neutropaenia compared to 4 out of 160 patients with Smit. The two corresponding Beta distributions (205; 1) and (160; 4) were used in the model with probabilities of 0.56 (i.e.250 / 160+250) and 0.44 (its complement). The following were combined: for gemcitabine cisplatin, the distribution rates from Scagliotti (2002) and Smit (2003); for vinorelbine-cisplatin, the distributions from Scagliotti (2002) and Fossela (2003); for docetaxel-cisplatin the distributions from Fossela (2003) and Schiller (2002), for paclitaxel-carboplatin the distributions from Scagliotti (2002) and Schiller (2002), and for paclitaxel-cisplatin, the distributions from Smit (2003) and Schiller (2002).

Results

Central Assumptions

° Cost of chemotherapies entirely in hospital

At the end of the 52 week model (table 8): gemcitabine-cisplatin administered entirely in hospital as 3 week cycles emerges as the least expensive strategy, with a follow up cost of 8,103 €. The follow-up costs of the associations docetaxel-cisplatin, vinorelbine-cisplatin, paclitaxel-cisplatin, gemcitabine-cisplatin administered over 4 weeks, and paclitaxel-carboplatin, were 8,749 €, 8,949 €, 9,043€, 9,605 € and 9,926 €, respectively, with incremental costs over gemcitabine-cisplatin administered over 3 weeks ranging between 646 and 1823 €.

If transport costs between home and hospital are excluded, the ranking of the strategies in terms of follow up costs changes. Gemcitabine-cisplatin 3 weeks remains the least expensive strategy, with a follow-up cost of 7,537 €, Gemcitabine-cisplatin 4 weeks becomes considerably less expensive because of the savings made from the many visits to hospital required by its administration regimen (7400 € vs 9600 €) and it rises 3 places from its initial ranking. Vinorelbine-cisplatin benefits from the same savings for the same reasons (8060 € vs 8949 €). The difference from the taxans is reduced, with an incremental cost of gemcitabine-cisplatin 3 weeks ranging from 840 € against docetaxel-cisplatin up to 2,048 € against paclitaxel-carboplatin, and to 1143€. against paclitaxel-cisplatin.

° Cost of alternating chemotherapies: Hospital and domiciliary care

The three taxans: docetaxel-cisplatin, paclitaxel-cisplatin and paclitaxel-carboplatin administered in hospital were compared to the three treatment options vinorelbine-cisplatin, and gemcitabine-cisplatin administered at home every two weeks out of 3 or 4. (table 9).

Gemcitabine-cisplatin administered over 3 weeks with alternate administrations at hospital (HH) emerges as the least expensive strategy (7,400 €). The annual follow-up costs for vinorelbine-cisplatin and gemcitabine-cisplatin administered in 4 week cycles with alternative administrations at home were 7,730 € and 9,085 €. Administration of these two compounds at home therefore achieves savings of 703 € and 2,205 € compared to management exclusively in hospital.

The taxans, docetaxel-cisplatin, paclitaxel-cisplatin, paclitaxel-carboplatin, administered exclusively in hospital generate additional costs compared to gemcitabine-cisplatin administered over 3 weeks alternately which are even greater than before, the sums ranging between 1,349 (DC) and 2,526 € (PCa) at hospital and at home.

Management by day hospitalisation at the start of the cycle. A third administration regimen for vinorelbine and gemcitabine was studied. These compounds may be administered as day hospitalisation only on D1 at the start of each chemotherapy cycle, with the other courses being administered at home.

At the end of the 52 week model, vinorelbine and gemcitabine over 3 and 4 weeks administered on D1 in hospital and then at home incurred follow-up costs of 7121, 7400 and 8606 € respectively. With administration at hospital every 4 weeks, vinorelbine emerges as the least expensive chemotherapy with an incremental cost of 279 € compared to gemcitabine administered over 3 weeks. Gemcitabine administered over 4 weeks with management in hospital on D1 every 4 weeks incurred an annual follow-

up cost of 8 606 €.

These compounds which can be administered at home therefore allow annual savings of 1,628 to 2,805 € to be achieved per patient compared to the taxans.

Determinist Sensitivity Analysis

Incorporating the toxicity data from Smit for gemcitabine-cisplatin and those for treatment drop outs published by Scagliotti produces the least favourable hypotheses for gemcitabine-cisplatin. Similarly, the toxicity data from Fossela and Schiller provide the most favourable hypotheses for gemcitabine-cisplatin. These two scenarios were considered in order to establish the upper and lower limits of this evaluation.

° Administrations exclusively in hospital

Using the least favourable hypotheses, gemcitabine-cisplatin administered exclusively in hospital (table 10) emerges as the least expensive strategy in terms of annual follow up costs, followed by vinorelbine-cisplatin (increment of 121 €): The association gemcitabine-cisplatin using the Smit toxicity data is undoubtedly more expensive than it was initially although it releases savings compared to the taxans with an incremental cost of between 202 € and 1,379 € per patient. The cost of the most common adverse events is compensated by lower chemotherapy cost than the taxans, with a incremental cost in favour of gemcitabine-cisplatin ranging from 440€ (DC) to 2125€ (PCa).

Using the most favourable hypotheses, gemcitabine-cisplatin is the least expensive strategy both in terms of acquisition costs, administration costs, costs of toxicity and total cost. It provides savings of 962 € per patient compared to vinorelbine-cisplatin, 1,567 € compared to docetaxel-cisplatin, and 2,393 € and 2,379 €. compared to paclitaxel associated with either cisplatin or carboplatin respectively.

° Cost of alternating chemotherapies: Hospitalisation and domiciliary care

When the least favourable hypotheses for toxicity and treatment drop-outs are used to detriment of gemcitabine-cisplatin administered alternatively in hospital and at home (HH) (table 11), its follow up costs become higher than those of vinorelbine-cisplatin (increment of 579 €). Using Smit's toxicity data, the association gemcitabine-cisplatin is undoubtedly more expensive although it is nevertheless far less expensive than the taxans. The management cost of the increased adverse effects is more than compensated by the lower cost of the chemotherapies, of 1,628 to 2,828 € lower than that of the taxans for gemcitabine-cisplatin. The net increment compared to the taxans is between 905 € and 2,082 € per patient per year.

Using the most favourable hypotheses, gemcitabine-cisplatin is the least expensive strategy, in terms of costs of chemotherapy, treatment of adverse effects and annual follow up costs. It provides savings of 572 € per patient per year compared to vinorelbine-cisplatin, 2,360 € compared to docetaxel-cisplatin, 3,172 € compared to paclitaxel carboplatin and 3,186 € compared to paclitaxel cisplatin.

° Cost equivalence testing

Gemcitabine-cisplatin over 3 weeks appears to be the least expensive strategy. We tried to establish the price of gemcitabine at which the follow up costs of a patient treated with gemcitabine-cisplatin over 3 weeks would become equivalent to those of a patient treated in hospital with docetaxel-cisplatin or vinorelbine-cisplatin. In order to obtain equivalent annual follow up costs for gemcitabine-cisplatin over 3 weeks and docetaxel-cisplatin exclusively in hospital, the unit cost of a bottle of gemcitabine must be increased by 24 %. To obtain the same follow up costs for patients managed in hospital on gemcitabine-cisplatin over a 3 week cycle to those of patients treated with vinorelbine-cisplatin, the unit price of a bottle of gemcitabine has to be increased by 31%. For the same follow up costs to those of paclitaxel-carboplatin its price has to be increased by 67 %.

The unit price of gemcitabine bottles has to be increased by 14% to achieve identical follow up costs for alternate administration of gemcitabine-cisplatin over 3 weeks and vinorelbine-cisplatin alternating in hospital and at home. The price of the bottles has to be increased by 54 and 92% respectively for equivalent cost to docetaxel-cisplatin and paclitaxel-carboplatin, which can only be administered in hospital.

Probabilistic Sensitivity Analysis

° Administrations exclusively in hospital

At the end of the model, for equivalent efficacy, the numbers of patients in each of the arms are identical. The average maximum follow up period for these patients is 34.8 weeks [95% CI: 32.585 – 36.177] regardless of the treatment option used.

The median follow up costs of gemcitabine-cisplatin administered over 3 weeks are 8,109 €, compared to 8,103 € for its determinist value. The follow up costs of docetaxel-cisplatin, vinorelbine-cisplatin, paclitaxel-cisplatin, gemcitabine-cisplatin administered over 4 weeks and paclitaxel-carboplatin are 8,778 €, 8,943 €, 9,068 €, 9,602 €, 10,140 € respectively. These incremental mean costs between gemcitabine-cisplatin administered over 3 weeks and the other treatment options are all statistically significant and, in the same order, are: 669 € [95% CI:14 – 1,309], 834 € [95% CI: :135 – 1,539], 959 € [95% CI: 262 – 1,647], 1,493 € [95% CI: 799 – 2,180] and 2,031 € [95% CI: 1,336 – 2,711].

If the severe toxicity rates are added in, the strategies remain ranked in almost exactly the same order. In terms of cost they emerge in the following increasing order:

gemcitabine-cisplatin 3 weeks, vinorelbine-cisplatin, docetaxel-cisplatin, gemcitabine-cisplatin administered over 4 weeks, paclitaxel-cisplatin, paclitaxel-carboplatin; with mean annual follow up costs of 8,312 € [95% CI: 7,902 – 8,734], 9,027 € [95% CI: 8,625 – 9,423], 9,165 € [95% CI: 8,523 – 9,933], 9,602 € [95% CI: 9,218 – 9,979], 10,024 € [95% CI: 8,921 – 10,860] and 10,339 € [95% CI: 9,858 – 10,801] respectively.
The additional costs of the other treatment options compared to gemcitabine-cisplatin administered over 3 weeks are all positive and statistically significant: 715 € [95% CI: 725– 689] for VC, 852 € [95% CI: 621 – 1,199] for DC, 1,290 € [95% CI: 1,317 – 1,245] for GC 4 weeks, 1,712 € [95% CI: 1,019 – 2,126] for PC and 2,027 € [95% CI: 1,956 – 2,067] for PCa.

