

PAN ARAB JOURNAL OF ONCOLOGY

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A
Celebration
of
Life



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mghosn.hdf@usj.edu.lb
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skhatib@khcbi.jo
Jordan

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gffccku@yahoo.com
kalsalehdr@hotmail.com
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Jkxader@khcc.jo
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Pan Arab Publishing Company
P.O. Box: 2509
Amman 11953- Jordan
Beer Al Sabe' St.
Shocair Medical Complex
2nd floor – office No. 201
Phone: +962 6 566 78 53
Fax: + 962 6 562 38 53
www.e-pamj.com

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Dear Colleagues,

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.

The issuing of this Journal (Pan Arab Journal of Oncology – PAJO) is a dream that came true as the idea of having it was initiated long time ago by the former members of the Executive Committee of (AMAAC), while the decision was finally taken during the Executive Board Meeting of the Arab Medical Association Against Cancer (AMAAC) which was one of the affiliated activities of the “Pan Arab Breast Cancer Symposium” that was held in Amman 28 – 30 June 2007 as part of the activities of (AMAAC). Also, the Editorial Board of the Journal was formed during that event too.

The elected Editor in Chief of the Journal is Dr. Marwan Ghosn, who I wish together with all the members of the Editorial and Advisory Board all the best of luck and more remarkable achievements yet to come in the near future.

Sami KHATIB, MD



Dear Colleagues and Friends,

Welcome to the 1st issue of the Pan Arab Journal of Oncology (PAJO), the new & official peer-reviewed publication of the Arab Medical Association Against Cancer (AMAAC).

The “survivor”, the spirit of the 1st issue, is chosen to give a garden of hope to our patients and to motivate and encourage our colleagues to continue their efforts to improve the management of patients and to increase awareness for screening and early detection of cancers.

The PAJO is designed to achieve many objectives. One of our aims is to be the number 1 in-house magazine of the Arab Oncologist through its coverage to numerous activities in countries all over the Arab World and its opening to the newest international discoveries & guidelines.

Articles by experts from different parts of the globe are gathered in this 1st issue to cover a variety of interesting topics:

- The Brazilian flora, the most diverse in the world, has become an interesting spot to prospect for new chemical leads or hits due to its species diversity and associated chemical richness. An updated review of the current status of biological screening program and recent results of new antitumor and antibacterial chemical leads are presented.
- New Therapies targeting the Chronic Myeloid Leukemia particularly those for which clinical data are already available are detailed.
- A historical perspective of the development of pediatric hematology oncology in Lebanon is described.
- Palliative care at the end of life of pediatric cancer patients at the Children’s Cancer Center of Lebanon is discussed.
- A review in the role of conservative surgery with presentation of fertility in gynecologic malignancy.
- An update on the role of novel Antiangiogenic drugs in advanced renal cell carcinoma is presented.
- The results of a clinical trial comparing the intraperitoneal chemo hyperthermia versus intraperitoneal chemotherapy in the treatment of patients with malignant ascites are developed.
- The recent trends of cancer epidemiology in Lebanon are presented.
- A personal point of view on the cost and advantages of new technologies in oncology.

Now, you can read the PAJO and you will also be able as well to mark your calendar to attend the upcoming regional activities that will be published in each issue. And there is more to come....

We would like to thank the International Advisory Board members who agreed to give scientific and moral support to the PAJO and the authors who contributed to the successful launch of the 1st issue.

We would like also to thank the PAJO Editorial Board for their contribution, effort and support.

A warm thank to the AMAAC Board for their trust and support of PAJO.

A regional advisory board by sub specialities will be implemented to evaluate and support the continuous activities of PAJO.

We are looking forward to work with all Arab Oncologists to make the PAJO, a scientific space, to share, communicate, discuss, advise and present the most advanced data and an invaluable reference tool in the field of malignant hematology and oncology.

Your time to send us your opinions, comments, suggestions and contributions is highly appreciated.

As Dr Khatib wrote in his editorial, the PAJO was a dream that came true and indeed, a journey of a thousand miles begins with one step!!

Marwan GHOSN, MD

Screening for new antitumoral and antibacterial drugs from Brazilian plant extracts

Younes RN*, Varella AD, Suffredini IB

Abstract

Natural products have provided, in the last 40 years, significant number of new drugs currently used in the management of most diseases. The discovery and introduction in the market of important compounds, like paclitaxel, the vinca alkaloids, etoposide, and many antibacterial drugs support the development of programs dedicated to drug discovery. Natural products have been rediscovered as an important tool for drug development despite advances in combinatorial chemistry, due to the complex molecular structures able to interact with mammalian cell targets. The Brazilian flora, the most diverse in the world, has become an interesting spot to prospect for new chemical leads or hits due to its species diversity and associated chemical richness. Screening programs have been established in Brazil as a strategy to identify potentially active substances. High throughput screening techniques allow the analysis of large numbers of extracts in a relatively short period of time, and can be considered one of the most efficient ways of finding new leads from natural products. An updated review of the current status of biological screening program is presented and recent results of new antitumoral and antibacterial chemical leads are discussed.