° Alternate administration in day hospital and domiciliary care
At the end of the modelling, gemcitabine-cisplatin administered over 3 weeks alternately in hospital and at home (HH) is still less expensive with follow up costs of 7,315 €, compared to 7,310 € for its determinist value. The mean incremental cost between gemcitabine-cisplatin over 3 weeks (7,315 €) and vinorelbine-cisplatin (7,686 €) is not significant [95% CI:-192 + 933]. Docetaxel-cisplatin, gemcitabine-cisplatin over 4 weeks, paclitaxel-cisplatin and paclitaxel-carboplatin are significantly more expensive than gemcitabine-cisplatin over 3 weeks, with mean additional costs of 1,463 € [95% CI: : 863 – 2,044], 1,753 € [95% CI: 1,121 – 2,382] and 2,825 € [95% CI: 2,185 – 3,446] respectively.
We used the same method as above to take account of the different toxicity rates published in the various trials. The mean annual follow up costs for gemcitabine-cisplatin over 3 weeks, and vinorelbine-cisplatin and gemcitabine-cisplatin over 4 weeks administered alternately in hospital and at home were slightly greater compared to those obtained in the previous sections: 7,579 € [95% CI: 7,167 – 8,034], 7,827 € [95% CI: 7,511 – 8,142] and 9,031 € [95% CI: 8,673 – 9 378] respectively.

° Administration in day hospital and at the start of the cycle followed by domiciliary care
At the end of the model, vinorelbine-cisplatin emerges as the least expensive treatment option (7,055 €) because of its administration frequency over 4 weeks. The cost of gemcitabine-cisplatin administered over 3 weeks is associated with a non-significant cost difference of + 260 € ; [95% CI:-272 + 791]). Gemcitabine administered over 4 weeks and all of the associations containing taxans are significantly more expensive, with additional costs compared to vinorelbine-cisplatin ranging from 1,449 € to 3,085 € .

Discussion

Schiller[44] et al, Novello and Scagliotti[45] recently conducted a cost minimisation study based on the trials available to them at the time. Schiller[44] et al. compared the total treatment cost of lung cancer from two phase III trials[78] from the perspective of the health care system in 5 European countries (France, Germany, Italy, Spain, United Kingdom). The second team[45] undertook an exclusively Italian analysis. Four types of costs were included for both studies: chemotherapy acquisition cost, chemotherapy administration cost, hospitalisations because of severe toxicity and other medical resources used (consultations, radiotherapy, concomitant treatments). A univariate sensitivity analysis was conducted in both publications.

In Schiller et al[44], the mean cost per patient, all types of management, primary care and hospital combined, with gemcitabine-cisplatin over 4 weeks costed using the Comella database, was 5,640 € in France, and 5,310 € in Italy in 2000. (The Novello and Scagliotti estimate of per patient cost on gemcitabine-cisplatin in Italy was significantly higher (8,094 €), even if administered in day hospital)[45]. The total incremental treatment cost between gemcitabine-cisplatin and vinorelbine-cisplatin at the same date, all types of management combined, from the same study by Schiller, was 1,832 € in France. When both treatments were administered exclusively at hospital their cost increment in France was 2,401 €. If both treatments were administered exclusively at home their highest cost increment was 1,655 € in France.

According to the study authors the savings made with the association gemcitabine-cisplatin compared to vinorelbine-cisplatin were mostly explained by a reduction in the number of hospitalisations for chemotherapy or treatment of severe toxicities, with an incremental hospital cost of 1,480 € per patient in France.

Our results are more conservative. The incremental cost of the GC protocol administered over 3 weeks and not over four, compared to the VC protocol is less. The expected savings in the model using GC exclusively in hospital in preference to VC were less than one third (669 €) of those published by Schiller for France and there is no statistically significant difference between the two regimens when they are administered alternately at home and in hospital.

On the other hand our study confirms the magnitude of the additional costs associated with the use of taxans compared to the GC protocol. In the Schiller study, the total costs of docetaxel-cisplatin were higher than those of gemcitabine-cisplatin over 4 weeks, also administered in hospital, with an additional cost of 584 € in France. The differences found between gemcitabine-cisplatin over 4 weeks and paclitaxel-cisplatin, both administered in hospital, were in the region of 1,660€ in France. The difference compared to paclitaxel-carboplatin was 2,668 €. In the central hypotheses of the model, the GC protocol administered over 3 weeks in hospital results in a reduction in total costs (including transport costs) ranging from 834 € compared to DC [95% CI: 135 – 1,539], to 1,493 € compared to

PC[95% CI: 799 – 2,180] and 2,031 € compared to PCa [95% CI: 1,336-2,711]. Both Schiller and our figures stand out. These savings are even greater when gemcitabine-cisplatin is administered alternately in hospital and at home using the central hypotheses of the model. Their figures range from 1,463 € [95% CI: 863-2,064] compared to docetaxel-cisplatin to 2,825 € [95% CI: 2,185-3,664] compared to the association paclitaxel carboplatin, and 1,753 € [95% CI:1 617 – 1,876] for paclitaxel-cisplatin.

Our study does have limitations. The choice of comparators, range of toxicities included, cost centres used and the very principle of a cost minimisation study are open to debate.

A search of the Medline, DARE (Database of Abstracts of Review of Effectiveness), NHS EED (NHS Economic Evaluation Database), and HTA (Health Technology Assessment database) databases identified 18 randomised trials[2-19]. The administration regimens for VC over 3 weeks were not included in the range of possible protocols for two reasons (i) they do not represent the wording of the European MA although they may be used as such in actual practice. (ii) to our knowledge only two trials have attempted to validate this protocol: the Gebbia 2003 trial, the sequential design of which does not allow the results to be attributed only to the VC arm administered on D1, D8, and the Martini trial 2005, the results of which were not available at the time when the model was constructed. The studies by Cardenal 1999[4], Crino 19995, Wozniak 1998[3] and Le Chevalier 1999[6] were excluded as being too old. The most recent articles by Sandler 2000[2], Gebbia 2003, Zatloukal 2003[16], Souquet 2002[18], and Kubota 200419 which contain only one of the comparators studied and the study by Gridelli 2003[15] in which the gemcitabine-cisplatin and vinorelbine-cisplatin arms were not separated was not used in the modelling. The study by Comella 2000[8] which contains far smaller numbers (60 eligible patients per arm) was also excluded because of the atypical nature of the administration regimens. The study by Melo 2003[17] which presents the results obtained with two of the associations studied containing cisplatin was only published in the form of an abstract at ASCO and as a result the data are not readily used. The articles by Kelly and Rossell were only used as marginal information to validate the toxicity rates used. We ultimately only selected trials which contained at least three comparators due to a desire to use the best possible level of evidence. We did however use indirect comparisons. These were made choosing the arms of trials in which the doses administered represented the doses recommended in the SmPC. No combining technique was used to compare treatments.

Some toxicities were not included into the model. Administration of paclitaxel-cisplatin and paclitaxel-carboplatin causes neurotoxicities (13% sensory neuropathy with paclitaxel-carboplatin vs 3% with vinorelbine-cisplatin, $p < 0.001$, Kelly[12]) and cumulative cardiac toxicities. In view of the short term of treatment, neither of these were included. Renal toxicity which occurs after administration of gemcitabine-cisplatin (1% grade 5 vs 0% for paclitaxel-cisplatin $p < 0.001$ Schiller[7]) was not included. The impact of this omission on the cost estimate is probably small as the likelihood that these would develop is no more than 1%. Allergies, skin rash, alopecia or symptoms of fatigue were not included. We only considered severe grade 3, 4, 5 haematological and gastro-intestinal toxicities, treatment of which requires hospital management.

The study was conducted from the "health care system" perspective. All expenditure contributing to the increase in final medical resource used was identified and allocated values, including health care, and transport, costs of which are reimbursed in France by the Social Security system. This (very) party limits the ability of our results to be extrapolated to countries in which the social protection system is not as generous.
The very principle of the cost minimisation study could be considered debatable in 2006. Undoubtedly, "the absence of evidence is not the evidence of absence" although it should be noted that none of the new dual therapies introduced recently onto the market has clearly been shown to be superior in terms of global survival or median time to progression compared to its same generation comparators. We therefore conducted a "probability-based cost minimisation analysis" in light of the different toxicity profiles of each of the associations compared to the different places in which they could be administered.

Conclusion

Lung cancer is a disease which is life-threatening in the very short term. It requires the rapid introduction of treatments which delay or stabilise progression of the disease or even improve survival, minimising the adverse effects due to the chemotherapy. In the absence of randomised clinical trials this study indirectly compares the costs of management of the six protocols studied to the National Health Insurance funds from published data. Gemcitabine-cisplatin used exclusively in hospital reduces the hospital expenditure compared to all of its comparators. Its alternate use in hospital and at home does not achieve significant savings compared to vinorelbine-cisplatin even if administered using the same regimen. Conversely, it releases significant savings per patient treated compared to taxans administered exclusively in hospital.

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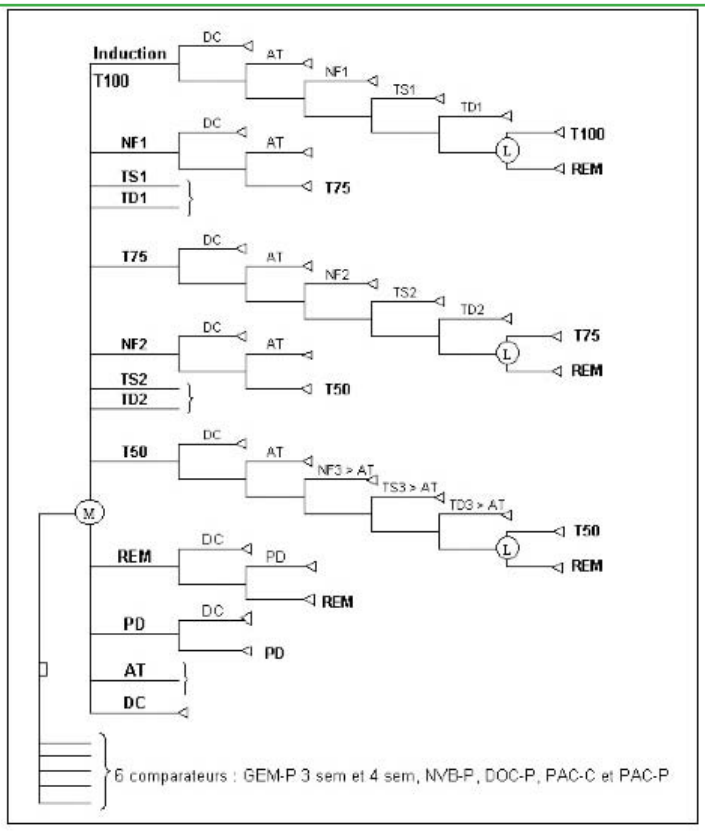
FIGURES

	D1	D8	D15	D22	D29		
GC 4 week	1000 mg/m²	1000 mg/m²	1000 mg/m²		1000	1000	1000 mg/m²
(Schiller)	100 mg/m²				100 mg/m²		
VC 4 week	25 mg/m²	25 mg/m²	25 mg/m²	25	25 mg/m²	25 mg/m²	25 mg/m²
(Scagliotti MA)	100 mg/m²				100 mg/m²		
GC 3 week	1250 mg/m²	1250 mg/m²		1250	1250		1250 mg/m²
(Scagliotti MA)	75 mg/m²			75			75 mg/m²
PCa	225 mg/m²			225			225 mg/m²
(Scagliotti MA)	AUC = 6			AUC			AUC = 6
DC	75 mg/m²			75			75 mg/m²
(Fossela)	75 mg/m²			75			75 mg/m²
PC	175 mg/m²			175			175 mg/m²
(Smit MA)	80 mg/m²			80			80 mg/m²

Figure 1. Administration regiments



6 comparators: GC 3 week and 4 week, NC, DC, PCa and PC

Figure 2. Architecture of the model

TABLES

Table 1. Efficacy data

Regimens	CT Drug	D1 (mg/m²)	D8 (mg/m²)	D15 (mg/m²)	Cycle Every
GC AMM, Schiller	G C	1000 100	1000	1000	4 weeks
VC Scagliotti MA	V C	25 100	25	25	4 weeks
GC Scagliotti MA	G C	1250 75	1250		3 weeks
PCa Scagliotti MA	P Ca	225 AUC=6			3 weeks
DC Fossela	D C	75 75			3 weeks
PC Smit MA	P C	175 80			3 weeks

Table 2. Toxicity data

Protocol / Toxicity	GC 3 W *(Scagliotti 2002)*	VC *(Scagliotti 2002)*	PCa *(Scagliotti 2002)*	GC 4 W (Schiller 2002)	DC *(Fossela 2003)*	PC *(Smit 2003)*
Febrile neutropenia (%)	1/205 0.5% [1]	6/203 3% [1]	2/203 1%[1]	11/288 4% [2]	20/406 4.9% [3]	2/159 1.3%
	4/160 2.5% [4]	18/396 4.5%[3]	11/290 3.8 % [2]		32/289 11% [2]	48/300 16% [2]
Blood transfusion (%)	16/205 8% [1]	16/203 8% [1]	4/204 2%[1]	16/205 8% [1]	42/406 10.3% [3]	16/205 8% [1]
	70/160 43.7% [4]	77/396 19.5%				
Gastro- intestinal toxicity (%)	13/205 6.6% [1]	13/205 13.6% [1]	1/204 0.5%[1]	106/288 37%[2]	40/406 9.9% [3]	14/159 8.8% [4]
	20/160 12.5% [4]	65/396 16.4 % [3]	26/290 8.9 % [2]		69/289 23.8% [2]	75/300 25% [2]

[1] Scagliotti 2002, [2] Schiller 2002, [3] Fossela 2003, [4] Smit 2003

Table 3. Acquisition and administration cost of chemotherapies

	1 day hospitalisation		1 domiciliary care visit	
	Chemotherapy	DRG tariff + chemotherapy + return transport	Chemotherapy	DRG tariff + chemotherapy + consultation
Vinorelbine 25 mg/m²	133	640	144	362
Gemcitabine 1000 mg/m²	357	782	388	606
Gemcitabine 1250 mg/m²	447	871	485	703
Docetaxel 75 mg/m²	1 179	1 603	-	-
Paclitaxel 175 mg/m²	1 329	1 753	-	-
Paclitaxel 225 mg/m²	1 709	2 133	-	-

Table 4. DRG from the v9.0 classification

Wording	CMD	DRG	DRG tariff	DRG + Transport
Respiratory system tumours without CMA	4	1 112	3 793,28	3 876,2*
Palliative care with or without procedure	23	7 956	6 464,8	6 657,8**
Reticular endothelial or immune system diseases with CMA	16	6 152	4311,29	4 504,3**
Transfusion by sessions	24	8 306	682,60	875,6*
Other gastro-intestinal disorders, age 18 to 69 years old with a CMA or age > 69 years	6	2 104	3612,42	3 695,4*

*Legend: * All travel means combined, ** Transport by ambulance*

Table 5. Toxicity rates used in the sensitivity analysis

Severe toxicity rate (%)	Gemcitabine-Cisplatin 3 weeks	Paclitaxel cisplatin	Vinorelbine-cisplatin	Docetaxel-cisplatin	Paclitaxel-carboplatin	Paclitaxel-cisplatin
	Smit 2003[11]	Smit 2003[11]	Fossela 2003[10]	Schiller 2002[7]	Schiller 2002[7]	Schiller 2002[7]
Febrile neutropaenia	4/160 - 2.5 %	2/159 - 1.3%	18/396 - 4.5%	32/289 - 11%	11/290 - 4%	48/300 - 16%
Blood transfusion	70/160 - 43.7%	38/159 - 23.9%	77/396 - 19.4%	42/406 - 10.3% (Fossela 2003[3])	4/204 - 2% (Scagliotti 2002[1])	16/205 - 8% (Scagliotti 2002[1])
Nausea and vomiting	20/160 - 12.5%	14/159 - 8.8%	65/396 - 16.4%	69/289 - 24%	26/290 - 9%	75/300 - 25%

Table 6. Distribution of variables

Variable	Distribution
Median Global Survival for gemcitabine-cisplatin	Normal(42,4;3,1122)
Median Time to Progression for gemcitabine-cisplatin	Normal(22,95;2,1938)
Probability of treatment drop out with gemcitabine-cisplatin	Beta(205;26)
Probability of treatment drop out with vinorelbine-cisplatin	Beta(203;47)
Body Surface Index	Normal(1,75 ; 0,13588)
Proportion of patients in Public/PSPH hospitals	Beta(3228;1381)
Transport costs	Normal(82,97 ; 12,53)

Table 7. Distribution of probabilities of severe toxicities

Variable	Trial	
after GC 4 weeks	***Schiller 2002***	
Probability of developing febrile neutropaenia	Beta (288;16)	
Probability of blood transfusions	Beta(205;16)*	
Probability of developing severe gastro-intestinal disorders	Beta(288;106)	
after GC 3 weeks	***Scagliotti 2002***	***Smit 2003***
Probability of developing febrile neutropaenia	Beta (205;1)	Beta (160;4)
Probability of blood transfusions	Beta(205;16)	Beta(160;70)
Probability of developing severe gastro-intestinal disorders	Beta(205;13)	Beta(160;20)
after VC 4 weeks	***Scagliotti 2002***	***Fossela 2003***
Probability of developing febrile neutropaenia	Beta (203;6)	Beta(396;18)
Probability of blood transfusions	Beta(203;16)	Beta(396;77)
Probability of developing severe gastro-intestinal disorders	Beta(203;27)	Beta(396;65)
after PCa 3 weeks	***Scagliotti 2002***	***Schiller 2002***
Probability of developing febrile neutropaenia	Beta (204;2)	Beta(290;11)
Probability of blood transfusions	Beta (204;4)	
Probability of developing severe gastro-intestinal disorders	Beta(204;10)	Beta(290;26)
after DC 3 weeks	***Fossela 2003***	***Schiller 2002***
Probability of developing febrile neutropaenia	Beta(406;20)	Beta(289;32)
Probability of blood transfusions	Beta(406;42)	
Probability of developing severe gastro-intestinal disorders	Beta(406;40)	Beta(289;69)
after PC 3 weeks	***Smit 2003***	***Schiller 2002***
Probability of developing febrile neutropaenia	Beta (159;2)	Beta(300;48)
Probability of blood transfusions	Beta(203/16)*	
Probability of developing severe gastro-intestinal disorders	Beta(159;14)	Beta(300;75)

Table 8. Exclusively in hospital

Strategy	Cost ($€_{2004}$)	Incremental cost
GC 3 Weeks Hosp	8 103	
DC	8 749	646
VC Hosp	8 949	846
PC	9 043	940
GC 4 Weeks Hosp	9 605	1 502
PCa	9 926	1 828

Table 9. Administration at hospital and in a domiciliary care visit

Strategy	Cost ($€_{2004}$)	Incremental cost
GC 3 Weeks Hosp/HH	7 400	
VC 4 Weeks Hosp/ HH	7 730	329
DC	8 749	1 349
PC	9 043	1 643
GC 4 Weeks Hosp/ HH	9 085	1 685
PCa	9 926	2 526