Key words: biodiversity, screening, natural products, Amazon Rain Forest, Atlantic Forest.

The absolute number of cancer deaths is declining, according to epidemiological studies most developed countries. Nonetheless, cancer still considered a major public health problem, second only to cardiovascular diseases in mortality rates¹. Systemic chemotherapy for advanced and metastatic disease has evolved dramatically with the introduction of new drugs and regimens, either as isolated treatment, or in adjuvant settings, associated to surgery or radiation therapy². Several new molecules have been developed into commercially available drugs that had origin in extracts derived from natural resources, such as paclitaxel, the vinca alkaloids and etoposide.

Infections are still considered one of the main causes of human and animal morbidity and consequent mortality. Controlling resistant bacteria is an ever-growing endeavor and is a major concern for specialists around the world^{3,4,5,6}. The introduction of new antibiotics became a matter of public health. Fortunately, the research in this area is widespread, and, as for cancer, natural products can be considered one of the main sources of new drugs. Data published in 1997⁷ and updated in 2003⁸ showed that over 50 % of all new antibiotics approved by FDA were extracted from natural sources, or were derived from a natural lead, or synthesized (or semi-synthesized) based on known natural product.

Natural products still play an important role as a source of new antitumoral and antibacterial leads, despite the recent progress in combinatorial chemistry. Although more than 100,000 synthetic compounds can be originated by combinatorial chemistry at any given time, still a high percentage of these products do not present the specific spatial structure required to interact with mammalian targets⁹. The design of new anticancer drugs entered in a new era since then, and combinatorial chemistry is now an important tool for the introduction

of new drugs into the market. However, the chemical diversity found in natural products offers new and original options, adding to the thousands of products obtained from combinatorial chemistry. Compounds isolated from plants, especially small molecules, frequently show biological activity as inhibition of macromolecular target, such as proteins. On the other hand, synthetic products, sometimes even a hole library, may not show any significant activity, because most of these products are usually big molecules, with no distinctive biological activity¹⁰.

The effectiveness of drugs such as paclitaxel, docetaxel, etoposide and the vinca alkaloids¹¹, together with important antibiotics as vancomycin, and penicillin are few examples of the importance of natural products in drug discovery. Moreover, little is known about the pharmacology or the phytochemistry of plants and animals representative of the biodiversity found in countries such as Brazil. The number of superior plants is estimated to be between 200,000 and 250,000 species¹² and only near 20% of the plants have been pharmacologically evaluated⁸. Brazil concentrates 20% of the world's biodiversity¹³, and over 17% of the Brazilian biodiversity can be found in the Amazon Rain Forest¹⁴. The Atlantic Forest contains approximately 35% of the world's Angiospermae, and more than 8% of the Pteridophytae¹⁵. In view of this species richness and considering that these forests are currently considered as major areas for conservation¹⁶, scientific interest was renewed in Brazilian forests are a potential source for new pharmacological compounds.

Bioprospection of natural resources using screening procedures is not a new technique, for it has been used for decades, but it was implemented in Brazil only recently. The US/NIH National Cancer Institute (NCI) had a large screening program capable of testing 10,000 compounds/extracts per year. More than

*Extraction Laboratory of the Universidade Paulista – UNIP, and Research Institute of the Hospital Sírio-Libanês, São Paulo, Brazil

Corresponding address to RNY at the Laboratório de Extração Universidade Paulista, Av. Paulista, 900, 1 andar, São Paulo, SP, Brazil, 01310-100. Email: extractlab@unip.br

114,000 extracts obtained from 35,000 plant species have already been tested in that program, and only 4% have shown significant activity¹⁷. Nowadays, the NCI bank of extracts has more than 200,000 extracts from marine and terrestrial plant and animal extracts and isolated compounds. From this program, some of the important anticancer drugs were discovered, as paclitaxel (from *Taxus brevifolia* Nutt.), camptothecin (Camptotheca acuminata Decne) and podophyllotoxin/etoposide (semi-synthetically obtained) (from *Podophyllum peltatum* L.)^{18,19}, all of them are currently being routinely used in cancer therapy.

Our group, at the Universidade Paulista-UNIP, in São Paulo, Brazil, concentrates its efforts on collecting plants from the Amazon rain forest (Manaus, AM) and from Atlantic Forest (Iguape, Cananéia e Registro, SP). The university continuously provides the local facilities, including laboratories, boats, and personnel in both regions, as well as a complete infrastructure with capacity for testing approximately 500 extracts a year, in the main laboratory, located in São Paulo.

The establishment of a bank of extracts was a priority, since the beginning of the project. Special attention, investment and technical support have been spent in selecting and processing plant material. For that reason, today the laboratory developed one of the most standardized banks of extracts, composed by plants native to the Amazon and Atlantic Forests. Due to the enormous biodiversity, sample collection strategies had to be defined, in order to create a well established bank of extracts. Plant collection can be based on native traditional knowledge, based on chemotaxonomic information, or on random prospection, i.e., collection of all possible plant samples containing flower or fruit. The random approach is easier in the field, where plants are collected. Special attention is given to plants in the reproductive cycle, allowing for better taxonomic identification. There are advantages and disadvantages in this approach. The advantage is that collecting a good variety of species certainly adds value to the bank of extracts. Conceivably, a wide variety of plants may lead to a wide variety of pharmacological activity and phytochemicals, once the random collection contains both the plants used as medicine by traditional communities and the plants that are not traditionally used, but which may still present active compounds. The downside is the higher investment needed to perform random collections, due to the diversity of natural resources. Effort and significant resources are necessary to process the plants, and more frequent expeditions are needed to detect flowering of the plants on a regular basis. The high number of species to be identified, processed and tested requires a well-established and dedicated technical and scientific personnel.

An important issue in natural products drug discovery in Brazil is the regulatory laws that control the access

to biodiversity. Bioprospection in Brazil is regulated by strict laws based on the Convention of Biodiversity. The law basically regulates the access to the Brazilian genetic patrimony and allows its bioprospection. That means that any Brazilian citizen or foreigner who desires to bioprospect in Brazil must apply for a license to access the biodiversity and collect material, and another license to do the biological research. Foreigners must have a Brazilian counterpart. Local authorities are trying to establish more effective systems to support the important research efforts developed by established and prospective scientific institutions in the country, allowing more widespread, and at the same time controlled bioprospection. Foreign support to develop meaningful steps involved in finding new drugs is a still necessity, as the Brazilian authorities and private industries do not have the tradition of investing in basic research. Meanwhile, tapping the Brazilian biodiversity is a slow and painstaking endeavor, and the results are slowly showing their potential.

UNIP bank of extracts has approximately 2,000 aqueous and organic extracts obtained from different parts of plants, or from whole plants, depending on biomass availability. Most of them were collected in the Amazon Rain Forest, using a laboraroy boat, especially equipped for the present project.

After collection, the initial plant processing, such as cleaning the material from insects and other species, separating the organs (leaves, stem, fruits, flowers, wood, roots, barks, etc.), is usually conducted inside the boat, as well as the initial taxonomic identifications, up to the level of gender, whenever possible.

The crude plant material is brought to São Paulo to be processed. Plant organs are separated and then completely dried in air-circulating stove at 40 °C. The material is ground in a hammer-mil. The ground material is placed in glass percolators and an organic extract is obtained through initial maceration with equal volumes of dichloromethane and methanol, followed by maceration with water with the same plant material previously used, resulting in two extracts from each plant. Solvents from organic extract are evaporated with a rotary evaporator and water from aqueous extracts is lyophilized. The organic and aqueous dry extracts are kept in freezers at -20 °C until use.

Two in vitro biological assays were selected to study the extracts: 1) a cytotoxic assay based on human cancer-cell lines, and 2) a antibacterial assay performed on four resistant bacteria (*Staphylococcus aureus*, *Enterococcus faecalis*, *Pseudomonas aeruginosa* and *Escherichia coli*). As both techniques are conducted in 96-well plates, a large number of samples can be tested in a short period of time, and only a small amount of each sample is required. Because of the small amount of samples needed to run the in vitro assays, only a small amount of each plant organs is collected. This allows

for the collection of a wide range of species on each boat trip into the forests. Recollections of a specific plant are only required whenever extracts show activity in the screening assay, and further identification studies are anticipated.

The antitumoral screening assays performed in the Laboratório de Extração at UNIP is directed against six human cancer cell lines provided by the National Cancer Institute (DTP/NCI/NIH/USA). The cancer cell lines were chosen according to the most prevalent malignant diseases occurring in Brazil²⁰. The assay is briefly described as follows²¹. Suspensions of breast, prostate, lung, colon, central nervous system, and leukemia cell lines are prepared at concentrations of 10,000, 7,500, 7,500, 15,000, 15,000 and 200,000 cells per well, respectively. After one day incubation, samples of extracts are added at an initial concentration of 100 µg/mL. Microplates are incubated for 48 h before being analyzed by the SRB colorimetric method. Analysis is carried out in microplate reader, at 515 nm. The percentage of lethality is obtained for each sample, and the extracts that are able to kill 15 % of the cell lines are chosen to be fractionated. The fractions are re-evaluated against the cancer cell lines so the active ones are identified and submitted to further fractionation. This procedure continues until the active substances are isolated. The isolated substances are identified using traditional techniques, such as UV, NMR, MS and IR spectrometer analysis, in a collaborative basis. Fractionations are being done now with some of the active extracts.