Table 10. Most / least favourable hypotheses

Strategy	Cost of chemotherapies ($€_{2004}$)	ΔC	Cost of Toxicities($€_{2004}$)	ΔC	Follow up cost ($€_{2004}$)	ΔC
Least favourable hypotheses: Different treatment drop-outs and Smit's toxicity data						
GC 3 Weeks Hosp	7 721		826		8 547	
VC Hosp	7 824	103	602	- 224	8 426	- 121
GC 4 Weeks Hosp	8 037	316	1 568	742	9 605	1 058
DC	8 163	442	586	- 240	8 749	202
PC	8 646	925	397	- 429	9 043	496
PCa	9 846	2 125	80	-746	9 926	1 379
Most favourable hypotheses: toxicity data from Fossela and Schiller						
GC 3 Weeks Hosp	7 806		297		8 103	
GC 4 Weeks Hosp	8 037	231	1 568	1 271	9 605	1 502
VC Hosp	8 199	393	866	569	9 065	962
DC	8 336	530	1 334	1 037	9 670	1 567
PC	8 929	1 123	1 567	1 270	10 496	2 393
PCa	9 992	2 186	490	193	10 482	2 379

Table 11. Most / least favourable hypotheses

Strategy	Cost of chemotherapies ($€_{2004}$)	ΔC	Cost of Toxicities($€_{2004}$)	ΔC	Follow up cost ($€_{2004}$)	ΔC
Least favourable hypotheses: Different treatment drop-outs, Smit's toxicity data						
VC Hosp/ HH	6 662		603		7 265	
GC 3 Weeks Hosp/ HH	7 018	356	826	223	7 844	579
GC 4 Weeks Hosp/ HH	7 466	448	1 568	742	9 034	1 190
DC	8 163	1 145	586	- 240	8 749	905
PC	8 646	1 628	397	- 429	9 043	1 199
PCa	9 846	2 828	80	- 746	9 926	2 082
Most favourable hypotheses:toxicity data from Fossela and Schiller						
GC 3 Weeks Hosp/ HH	7 013		297		7 310	
VC Hosp/ HH	7 017	4	865	568	7 882	572
GC 4 Weeks Hosp/ HH	7 466	453	1 568	1 271	9 034	1 724
DC	8 336	1 323	1 334	1 037	9 670	2 360
PC	8 929	1 916	1 567	1 270	10 496	3 186
PCa	9 992	2 979	490	193	10 482	3 172

Macrophagic Activation Syndrome: A case report and literature review

Arabi Abdessamad[1], Brahimi Mohamed[1], Bekadja Mohamed Amine[1], Iles F.[2], Djemai M.[2]

(1) Macrophagic Activation Syndrome Department of Haematology and Cell Therapy, University Hospital 1st November 1954, Oran, Algeria; (2) Private Surgical Clinic "El-Hikma", Oran, Algeria.

✉ *Corresponding author: Arabi A., Médecin Hématologiste, service d'hématologie et de Thérapie cellulaire, Etablissement Hospitalier Universitaire (EHU), Oran, Algérie; Email: abdessameddz@yahoo.fr*

Keywords: infection, pancytopenia, myelogram, macrophagic activation syndrome.

Abstract

A 73 years old man was admitted in a private surgical clinic for total hip prosthesis. After the surgical act, although there were no signs of infection, the patient received a large spectrum antibiotherapy and was, then, allowed to leave the clinic. He was hospitalized again 27 days latter; his general state had very badly deteriorated; pancytopenia spreads readily and the myelogram allowed the diagnosis of Macrophagic Activation Syndrome (MAS). Two days after his admission, the patient deceased.

Infection is the major cause of subsequent MAS. In the case of our patient, the administered antibotherapy may be had protected him against bacterial infections but was unsuccessful against viral, fungic or parasitic causes, which are aggravated in the case of an aged patient.

In this paper, we also gave results of the literature concerning clinical and biological features, as well as physiopathology and treatment.

Introduction

Macrophagic Activation Syndrome was initially described in 1950. It was individualized since the description of the post-viral hemophagocytosis by Risdall in 1979 (1).

In 1988, another study showed that its prevalence is estimated to 0.8% (2).

To our knowledge, no series were reported by researchers in the relevant literature, almost papers described individual cases (3, 4).

However, more recently, in 2000, 85 cases, including 55 of infectious, were reported in France during one single year (5). This suggests that this severe pathology is not very well elucidated. We, then, consider that any case reported with extensive description, including clinical and biological features, precise etiology if possible, will contribute to a better understanding of the pathology. We present, hereafter, a 73 years old man, MAS case treated in 2007.

Case Report

B.M, a 73 years old man, was admitted in March 2007 in a private surgical clinic for total hip prosthesis.

On admission, he was in a good general state; he weighed 80kg, and measured 175cm, his temperature was 37°2C; there was no pallor, cyanosis or jaundice; his blood pressure was 140/80mm Hg, the pulse rate was 80/min. There were no ganglions no splenomegaly and no hepatomegaly. The physical examination of other systems was unremarkable.

The pre operatory assessment was as follows: Absence of anaemia (haemoglobin = 13g/dl); leukocytes were normal (WBC 7,5x109/l) with normal distribution; platelet count was normal (190x109/l), Blood sedimentation rate was 2/6, Prothrombin time was at 90% and Activated Céphaline time was 28sec (control=30sec), Glycaemia: 0,89g/l, urea: 0,50g/l creatin : 12,2mg/l, Blood grouping revealed an O Rhesus positive group, Electrocardiogram and ultrasound Doppler were normal.

The patient was operated on 1st april. A systematic antibiotherapy, associating Bristopen, Gentamycine and Bactrim was started. The patient, also, received Fraxiparine and Di-antalvic against pain.

The following day, the patient presents an anaemia (Hb=9g/dl) which was related to the bleeding during surgery. He received red blood transfusions (three units); all the remaining of assessment was normal.

The patient left the clinic on April 8th, 2007.

He was hospitalized once again on April 27th, 2007 for luxation of the prosthesis.

The general state had very badly deteriorated: temperature at 39°C, he was obnubilated; blood pressure was 130/80 mm Hg and pulse 110/min.

There was a generalized cutanous rash; with no adenopathy, no hepatomegaly but tangible splenomegaly; crepitate rales were present in the two pulmonary bases.

The biological test showed anaemia (Hb = 9,4g/dl); leukocytes and platelets were normal; haemostasis assessment was normal; glycemia was at 1,10g/l, creatinine at 10,6mg/l; HBsAg, HCV, and HIV serology were negative.

Reanimation started, with antibiotic, urinary disinfectant and steroid therapy.

The patient, also, received red blood transfusions (two units).

On 29th april, despite blood transfusion, anaemia becomes serious (Hb=8g/dl); there was leukopenia (WBC 1x109/l) and thrombopenia (90x109/l).

A hematologic opinion is then required: in front of the deteriorated general state, with high fever, cutaneous rash, splenomegaly and pancytopenia: a macrophage activation syndrome is envisaged.

Myelogram confirmed this diagnosis; it revealed modularly infiltration by 7% of macrophages with benign cytological

aspect; they present intracytoplasmic vacuoles and blood cellular elements (erythroblast, leucocytes and platelets) (Figure 1)
Triglycerids were elevated at 4,50g/l; it was not possible to make dosage of ferritine.
The patient dies on May 1st, 2007.

Discussion

This pathology is present in childhood (family lymphohystiocytosis, Chediak-Higashi syndrome, Griscelli syndrome, Portillo syndrome (6). There is also reactional MAS in infectious pathology (7): bacterial infectious, viral infectious, fungic infectious and parasitic infectious.
MAS can be associated to aggressive lymphoma, acute leukaemia, myeloma, myelodysplasic syndrome, myeloproliferatif syndrome and solid tumours (8, 9).
It can also be associated with systemic diseases like lupus (10), connectivite, scleroderma and polyarthritis rheumatoid (11, 12).
MAS had been reported with some drug consummations like as phenytoine , valproique acid and parenteral nutrition of lipidic acqueous solutions; it can, also be seen after blood transfusion or vaccination(13).

On the clinical level, fever until 40°C is present in more than 90% of the observations; there is organomegaly (hepatomegaly, splenomegaly, peripheral adenopathy), cutaneous signs including papulous rash, nodules, lesions of vascularite, purpura, icterus related to the hepatic attack (14); digestive, neurologic and pulmonary signs can be observed. Visceral haemorrhage related to intravascular coagulation, with collapses, respiratory distress is possible (15, 16).

On the biological level, the anomalies are numerous but not specific, such as: Constant bi or pancytopenia; deep thrombopenia are the earliest anomalies. -Haemostasis disorders are found in 50-70% of the cases (hypofibrinogenemia, disturbed Quick time and activated cephaline time; sometimes there may be a real intravascular disseminated coagulation; it constitutes a factor of bad prognosis). -Hepatic disorders are found in 40% of the cases; they, generally, are signs of cytolysis. The positive diagnosis is cytological or histological: infiltration by 3% or more of macrophages; these macrophages contain in their cytoplasm blood cellular element (17).

On the physiopathological level, for most authors, this pathology seems to be caused by an abnormal activation of T-lymphocytes, which produce big quantities of inflammatory cytokines, which stimulate the macrophage answer (18). At the same time, the activation of macrophages is responsible for general inflammatory syndrome and fever (production of IL1, TNF and IL6).
Pancytopenia is related to the phagocytosis of blood cells, to the amplification of the lymphocytic answer (by production of IL2, IL1 and TNF) (19) and to the inhibiting action of erythropoiesis by IL1 and TNF (20).
Organomegaly is related to the tissue infiltration by activated macrophages.
High level of triglycerides, habitual in MAS, is related to the inhibition of the lipoprotein lipase by association TNF and IL1.
Hyperferritinemy would result from the erythrophagocytose, hepatic dysfunction and mainly from specific inflammation. Stimulation of the production of hepcidine by IL6 could play a predominant role, thus modifying the iron metabolism (13).
Some authors put the emphasis on the key role of TNF; it is an indicator in the MAS prognosis.
Viral infection, with herpes virus, CMV, EBV can conduct to a deregulation of TNF production, which would explain the frequency of MAS in this type of infection (21, 22). Other authors showed recently the role of the interferon gamma in the pathogenesis of MAS (23).