The antibacterial assay is performed against the above-mentioned four strains of bacteria, obtained from American Type Culture Collection. Briefly, suspensions with defined concentrations of bacteria are prepared and transferred to the microplate wells. The extracts are added to the corresponding wells in a single concentration of 100 µg/mL²². After 24-h incubation, the extracts are evaluated and the active ones, i.e., those able to inhibit bacterial growth, are submitted to the analysis of minimal inhibitory concentration (MIC) and minimal bactericidal concentration (MBC). Extracts showing MIC ≤ 200 µg/mL, are selected for further bioguided fractionation.

The Laboratório de Extração has now screened over 1,220 plant extracts against the six human cancer cell lines and against the four bacteria, totalizing 12,200 tests. From the initial screening processes, 72 extracts showed significant activity against at least one of the cancer cell lines and 50 extracts showed antibacterial activity against one or more bacteria used in the assay, at the initial concentration of 100 µg/mL. Those active extracts were fractionated using solid phase extraction syringes and a gradient of solvents composed by dichloromethane, acetonitrile, ethanol, methanol and water. The fractions were tested in the biological assays in a concentration of 100 µg/mL. Results are being currently analyzed and submitted

to phytochemical evaluation, in order to further detect the main classes of compounds responsible for the observed biological activity. The compounds within each active fraction should be isolated and identified. Other biological assays should be established in order to evaluate and determine the mechanisms underlying the antitumor or the antibacterial drug activity.

The optimization of drug discovery using screening techniques and high throughput analysis, as well as the advancement of techniques involving spectrometry allowed the identification of tens of thousands active marine and terrestrial natural products, some of them now in clinical trials, as topotecan, irinotecan and camptothecin from terrestrial sources and bryostatin, dolastatin-10 and ecteinascidin 743 from marine sources. Prospecting the Brazilian rain forests is challenging, but the possibility of new effective compounds supports the current efforts in the search for new lead products^{23,24,25,26,27,28,29,30}.

The encouraging results obtained from the screening project represent an important step towards the effective identification of active drugs against cancer and infectious diseases. Other assays are currently being evaluated and established to evaluate potential activity of the plant extracts against a wide variety of common diseases. Intensive involvement of national and international researchers and laboratories in the systematic screening of active products is required, and will certainly lead to further introduction of more effective drugs against cancer and other diseases into medical armamentarium.

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Cancer epidemiology in Lebanon: recent trends from the National Cancer Registry

Salim M. Adib, MD ; DrPH Joey Daniel, MPH

Abstract

Corresponding author:
Salim M. Adib, MD,
DrPH, National Cancer
Registry Coordinator,
PO Box 175027, Beirut,
Lebanon, E-mail:
salim.adib@usj.edu.lb

Introduction & methods: The National Cancer Registry (NCR) in Lebanon was officially restarted in 2002. A report on Cancer in Lebanon 2003 derives its data from a passive “capture” surveillance system and an active pathology-based “recapture” system. **Results:** In 2003, 7,888 new cases were diagnosed, of which 43% were obtained through the passive “capture” system, and the other 57% from the active “recapture” system. Of those cases, 51.3% were in women and 49% in men. Pediatric cases in patients less than 15 years of age accounted for 3.3% of the total. Mean ages of cases among men was 59.3 ± 18.3 years, and among women 55.1 ± 16.8 years ($p < 0.05$). The five most frequently diagnosed cancer sites in males in 2003 were: prostate, lung, bladder, colorectum and lymphomas. In females these were: breast, colorectum, ovary, lymphomas and lung. Breast remains the most commonly diagnosed cancer in Lebanon. The age-adjusted incidence rate was 173.52 per 100,000. **Discussion & conclusions:** With NCR data, upward trends surmised since the early 1990s are confirmed. Cancer incidence in Lebanon was higher than in other neighboring Arab countries. Special attention should be focused on breast cancer which remains the most frequently diagnosed malignancy in Lebanon. The relative frequency of colo-rectal cancer requires the setting up of national guidelines for early detection. Two other frequently diagnosed cancers are associated with smoking: lung and bladder, and their prevention should be a strong argument for stringent tobacco control policies.

Key-words: Incidence, Middle-East, Arab world

Introduction

The National Cancer Registry (NCR) in Lebanon was officially restarted in 2002, to compile and complete partial hospital-based registries which had already been in place for several years (1-2). Up to that date, one punctual effort to register all cases had been conducted in 1998 (3), more than 30 years after the last such task had been completed in 1966 by Kamal Abou-Daoud, the father of modern epidemiology in Lebanon (4). Within its first year, NCR produced a first, if incomplete report on “Cancer in Lebanon 2002” (5). NCR activity has been hampered by financial constraints, political instability, and bureaucratic difficulties. All these obstacles have already been addressed in a more or less satisfactory manner. Nevertheless, some delay occurred which meant that a Cancer 2003 report could not be published until 2006 (6). Some findings from that report are presented and commented below.

Structure of the Lebanese NCR

NCR derives its data from a passive “capture” surveillance system and an active pathology-based “recapture” system. Passive reporting originates mainly from the MOPH Drug Dispensing Center (DDC). DCC provides cancer drugs free of charge to patients with no health coverage, estimated at 40% of the population. All eligible cancer patients who elect to use the DDC services have to bring a completed report form which is then received and entered at NCR. The passive system also includes forms emanating from the medical services of the Army and the National Security Forces. The National Social Security Fund (NSSF) which covers about 40% of the population is also

supposed to contribute forms to the capture system, although this contribution has yet to become consistent. NCR has also been receiving from UNRWA annual cumulative reports of cancer cases diagnosed among Palestinians in Lebanon.

An active, more complete pathology-based surveillance process, the “recapture system” had to be added to complete the National Registry. A decree 511/1 from the PH Minister in June 2002 was used as the legal framework to start elaborating this system. All pathology laboratories in hospitals and private practices across Lebanon have been collaborating into that system, at various degrees of completeness of case information. The “Cancer in Lebanon 2003” report consists of the reconciliation of data from the two surveillance sources.

Results

Description of cancer cases recorded in 2003

The 2003 report involves 7,888 cases diagnosed during 2003, of which 3400 (43%) were obtained through the passive “capture” system, and the other 57% from the active “recapture” system. Extrapolation from the 1998 LCEG (3) had put the expected number of cases in 2003 between 6800 and 8500 cases, with an approximate average of 7,555 cases. This expected figure compares favorably with the observed one and suggests a near complete accounting for all incident cancers diagnosed in Lebanon in 2003. Experts believe that nevertheless, about 10% of cases in Lebanon in 2003 may have been prevalent ones diagnosed in earlier years. Of 7,888 cases, 51.3% were in women (4047 cases) and

49% (3841 cases) in men. Pediatric cases in patients less than 15 years of age accounted for 3.3% of the total. About 1/3rd of pediatric cancers were leukemias, followed by brain and bone cancers. The average age of children with cancers was 7.6 years (SD=4.0) with a median of 8 years.

The overall age-distribution showed the usual ascending trend after 40 (Figure 1). Mean age of cases was 57.1 years (SD=17.7; median 60 years), with a significant difference on average ($p < 0.05$) between men (59.3

Table 1: Demographic characteristics of incident cancer cases in Lebanon 2003 (N = 7888)

Variable	N	%
Gender	3841	48.7
Men	4047	51.3
Women		
Age-groups		
< 15	237	3.3
15-19	90	1.3
20-24	87	1.2
25-29	126	1.8
30-34	185	2.6
35-39	340	4.7
40-44	455	6.4
45-49	604	8.4
50-54	636	8.6
55-59	712	9.9
60-64	821	11.5
65-69	928	13.0
70-74	864	12.1
≥ 75	1077	15.0
Total*	7163	100
Mean age in years by sex (SD,median) **		
Men	59.3	(18.7; 64)
Women	55.1	(16.8; 56)
All	57.1	(17.7; 60)

* Some data are missing

** $p < 0.01$

± 18.3 years) and women (55.1 ± 16.8 years). The median age at diagnosis for women was 56 years versus 64 for men. Details are shown in Table 1.

The younger age of diagnosis in women compared to men has been a consistent finding in the past decade. It can be largely attributed to the predominance of breast cancer, a cancer located in an external organ, therefore likely to be detected relatively earlier than cancers of inner organs which predominate in men. The median age for breast cancer diagnosis in women was 53 years, compared to 60 in the 28 recorded breast cancer cases in males (1.6% of all breast cases) ($p=0.02$). In almost all other cancers, diagnosis occurred predominantly after 60 years. Apart from breast cancers in women, exceptions included non-Hodgkin's lymphomas (NHL) at a median age of 59, Hodgkin's lymphomas (HL) at a median age of 31.5 years, and leukemia of all types at 41 years. No significant differences in

median age at diagnosis were found in any of those cancer types. Details regarding age at diagnosis by gender for most frequently diagnosed cancer types are presented in table 2.

Table 2 : Differences in ages by gender for selected cancer types in Lebanon 2003 (N=7888)

Types	Age (mean in years, SD)	Median	P-value
Breast (n=1587)			0.02
Males	60.0 (13.0)	61.5	
Females	54.0 (13.0)	53	
All	54.1 (13.0)	53	
Lung (n=810)			0.56
Males	62.8 (12.5)	64	
Females	62.2 (12.8)	64	
All	62.6 (12.6)	64	
Bladder (n =723)			0.68
Males	65.2 (11.8)	66	
Females	64.8 (11.8)	65	
All	65.2 (11.8)	66	
Prostate (n=676)			---
Males	69.9 (8.8)	71	
Colorectal (n=513)			0.28
Males	61.5 (15.2)	64	
Females	62.9 (14.8)	62	
All	62.2 (15.0)	65	
Non-Hodgkin's lymphoma (n=336)			0.90
Males	54.9 (19.3)	60	
Females	55.1 (19.1)	59	
All	55.0 (19.2)	59	
Hodgkin's lymphoma (n=122)			0.39
Males	38.3 (20.3)	31.5	
Females	35.3 (15.7)	32	
All	37.2 (18.8)	31.5	
Leukemia all types (n=319)			0.99
Males	39.1 (25.8)	40.5	
Females	39.1 (25.8)	40.5	
All	39.1 (25.7)	41	