On the therapeutic level, the treatment is still badly codified; symptomatic treatment is important (correction of dyshydratation, transfusion if severe cytopenia).
In the family lymphohystiocytose, Etoposide (VP16) seems to give encouraging results (24). Lymphocyte T activation had led to try treatment by antilymphocytic serum, steroid and cyclosporine (25). Marrow transplantation had been also tested in child Lymphohistiocytose; it had completely modified the prognosis (26).
In reactional MAS, treatment of the cause is essential: anti-infectious treatment in case of post-infectious MAS, chemotherapy in the malignant hemopathies (Etopiside, steroids, cyclosporine) (27), polyvalent immunoglobulins in case of post-viral hemophagocytosis (28, 29).

Conclusion

Up to day, there is very little understanding about this serious pathology. Nothing could have predicted such a result for our patient. We think that all the medical staff must know the diagnosis criteria of Imashuku, established in 1997, which remains valid until this day, i.e: Fever more than 7 days with peaks to 38°5 C. cytopénia concerning at least 2 lines not caused by bone marrow disease (Hb ffi 9g/dl; Polynuclear Neutrophilffi 1x109/l; plateletsffi 100x109); ferritinemiaffl 1000 ng/ml; LDHffl 1000 UI/l; and hemophagocytosis in bone marrow, spleen, liver or ganglion.

Etiological diagnosis remains difficult, but infection represents the major cause and it is recommended to keep vigilant, particularly with aged patients.

Vital prognosis remains compromised in half of the cases.

Prospective studies are necessary; these include a better understanding of the physiopathology. It is necessary to gather precise information on the causes; it is the only way that, recommendations about the potential aggravating factors, as well as treatment, may be possible.

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FIGURES

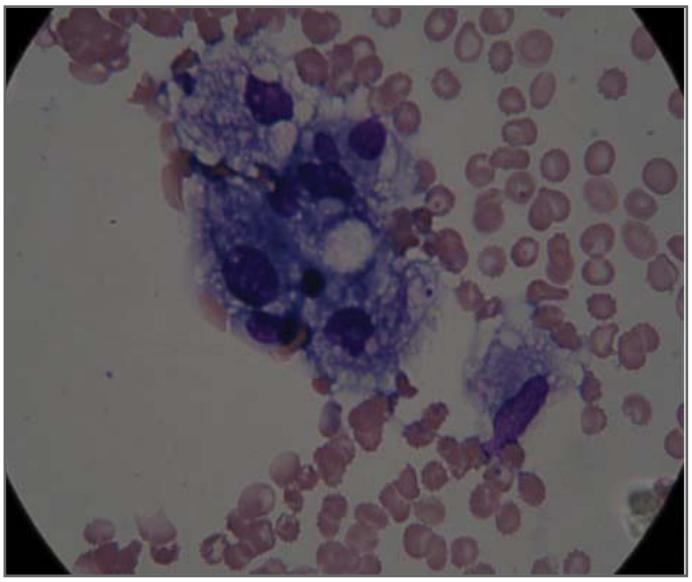


Figure 1. Bone marrow aspirate smear (May-Grünwald-Giemsa x100).

Meeting Highlights: Early Cancer From Prevention To Cure 2008

Sana Al- Sukhun, MD, MSc. Chairperson of scientific committee
Email: salsukhun@yahoo.com

Arab Medical Association Against Cancer (AMAAC) is committed to facilitating and disseminating the clinical and translational science that informs practice in cancer diagnosis, prevention, and treatment by encouraging communication and collaboration between professionals from diverse fields. The AMAAC Annual Meeting offers a unique opportunity for cancer professionals to learn, educate, and network.

The AMAAC meeting in Damascus – April, 2008 – was a collaborative effort among Al Bayroni Hospital, Italian Society of Oncology, and members of AMAAC from a variety of Arab countries. The meeting focused on themes that address the challenges and opportunities to treat and detect early cancer of breast, lung, prostate, colon, esophagus, and hepatocellular carcinoma (HCC)—how advances in clinical and translational science can reduce the burden of cancer.

Very interesting recent developments were presented on the topic of nutrition, diet, and food compounds. The effect of energy metabolism on cancer risk was explored. Risk is influenced by body mass index, caloric intake, birth weight, and exercise. All these factors influence serum levels of insulin and IGF-I, which mediate at least in part the effects of energy balance on risk. Anti-IGF-I-receptor drugs are in development, and Phase I/II trials are ongoing.

The role of tobacco was emphasized as the major preventable cause of death of humankind, and much of this preventable death involves cancer. Lung cancer, typically exhibiting an attributable risk of 75% to 85% for smoking, is by far the overriding issue, particularly in light of a 5-year survival rate of no more than 15%. It has also been recognized that smoking causes cancer of upper aerodigestive tract (oral cavity, nasal cavity, nasal sinuses, pharynx, larynx, esophagus), pancreas, stomach, liver, lower urinary tract (renal pelvis and bladder), kidney, and uterine cervix, and also causes myeloid leukemia.

Additionally, the impact of exposure to the sun – ultraviolet radiation including deliberate sun exposure in order to achieve «tanning» – on the development of both coetaneous melanoma and nonmelanocytic skin cancers was reviewed.

Central to prevention of cancer in many developing countries are two considerations: establishment of cancer registries and the institution of national cancer control programs (NCCP). In regards to cancer registries, most of our countries have established or working on establishing one, a testimony to the growing awareness in the region. One aspect of NCCP is screening in addition to prevention, early diagnosis, treatment, and palliative care. The French and Italian experience with establishing both programmes were reviewed, with particular focus on the Italian mammography screening program in Bologna. The importance of communication between referral hospital and surrounding community practices was emphasized to ensure proper follow up and dissemination of service to the community.

New techniques to guide biopsy of impalpable lesion in the breast were discussed. Annual mammography is advised for average risk women age 50 and older and biennial is recommended between ages 40 and 50 years.

Recent trends for hormonal therapy of breast cancer were reviewed. The pros and cons of aromatase inhibitors versus Tamoxifen were discussed. The issue of bone complications of therapy was explored and data to prevent and treat bone loss using bisphosphonate therapy was highlighted. The synergistic effect of combined hormonal blockade in the treatment of both breast and prostate cancer was analyzed.

In regards to lung cancer, systematic screening with either CT or chest x-ray is not unequivocally recommended by any major professional organization. Lung cancer screening has not been demonstrated to decrease deaths from lung cancer. Additionally, screening requires an ongoing commitment; cancers are detected on initial and annual studies, and a single baseline study is insufficient.

Those patients with early stages of lung cancer do benefit from adjuvant platinum based chemotherapy with significant improvement in overall survival.

When considering prostate cancer, there is no consensus on using any of the PSA modifications, and none of them has been shown to reduce the number of unnecessary biopsies or improve clinical outcomes. The total PSA cutoff of 4.0 ng/mL is still the most accepted standard because it balances the tradeoff between missing important cancers at a curable stage and avoiding both detection of clinically insignificant disease and subjecting men to unnecessary prostate biopsies.

Combined hormonal and radiation therapy for locally advanced node positive disease definitely improve survival (at least 2 years of hormonal therapy starting with or 2 months prior to radiation therapy).

An otherwise healthy individual, ages 50 and older needs to be screened for colorectal cancer. The following tests are options for screening: Annual occult blood test, flexible sigmoidoscopy every five years, annual occult test and flexible sigmoidoscopy every five years, double contrast barium enema (DCBE) every five years, or colonoscopy every 10 years. The decision about which option to select should

be made between the patient and physician, weighing cost and availability of the screening tests. Patients with positive occult test or abnormal DCBE should undergo follow-up colonoscopy for definitive diagnosis. Other screening tests are under development, but not ready for use in clinic yet. Those include fecal DNA test and CT colonography.

Adjuvant therapy for colon cancer has been studied for at least 40 years. Early regimens, consisting of 5-fluorouracil (5-FU) monotherapy, did not improve five-year survival following potentially curative resection. Interest in adjuvant chemotherapy was revived in the late 1980s by reports documenting a survival benefit from combination regimens such as methyl CCNU (semustine), vincristine, and 5-FU (MOF), and by the discovery of modulators of 5-FU activity (i.e., leucovorin [LV] and levamisole).The era of modern adjuvant chemotherapy was ushered in by data supporting the superiority of leucovorin (LV)-modulated 5-FU over both MOF and levamisole modulated 5-FU; and more recently, by the trials supporting the benefit of adding oxaliplatin to a 5-FU/LV backbone. Even in face of hepatic metastases, resection in this modern era offers a potentially long term survival in 30-35% of patients

The growing problem of HCC was thoroughly discussed in an afternoon session, considering the hepatitis epidemic in many countries in the region e.g. Egypt and Sudan. Surveillance of patients at risk for HCC should be performed using ultrasonography and alpha-fetoprotein at 6 to 12 month intervals. Patients at risk include those with Hepatitis B, a family history of HCC, Non-hepatitis B cirrhosis from alcohol, hepatitis C, genetic hemochromatosis, and primary biliary cirrhosis.
For those with advanced unresectable HCC, sorafinib (a multikinase and VEGF inhibitor) is the only and first targeted therapy to improve overall survival.

«Prevention of cancer» is a deceptively simple phrase. In fact, there is diversity of means, success rate, and resources that vary according to population, tumor type, age group, and sex. Certainly tobacco control can be identified as the principle achievable means of reducing the burden of cancer worldwide. Hopefully this knowledge will lead to the adoption of appropriate preventive measures.

Acknowledgement
I thank the members of the Executive, Organizing, and Scientific Committees led by Chairs Sami Al-Khatib, MD, and Amer El-Sheikh, MD, Nidal Estefan, MD, and my Co-Chairman Maha Manachi, MD, respectively, for their outstanding efforts to build the unique sessions in a friendly environment that brought together professionals with converging interests.