Anatomical cancer sites in adults

Most common anatomical cancer sites are presented by gender in table 3. The five most frequently diagnosed cancer sites in males in 2003 were: prostate (18%), lung (16%), bladder (15%), colo-rectum (8%) and lymphomas (7%). In females these were: breast (42%), colo-rectum (7%), ovary (5%), lymphomas (5%) and lung (4.5%). Bladder cancer was still relatively important in women (3.5%) though at a lower level than in men. Breast remains the most commonly diagnosed cancer in Lebanon, albeit at higher rates than hitherto described. About 4 in 10 of all cancers diagnosed in women is now a breast cancer, 1 in 5 (22%) for the entire cancer case-load. It is followed by bladder (9%), prostate (8.5%), colo-rectum (8%) and lymphomas of all types (6%). Cancers with unspecified or ill-defined sites constituted 1.3% of the total case-load in 2003 (n=115).

Table 3 : Most common cancer sites by gender, Lebanon 2003 (N=7888)

Primary sites (ICD-10) (n, %)	Males	Females	All
Breast (C50)	28 (0.7)	1710 (42.3)	1738 (22.0)
Trachea – Lung & bronchus (C33-34)	614 (16.0)	261 (4.5)	875 (11.1)
Bladder (C67)	583 (15.2)	140 (3.5)	723 (9.1)
Prostate (C61)	676 (17.6)	-- --	676 (8.5)
Colon (C18)	225 (5.8)	228 (5.6)	453 (5.7)
Non Hodgkin's lymphoma (C82-85)	192 (5.0)	166 (4.1)	358 (4.5)
Stomach (C16)	121 (3.2)	104 (2.6)	225 (2.8)
Lymphoid leukemia (C91)	124 (3.2)	79 (2.0)	203 (2.5)
Ovary (C55)	-- --	190 (4.7)	190 (2.4)
Multiple myeloma & related types (C90)	93 (2.4)	70 (1.6)	163 (2.0)
Junction – Rectum (C19-C20)	88 (2.2)	73 (1.8)	161 (2.0)
Meninges & brain (C70-71)	103 (2.7)	57 (1.4)	160 (2.0)
TOTAL*	3841 (100)	4047 (100)	7888 (100)

* All skin cancers except melanomas, and in-situ cancers are not included in the registry.

Age-specific and age-adjusted incidence rates for in 2003

As expected, the age-specific incidence rates (ASIR) increased with age in both sexes. While incidences at older age are higher in men, the rise is steeper in women. The overall crude incidence rate for all ages and sexes in 2003 was estimated at 177.3 new cases per 100,000, and after age-adjustment at 173.52 per 100,000 (Table 4).

Table 4 : Age-specific cancer incidence rates (per 100,000) in the Lebanese population in 2003

Age-groups*	Males		Females		Total	
	n	ASIR	n	ASIR	n	ASIR
0-14	133	19.8	104	16.5	237	18.21
15-24	100	22.2	77	17.9	177	20.09
25-34	138	39.3	173	43.7	311	41.65
35-44	239	97.6	556	198.5	795	151.46
45-54	429	239.7	809	427.7	1238	336.29
55-64	756	491.1	771	477.7	1527	483.0
65-74	1023	946.0	767	684.6	1790	812.97
≥75	644	1462.0	432	961.3	1076	1209.12
TOTAL	3841	174.3	4047	180.1	7888	177.3
ASR	---	169.34	---	176.81	--	173.52

ASIR: Age-specific incidence rate per 100,000

ASR: Age-standardized rate per 100,000

*Only cases with known age were included in each ASIR, while all cases were included in the total

4. Discussion and comments

The comparison of incidence rates with 1998 (3) is not immediately feasible since the ways used to estimate the denominators has changed. Those used in 2003 are those used by the MOPH Epidemiological Surveillance Program to calculate the incidence of

infectious diseases and selected rates in the National Cardio-Vascular Registry (6). Those denominators are therefore now the norm to be used in future years, taking in account the annual growth rate of the population. These are all estimates however, and cannot replace the valid population description which can only be obtained from a general census of the Lebanese population. With NCR providing consistent annual reports, upward trends surmised since the early 1990s will be asserted with more accuracy. Findings in 1998 showed that cancer incidence in Lebanon was higher than in other neighboring Arab countries. This is still confirmed with these data. For example, in 2002, Jordan reported 4187 for a population of 5,300,000 (compared to the estimated 4,500,000 in Lebanon) (7). Reasons for these discrepancies should be addressed separately through inter-Arab studies.