1st AMAAC Award

His past experiences - personal, educational, and professional - have helped him to expand his horizons and to cultivate his interest in applying for AMAAC Fellowship program.

Tamer Mohamed Refaat who got Master Degree in Radiation Therapy on June 2006 and appointed as an Assistant lecturer in the Clinical Oncology and Nuclear Medicine Department, Faculty of Medicine, University of Alexandria, Egypt is the first AMAAC Fellow. Tamer's early interest in Radiation Oncology began in 2002 through his career as trainee then resident in Alexandria Clinical Oncology and Nuclear Medicine Department. He devoted a great deal of his residency period in getting acquainted with the recent updates in the management of cancer patients in general and female cancer patients in particular. Furthermore, he broadened his perspective on fundamental issues within the research in oncology by participating in and organizing seminars, training programs, coordinating multinational and national Phase III A & B and Phase IV clinical trials and through conducting his master thesis in which he recruited 120 obese breast cancer females. Dr Refaat is registered to a credit hours doctorate degree program since September 2007, his doctorate degree thesis entitled "Comparative study of two different brachytherapy modalities in boosting bulky cervical cancer following concurrent chemoradiotherapy".

The main objectives of the fellowship are to help him accomplish a pioneer doctorate degree thesis with Lille II University, Faculty of Medicine, Radiation Therapy Department, Oscar Lambert Center, France and more important, parallel to his main research project he will have that valuable opportunity of having a training schedule and clinical rounds at the radiation therapy department. Where he will receive structured training on the modern techniques of Brachytherapy as well as the methods and strategies of conducting regular audit of the clinical practice and how to design tailor made guidelines for different clinical situations based on clinical evidence. Aiming to implement this training back home by introducing modern state of the art strategies and treatment modalities for cancer patients, this continues to cause death and misery among patients in Egypt. After all it is the mission of the university to be the leader of the society and the whole nation.

SEMCO-ASCO Conference

Ahmad El-Ezzawy, MD
Email: worldcooperation@gmail.com

The South and East Mediterranean College of Oncology (SEMCO) held its third Conference and second advanced course in association with American Society of Clinical Oncology (ASCO) during the period 26-28 March 2008 with collaboration of Ain Shams Clinical Oncology Department. The course was held at the Training and Education Enhancement Centre at Ain Shams University Hospitals, Cairo, Egypt.

The Advanced ASCO Course was titled «Cancer in the Older Population» and was chaired by Prof. Hussein Khaled, Prof. Ahmed Elzawawy and Prof. Atef Yousef, ASCO Courese President was Prof. Lodovico Balducci and International Faculty included Prof. Mohammad Hussein (USA), Prof. Riccardio Audisio (UK), Prof. Ama Rohatiner (UK), Dr. Christina Davies (UK), Prof. Branislav Jeremic (IAEA , Austria), Prof. Munir Kinay (Turkey), Prof. Nazim Turhal (Turkey), Dr. Joe Harford (USA), Prof. Manoj Pandey (India), Dr. Anne Merriman (Ireland) and distinguished regional colleagues from Egypt , Jordan (Dr.Jamal Kheder) and Iraq (Prof. Nada Alwan).

The course covered through eight scientific sessions over two days (26th and 27th March) and followed by one day conference of Ain Shams Clinical Oncology Department on miscellaneous topics on cancer field. During the course SEMCO launched its initiative to encourage international scientific publications in the East and South Mediterranean Region with a lot of support of local and international faculty.

The conference and course was successful and attended by 200 colleagues of various specialties and experiences in management of cancer in the older population and researches. Most of the lectures are available for all, and they could be downloaded from the web www.icedoc.org and visit what is under the icon of SEMCO.

Upcoming SEMCO activities:

> SEMCO-ASCO MCMC
November 20-22, 2008 - Izmir, Turkey
For registration and information, please visit the website www.ascosemco2008.org and contact Prof. Munir Kinay, Izmir, Turkey.

> SEMCO-ACOD*-AORTIC Conference**
January 14-16, 2009 - Alexandria, Egypt
* The host is ACOD (Alexandria Clinical Oncology Department)
**AORTIC is the African Organization for Research and training in Cancer.

> The 2nd African Breast Cancer Conference, SEMCO- Princess Nikky Breast Cancer Foundation.
March 16 – 17, 2009 - Cairo, Egypt

> The Third SEMCO-ASCO conference and advanced Course on Oncology integrated Palliative care.
April 15 – 17, 2009 - Cairo, Egypt

For more details please contact:
Pr. Ahmed Elzawawy: worldcooperation@gmail.com
& Dr. Atef Badran: atef.badran@gmail.com
www.icedoc.org

Nemrock 2008 in brief

Wafaa Abdel-Hadi, Clinical Oncology, Ms Sc.
Email: scullydoc@gmail.com

During 26th – 28th March, 2008, The Kasr El Aini School of Medicine Clinical Oncology Centre "NEMROCK" in Cairo held its 17th Annual conference at Ain Soukhna resort by the red sea. The aim of the conference was to fulfil and conclude some relevant guidelines that have proved of extreme effectiveness in the management of cancer patients. However, the financial burden associated with using such protocols comes between a better quality of life in developing countries' patients. Hence, The Theme of the Conference "Towards Cost-Effective Guidelines". The main topics were hemato-oncology and breast cancer. Nevertheless, it had a plenary session with different topics including, Renal Cell Carcinoma, Hepatocellular carcinoma, Targeted therapy in Lung Cancer, Present and Future of Radiation Oncology and the Cost Effectiveness of PET-Scan in the management of common malignant tumors.

Some of the most Prestigious Professors worldwide have participated in the conference, either by giving lectures or participating in case discussions and exchanging their experiences. It was a beautiful Orchestra played by eminent names like Dr David Khayat, Dr Thiery Le Chevalier and Dr Patrice Carde from France, Dr Vincent Valero from MD Anderson in USA. Also, It was a thrill to hear a special symphony from the Master of Geriatric Oncology Dr Matti Aapro, followed by intriguing yet enjoyable concertos by Dr Alain Monier, Dr Ahmed Galal, Dr Mohamed Osman, Dr Massimo Colombo, Dr Marc Montillo, Dr Anne la Prie. As for the Middle East lecturers, it was the light music performances by the Maestro of the conference Dr Hamdy Abdel-Azim, and his great colleagues Dr Shaouki Bazerbashi, Dr Taher El Twegieri and Dr Alaa El Haddad.

The Hemato-oncology session has stressed on topics like Multiple Myeloma, Radio-immunotherapy in B-cell Lymphoma, Treatment of CLL in the monoclonal antibodies era, Treatment of Aggressive B-cell Lymphoma and Less treatment. While the Breast cancer session has heavily illustrated the adjuvant treatment in triple negative patients, Taxanes in the adjuvant setting of Early breast cancer, Individualization of Adjuvant Chemotherapy for early breast cancer, The Value and Criticism of Adjuvant online, A decade of success in the management of Breast Cancer, Guidelines for the use of bisphosphonates including Aromatase Inhibitors Induced Bone loss(AIBL) and how to better select Aromatase Inhibitors treatment and Why upfront. A special session was made for treatment of Her2-neu Positive breast cancer Beyond Herceptin.

For dessert, The Breast Cancer forum was a delight. It was performed by Dr C Zeilinski, head of the oncology department in University of Vienna and moderated by Dr Hamdy Abdel-Azim. It included case presentation and a powerful Expert Panel for Metastatic breast cancer. Our best Oncologists gathered and participated in one room for case discussion, on top of the list were Dr. Dahesh Agarem, Dr Nagi El Saghir, Dr. Heba El Zawahry, Dr. Emad Hamada, Dr Tarek Hashem, Dr Yousry Gouda, Dr. Alaa Kandil, Dr Fouad Abu Taleb,Dr. Sami Khatib, Dr Salah El Messidy and Dr Vincent Valero from MD- Anderon , USA.

As for our Chairpersons whom we owe for taking control of the sessions and giving their time and effort for commenting on each lecture , our gratitude goes to : Dr Sami Khatib, director of the PanArab Society of Oncology, Secretary General of the Arab Medical Association Against Cancer (AMAAC), Dr Hussein Khaled, Dean of NCI-Egypt, Dr Hosna Mostafa ,head of the NEMROCK department, Dr Ehsan El Ghoneimy ,director of NEMROCK ,Dr. Wafaa El Metnawy, ex-head of NEMROCK and Dr Kamal El Ghamrawy , one of the pillars of NEMROCK .The list goes on to include our most prestigious oncologists and head of departments: Dr Fady Geara, Dr Marwan Ghosn, Dr Omar Zaki, Dr magdy el Serafy, Dr Hesham Atef, Dr Omar Fahmy, Dr Hamdy El Zawwam, Dr Ahmed Selim, Dr Mamdouh Haggag, Dr Ibtessam Saad el Din, Dr Yasser Abdel-Kader, Dr Amer Youssef, Dr Mona Abu El Eineen, Dr Magda Mostafa ,Dr Malaka Fouad, Dr Farouk Haggag, Dr.Loubna Sedky and Ofcourse Dr Samir Motawy and Dr Shawki El Haddad.

The conference also served all sorts of after-lectures entertainment. And that was just a small glimpse from the big performance that was carefully monitored and synchronized by Dr Hamdy Abdel-Azim, Dr Ehsan El Ghoneimy, Dr Mohamed Meshref, Dr Mohsen Mokhtar, Dr Neamat Kassem and myself, Wafaa Abdel-Hadi.

Hoping to see you in future events and continue our future PanArab collaboration for our fight against cancer to ensure better guideline managements and better quality of life.