The general distribution of cancer sites, and ages at diagnosis for men and women in 2003 have been consistent with previous reports in 1998 and 2002 (5). There are no gender differences in cancer occurrence, and half of the 2003 cases were diagnosed at 60 or younger. Special attention should be focused on breast cancer which remains the most frequently diagnosed malignancy in Lebanon. Also to be debated is the relative frequency of colo-rectal cancer which requires the setting up of national guidelines for early detection. Two other frequently diagnosed cancers are associated with smoking: lung and bladder, and their prevention as well as that of other cancers such as those of the larynx and oral cavity should be a strong argument for stringent tobacco control policies. Finally, more attention should be devoted to the increasing detection of prostate cancer and the decreasing ages of lymphomas in Lebanon.

Acknowledgment

The National Cancer Registry (NCR) in Lebanon is an institution of the Ministry of Public Health (MOPH). A decree 230/1 issued by the Public Health Minister, Dr. Mohammad Jawad Khalifeh in May 2005 re-established an NCR Committee to oversee its activities. The committee is formed essentially of representatives of cancer-related scientific societies (ex-officio) and some invited experts. Activities of NCR have been directed from the office of MOPH Director-General Dr. Walid Ammar and have been made possible through successive grants from the Italian Cooperation program in Lebanon.

Members of the NCR Committee with oversight on the latest report published in 2006 were: Assaad Khoury (MOPH Department of Preventive Medicine), Ali Shamseddine (Lebanese Society of Medical Oncologists), Salim Adib (Lebanese Epidemiological Association), Antoine Checrallah (Lebanese Society of Pathology), Azzam Dandashi (Parliament Committee on Health), Jawad Mahjour (WHO Representative in Beirut), Georges Saadé (Non-Communicable Disease Program), Michel Daher (Lebanese Cancer Society), Miguel Abboud (Children's Cancer Center), Muhieddine Seoud (Society of Obstetrics-Gynecology), Oussama Jradi (Lebanese Society of Hematology), Peggy Hannah (MOPH Health Education Unit), Marwan Ghosn (NCR Advisor), Howeyda Amin (NCR nosologist).

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Intraperitoneal Chemohyperthermia Versus Intraperitoneal Chemotherapy in Treatment of patients with Malignant Ascites

Laila Ahmed, Hosni Salama, Hanan Abdel Haleem, Sherif Hamdy, Sahar Lashin, Farouk Haggag*, Mohsen M. Abdel Mohsen*, Hany Khatab**and Waleed Fouad

Abstract

Tropical medicine,
* Clinical oncology,
** and Pathology
departments. Faculty
of Medicine, Cairo
University

Background and study aim: There is a theoretical potential to increase exposure of tumor cells to antineoplastic agents by delivering it intraperitoneally. Hyperthermia has been used to augment cancer treatment for decades. Hypothetically, combining both methods together should maximize the toxic effects of chemotherapy. In this study intraperitoneal chemotherapy was compared to intraperitoneal Chemohyperthermia regarding the effect on viability of malignant cells in ascitic fluid cytology. Body weight and abdominal girth were used as clinical parameters for ascites regression. **Patients and methods:** 40 Patients with malignant ascites were recruited. Patients were alphabetically randomized into 2 groups, group 1 included 20 patients who were treated using intraperitoneal chemotherapy. Group 2 included 20 patients who were treated with intraperitoneal Chemohyperthermia. **Results:** Viable malignant cells were significantly lower in group 2 than in group 1 in the first, second, third and fourth week of follow up of the two groups. Degenerative and necrotic cells were significantly higher in group 2 than in group 1 during the same follow up period. Body weight and abdominal girth in group 2 and in group 1 four weeks after the procedure were significantly decreased. Self limiting adverse effects as abdominal pain, anorexia, vomiting, constipation and low grade fever were observed in cases of Chemohyperthermia which were relieved by third day. Impairment in kidney functions as shown by increased creatinine occurred in some patients in group 1. **Conclusion:** Intraperitoneal Chemohyperthermia can affect the viability of malignant cells in patients with malignant ascites with minimal self limiting side effects than intraperitoneal chemotherapy alone. It also improves patient's quality of life due to regression of ascites.

Introduction:

Malignant ascites represents a tough challenge for doctors and a challenging threat for patients. Because patients with malignant ascites have poor prognosis, it is imperative to continue exploring for novel therapies. Intraperitoneal therapy gives us a new dimension for longevity and better life quality. Intraperitoneal administration of chemotherapy has the benefit of higher concentrations of cytotoxic drug delivered locally to the site of the tumor while minimizing systemic toxic effect¹. It has been proven by experiment that tumor tissue is more sensitive to heat than normal tissue². Hyperthermia has been used to augment other forms of cancer treatment for many years. There is evidence that the combination of chemotherapeutic agents and hyperthermia produces additive and synergistic killing effects on tumor cells. Hyperthermia also produces changes in blood flow and oxygen levels in tumor that may have beneficial clinical effects especially in combination with other agents³.