The Gulf Journal of Oncology

Dr. Khaled Al- Saleh, Editor in Chief

The Gulf Journal of Oncology was started as an official journal for the Gulf Federation for Cancer Control. The first issue was published in January 2007 & since then it is being published biannually. So far we have published 3 issues and the 4th one will come in July 2008. Eminent doctors from the Gulf Arab world, Europe & USA are on the editorial board of the journal. The journal publishes original research articles, review articles, controversies, reports from conferences and commentaries.
The main interests of the journal are Cancer Research, Cancer Care & Medical Education. We are publishing around 3000 copies which are circulated free of cost to the doctors & hospitals in the Gulf and Arab world. There has been a tremendous response from the readers and we are receiving lot of the scientific papers for the publication in the journal.
E-mail: gffccku@yahoo.com

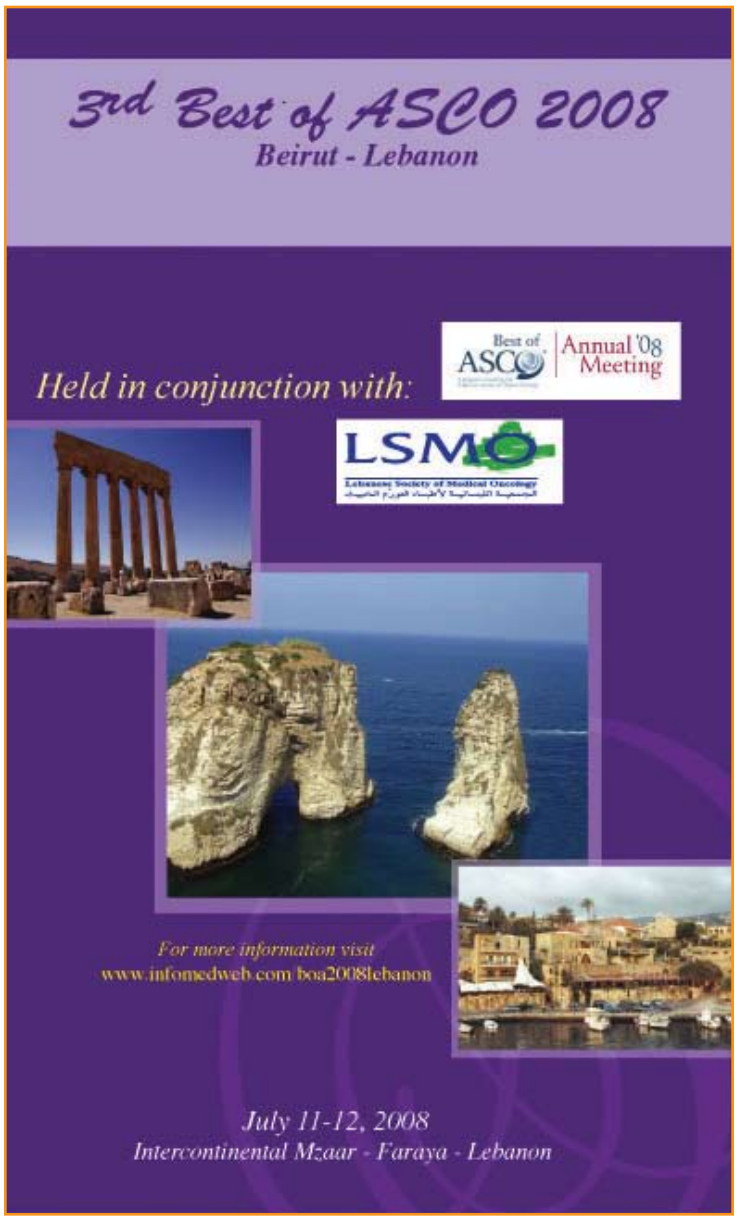
The Gulf Federation for Cancer Control

Scientific & Social Events

Activities within GCC between June 01, 2008 to January 01, 2009

No	Activity Name	Date	Location
1	Breast Cancer Workshop, Kuwait Oncology Society	11th June 2008	Kuwait
2	Breast Cancer Conference	25th October 2008	Jeddah , KSA
3	The 4th International Gulf Conference on Head & Neck Cancer	10-12th November 2008	Yemen
4	Layla Al- Othman – Short Story Festival, Cancer And Sport	December 2008	Kuwait

Best of ASCO



2nd LSH Regional Meeting

Clinical Trials in MENA

November 8 -9, 2008
Le Royal Hotel Amman, Jordan

Facilitating Clinical Trials in MENA Region

Under the Patronage of His Majesty King Abdullah II

Facilitating Clinical Trials in MENA Region

Organized by

Ministry of Health, Jordan
H.E. Dr. Salah Mawajdeh

International Pharmaceutical Research Center (IPRC), Jordan
Dr. Naji Najib

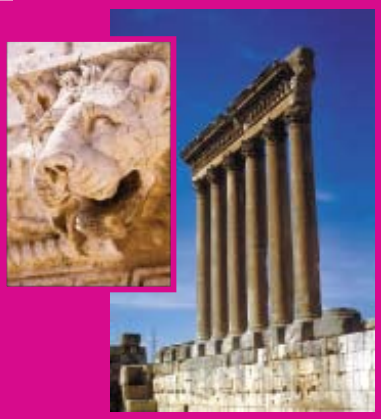
King Hussein Institute For Biotechnology and Cancer (KHIBC), Jordan
Dr. Samir Khleif

www.ctc08.org
Visit our website for the latest program information as it becomes available

LSMO 7

The Lebanese Society of Medical Oncology

LSMO 7 National Forum



November 13-14-15
2008 Le Royal Hotel Dbaye
Beirut-Lebanon

TOPICS:

Adjuvant therapies in:
- Gastro-intestinal malignancies, Non-small cell lung cancer, Breast, Urologic tumors … Sarcomas, neuroendocrine tumors, Cancer of unknown primary National cancer registry updates.

In parallel, special sessions and symposium will be conducted:
- Nursing special session
- Hitology workshop
- LSRO symposium

Call for abstracts:
Basic and clinical researches in cancer from Lebanon and the Arab world will be selected for oral presentation and for awards. Abstracts will be prepared according to attached information and submitted before October 15 2008.

All text should be typed as one paragraph not exceeding 200 words
- Names of cooperative study groups, if appropriate, should appear in the title. Include the name of all the authors and countries.
- Kindly submit your abstract to the following e-mail :**lsmo@lsmo.info**

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Twenty Years Fighting Against Cancer

Arab Medical Association Against Cancer

The Arab Medical Association Against Cancer (AMAAC)

Annual Conference 2009

7 - 9 May 2009

Grand Hyatt Hotel

Cairo - Egypt

Topics Are

Head & Neck
Lung
Breast
GIT
Hematopoietic Malignancies
Pediatric Oncology

Mark your Calendar

Visit our website
www.amaac.info

The Lance Armstrong Foundation *http://www.livestrong.org*

The Lance Armstrong Foundation is a registered 501(c)(3) nonprofit organization located in Austin, Texas. Founded in 1997 by cancer survivor and champion cyclist, Lance Armstrong, the LAF inspires and empowers people with cancer.

We believe that in the battle with cancer, unity is strength, knowledge is power and attitude is everything.
If you are looking for information about cancer or need help in dealing with cancer, explore our support resources.

Cancer Facts

o More than 10 million Americans are currently living with, through or beyond cancer.
o More than 1.3 million people in the U.S. will be diagnosed with cancer this year.
o Of adults diagnosed with cancer today, 64% will be alive five years from now.
o One in three people will be diagnosed with cancer during their lifetime.
o Three in four families will care for a family member with cancer.
Ref: American Cancer Society, Cancer Facts and Figures 2004

How the LAF is Making an Impact

We serve our mission through education, advocacy, public health and research programs.
- More than $9.6 million granted toward cancer survivorship and testicular cancer research
- More than $1.7 million invested in the development of 5 comprehensive cancer survivorship centers across the country
- Nearly $1.6 million invested in survivorship education and outreach initiatives with 60+ national and regional community partners including Fertile Hope, CancerCare, the Office of Native Cancer Survivorship, and the National Coalition of Cancer Survivorship
- A National Action Plan for Cancer Survivorship: Advancing Public Health Strategies developed in partnership with the CDC helps the public health community address cancer survivorship issues
- More than $2 million invested in 104 Community Program Partner initiatives that provide direct support and education to people living with cancer
- 500 cancer survivors and caregivers per month receive direct support and referrals from social workers and case managers through the LIVESTRONG™ SurvivorCare Program
- 200,000 visitors per month utilize valuable tools and information from the LAF Web sites.
- 7,200 volunteers across the country raise funds and awareness for the LAF.
- Approximately 55 million people across the globe wear a LIVESTRONG™ wristband in support of people living with cancer

Learn more about how your support helps

There are many ways you can support the LAF. You can make a gift now or learn about giving options. You can also get involved by becoming an advocate or participating in fundraising events.

http://www.ncsdf.org

JANUARY	Cervical Cancer Awareness Month
FEBRUARY	Screening and Early Detection Awareness Month
MARCH	Colorectal Cancer Awareness Month
APRIL	Cancer Fatigue Awareness Month
MAY	Melanoma and Skin Cancer Awareness Month
JUNE	National Cancer Survivors Day
JULY	Sarcoma Awareness Month
AUGUST	Pain Medicine and Palliative Care
SEPTEMBER	Gynecologic Cancer Awareness Month Prostate Cancer Awareness Month Leukemia and Lymphoma Awareness Month
OCTOBER	Breast Cancer Awareness Month
NOVEMBER	Lung Cancer Awareness Month Smoking Cessation
DECEMBER	5 A Day Awareness Month

Book your calendar Selection of International Cancer Events

SUBJECT	DATE	CITY, COUNTRY	WEBSITE	EMAIL
► JULY 2008				
ESMO Conference Lugano	July 3-6, 08	Lugano, Switzerland	www.esmo.org/activities/ecluconference	eclu@esmo.org
Third Annual Biological Basis of Breast Cancer Conference	July 12-13, 08	CA, USA	www.thecbce.com	jmccown@thecbce.com
7th International Conference on Head and Neck Cancer	July 19-23, 08	San Francisco, CA, USA	www.ahns.info	registration@ahns.info
Seventh International Congress on the Future of Breast Cancer	July 23-26, 08	Hawaii, USA		
3rd Interamerican Breast Cancer Conference	July 24-26, 08	Cancun, Mexico	www.imedex.com/calendars/oncology.asp	meetings@imedex.com
► AUGUST 2008				
International Union Against Cancer (UICC) World Cancer Congress	August 27-31, 08	Geneva, Switzerland	www.uicc-congress08.org	secretariat08@uicc.org
► SEPTEMBER 2008				
2008 Breast Cancer Symposium	September 5-8, 08	Washington, USA	www.breastcasymposium.org	
ASTRO's 50th Annual Meeting	September 21-25, 08	Boston, USA	www.astro.org	meetings@astro.org

SUBJECT	DATE	CITY, COUNTRY	WEBSITE	EMAIL
► OCTOBER 2008				
2008 ASTRO Annual Meeting	October 5-9, 08	Baltimore, USA	www.astro.org	meetings@astro.org
Twelfth Conference on Cancer Therapy with Antibodies & Immunoconjugates	October 16-18, 08	New Jersey, USA	www.gscancer.org	rchurch@gscancer.org
9th meeting of the International Society of Geriatric Oncology	October 16-18, 08	Monteral, Canada	www.cancerworld.org/siog	info@siogweb.org
Primer on Tumor Immunology and Biological Therapy of Cancer	October 30, 08	California, USA	www.isbtc.org	kpierce@isbtc.org
Workshop on Inflammation in Cancer Development	October 30, 08	California, USA	www.isbtc.org/meetings/am08/workshop08	kpierce@isbtc.org
► NOVEMBER 2008				
Chemotherapy Foundation Symposium, Innovative Cancer Therapy for Tomorrow	November 4-7, 08	New York, USA	www.chemotherapyfoundationsymposium.org	jaclyn.silverman@mssm.edu
2nd ASCO – SEMCO Multidisciplinary Cancer Management Course and Conference (MCMC)	November 20-22, 08	Ismir, Turkey	www.ascosemco2008.org	
► DECEMBER 2008				
50th ASH Annual Meeting and Exposition	December 6-9, 08	California, USA	www.hematology.org/meetings/2008/index.cfm	
31st San Antonio Breast Cancer Symposium	December 10-14, 08	Texas, USA	www.sabcs.org	sabcs@ctrc.net

OBJECTIVES & SCOPE OF THE PAJO ◄

The Pan Arab Journal of Oncology (PAJO) is the official Journal of the Arab Medical Association Against Cancer (AMAAC). It is a quarterly publication targeting health professionals interested in the oncology field. It is a multidisciplinary peer-reviewed journal that publishes articles addressing medical oncology, malignant hematology, surgery, radiotherapy, pediatric oncology, geriatric oncology, basic research and the comprehensive management of patients with malignant diseases in addition to international oncology activities, congresses & news.

The journal will be addressed, as a first step, mainly to the professionals in the hematology & oncology field in the Middle East region and North Africa. The goal is to share local & regional research activities news and to be updated with international activities.
We hope, with your support, to achieve our following objectives:

1. Promote and encourage research activities in the Arab World.
2. Disseminate & analyze epidemiological local, regional and international data.
3. Update health professionals with the most recent advances, news & developments in the field of oncology.
4. Improve the level of scientific publications arising form the Arab World.
5. Keep health professionals connected and exposed to the activities of different Arab cancer societies.
6. Share with our immigrant compatriots their activities & feedback in this field.
7. Involve all health professionals interested in the field of Oncology within the multidisciplinary scope of the Journal.
8. Encourage post graduates students to submit their research work.

INSTRUCTIONS FOR AUTHORS ◄

1. Manuscript Categories

1.1. Clinical trials

The Editor-in-Chief and an Associate Editor generally review Reports from clinical trials. Selected manuscripts are also reviewed by at least two external peer reviewers. Comments offered by reviewers are returned to the author(s) for consideration.
Manuscript acceptance is based on many factors, including the importance of the research to the field of oncology & the quality of the study. Authors should focus on accuracy, clarity, and brevity in their presentation, and should avoid lengthy introductions, repetition of data from tables and figures in the text, and unfocused discussions. Extended patient demographic data should be included in a table, not listed within the text.
Reports from Clinical trials are limited to 3,000 words of body text, excluding the abstract, references, figures, and tables. They are limited to six total figures and tables. All abstracts are strictly limited to 250 words. Titles are to be descriptive, but succinct.
Results of clinical studies should be supported by a clear description of the study design, conduct, and analysis methods used to obtain the results.
Reports of phase II & III studies should include from the protocol a clear definition of the primary end point, the hypothesized value of the primary end point that justified the planned sample size, and a discussion of possible weaknesses, such as comparison to historical controls.
Phase I studies will be well received if they have interesting clinical responses, unusual toxicity that pointed to mechanism of action of the agents, and important or novel correlative laboratory studies associated with the trials.

1.2. Review Articles

All reviews must be clinically oriented, ie, at least half the review must describe studies that detail human impact, marker effect on prognosis, or clinical trials.
Review Articles should be prepared in accordance with the Journal's Manuscript Preparation Guidelines, and will be reviewed in the same manner as Reports from Clinical Trials. Reviews are limited to 4,500 words of body text, excluding the abstract, references, figures, and tables. The editors also suggest a limit of 150 references.

1.3. Editorials / Comments / Controversies

The Editor-in-Chief may solicit an Editorial to accompany an accepted manuscript. Authors who wish

to submit unsolicited Comments and Controversies should contact the Editor-in-Chief, before submission to determine the appropriateness of the topic for publication in the Journal.
Editorials should be no more than four to five pages in length.

1.4. Articles on Health Economics

Articles about health economics (cost of disease, cost-effectiveness of drugs, etc) are highly encouraged.

1.5. Case Reports / Correspondence / Special Articles

Correspondence (letters to the Editor) may be in response to a published article, or a short, free-standing piece expressing an opinion, describing a unique case, or reporting an observation that would not qualify as an Original Report. If the Correspondence is in response to a published article, the Editor-in-Chief may choose to invite the article's authors to write a Correspondence reply. Correspondence should be no longer than three pages in length.
Special Articles present reports, news from international, regional societies as well as news from our compatriots.

2. Manuscript submission procedure

All manuscripts should be submitted in word and PDF format directly to the Editor-in-Chief by email at the following email: editorinchief.pajo@yahoo.com.
The manuscript should adhere to the journal requirements. Upon manuscript submission, corresponding authors must provide unique e-mail addresses for all contributing authors. Receipt of manuscripts will be acknowledged via e-mail. Upon completion of editorial review, the corresponding author will receive notification of the Editor's decision, along with the reviewers' comments, as appropriate, via e-mail.

3. Disclosures of Potential Conflicts of interest

In compliance with standards established and implemented by ASCO's Conflict of Interest Policy (J Clin Oncol 24:519–521, 2006), it is the PAJO's intent, as previously referred, to ensure balance, independence, objectivity, and scientific rigor in all of its editorial policies related to the Journal through the disclosure of financial interests, among other measures. All contributors to the Journal are required to disclose financial and other relationships with entities that have investment, licensing, or other commercial interests in the subject matter under consideration in their article. These disclosures should include, but are not limited to, relationships with pharmaceutical and biotechnology companies, device manufacturers, or other corporations whose products or services are related to the subject matter of the submission.
Disclosures of financial interests or relationships involving the authors must be addressed on the Author Disclosure Declaration form. The corresponding author may complete the form on behalf of other authors, or authors may complete their own forms and forward them to the corresponding author. This information will be sent to the Editorial Board. Statements regarding financial support of the research must be made on the manuscript title page, and disclosed on the form. This form is available upon request from the Editorial Office. All disclosures will appear in print at the end of all published articles.
The Journal requires all Editors and reviewers to make similar disclosures. Reviewers are asked to make disclosures when accepting a review.

4. Manuscript Preparation Guidelines

Title Page

The first page of the manuscript must contain the following information: (1) title of the report, as succinct as possible; (2) author list of no more than 20 names (first name, last name); (3) names of the authors' institutions and an indication of each author's affiliation; (4) acknowledgments of research support; (5) name, address, telephone and fax numbers, and e-mail address of the corresponding author; (6) running head of no more than 80 characters (including spaces); (7) list of where and when the study has been presented in part elsewhere, if applicable; and (8) disclaimers, if any.

Abstract

Abstracts are limited to 250 words and must appear after the title page. Abstracts must be formatted according to the following headings: (1) Purpose, (2) Patients and methods (or materials and methods, similar heading), (3) Results, and (4) Conclusion. Authors may use design instead of Patients and methods in abstracts of Review Articles. Comments and Controversies, Editorials and Correspondence do not require abstracts.

Text

The body of the manuscript should be written as concisely as possible and must not exceed the manuscript category word limits described herein. All pages of a submission should be numbered and double-spaced. Helvetica and Arial at 12pt size are the recommended fonts for all text (see Figures section for acceptable fonts for figures). The Journal adheres to the style guidelines set forth by the International Committee of Medical Journal Editors.

References

References must be listed and numbered after the body text in the order in which they are cited in the text. They should be double-spaced and should appear under the heading "REFERENCES." Abbreviations of medical periodicals should conform to those used in the latest edition of Index Medicus and on MEDLINE. The «List of Journals Indexed in Index Medicus» includes the latest abbreviations. Inclusive page numbers must be cited in the reference. When a reference is for an abstract or supplement, it must be identified as such in parentheses at the end of the reference. Abstract and supplement numbers should be provided, if applicable. When a reference is a personal communication, unpublished data, a manuscript in preparation, or a manuscript submitted but not in press, it should be included in parentheses in the body of the text, and not cited in the reference list. Published manuscripts and manuscripts that have been accepted and are pending publication should be cited in the reference list.

Reference Style

° Journal article with one, two, or three authors
1. Dolan ME, Pegg AE: O6-Benzylguanine and its role in chemotherapy. Clin Cancer Res 8:837-847, 1997

° Journal article with more than three authors
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