Patients and methods:

Forty patients were recruited in this study. All patients had malignant ascites and were referred to Tropical medicine and Oncology departments in Kasr Elaini hospital, Cairo University. After explaining the procedure, the hazards and the expected outcome, a written consent was taken from all patients. Study period was from April 2004-Sep 2005.

Inclusion criteria:

Age range of the patients was between 43-70 years. All patients had a histopathologically confirmed

diagnosis for their malignant ascites condition. It was either primary or secondary malignant ascites. Laboratory evaluation of these patients for prothrombin time bleeding time, activated partial thromboplastin time, thrombin time and creatinine were all normal. No previous therapy with cytotoxic chemotherapy or radiation therapy. Their life expectancy was 3 months or more according to stage of illness.

Exclusion criteria:

Any patient with history of cardiovascular diseases, allergic reaction, anaphylaxis or angioedema, bleeding disorder, impaired renal function tests or with history of previous trial of chemotherapy or radiotherapy was excluded.

Methods:

History and physical examination for all forty patients were done. All patients had laboratory evaluation which included: urine and stool analysis, complete blood count, liver function tests (bilirubin total, direct) AST,ALT, Alkaline phosphatase, total proteins, albumin, prothrombin time, prothrombin concentration. Serum tumor markers (alpha fetoprotein, CA19-9, CA 125). Abdominal ultrasonography was done to all patients using Hitachi EUB200 machine and 3.5 MHz linear transducer. Ascitic fluid aspiration was done and subjected to cytological examination. Ascitic sample was aspirated each session before and after treatment. Patients were alphabetically randomized into two groups: first group: included twenty patients who underwent intraperitoneal chemotherapy. Second group:

included twenty patients who underwent intraperitoneal Chemohyperthermia.

The machine used for hyperthermia was SLH-100 microprocessor controlled machine for perfusional hyperthermia. (picture 1) 2 wide bore cannulas were fixed to the sides of the patient, 5% glucose (500cc) were infused into peritoneal cavity. A disposable set was connected to both cannulas and the pump was switched on as soon as the adjusted temperature was reached. The infused peritoneal fluid was 45°-48° to keep the temperature of peritoneal fluid 42°-43°. Cisplatin 200mg was infused in the arterial end to circulate in the peritoneal fluid during the time of session. The session duration was at least 60 minutes. Steady flow 150-300 cc per minute with total cycled fluid 12-16 liters. Paracentesis of 2 liters was done before the session and another 3 liters at the end of the session.

The chemotherapeutic agent used was Cisplatin. It was infused intraperitoneally in a dose of 200 mg in group 1 and at the beginning of the hyperthermia session in group 2. Follow up was done by patient's weight and abdominal girth and by cytological examination of ascitic fluid at the end of first, second, third and fourth weeks after the session.

The machine used for hyperthermia: SLH – 100

This is a microprocessor-controlled machine for perfusional hyperthermia. It is both flexible in operator programming as well as safe in use for both patient and operator.

Results:

The age range of patients in group 1 was 48-68 years old (mean 54.9+/-6.0) while in group 2 the range was 43-66 years old (mean 54+/-6.3). all patients in group 1 were females. Group 2 included 12 females and 8 males. All patients suffered from weight loss, abdominal pains, fatigue and vomiting. Physical examination demonstrated: pallor, cachexia, hepatomegaly, peritoneal nodules, lymphadenopathy and ascites. The pretreatment laboratory evaluation is shown in table (1).

Table (1): Laboratory assessment of the studied patients with malignant ascites

Variable		Group I			Group II			P-value
		Mean ± SD	Min.	Max.	Mean ± SD	Min.	Max.	
CBC	RBCs	3.6 ± 0.6	2.2	4.7	3.3 ± 0.9	2.1	4.9	NS
	TLC	5225 ± 2403.5	2500	11000	5937.5 ± 3121	3000	13000	NS
	PLT	222350 ± 76662.1	67000	370000	228600 ± 64482.1	91000	340000	NS
LFTs	Alb (N = 3.5-5.5gm/dl)	3.8 ± 0.3*	3.2	4.4	3.4 ± 0.6*	2.5	4.6	0.013
	AST	109.7 ± 71.9	27	247	92.9 ± 80	25	316	NS
	T.Bil	1.2 ± 1	0.66	5.5	1.1 ± 0.9	0.48	3.5	NS
	D.Bil	0.6 ± 0.9	0.17	4.3	0.5 ± 0.7	0.11	2.7	NS
KFTs	Urea	21.6 ± 2.5	16	25	22.5 ± 1.5	19	24	NS
	Creatinine(N = 0.4 - 1.5mg/dl)	0.8 ± 0.28	0.3	1.4	0.9 ± 0.3	0.5	1.5	NS
Tumour markers	AFP (N = 0-9ng/ml)	8.3 ± 7.8	0.67	34	8.0 ± 7.2	0.7	27	NS
	CA19-9 (N = 0-37 u/ml)	19.5 ± 1	4	34	22.2 ± 14.0	5	54	NS
	CA125 (N = 0-35 u/ml)	130.5 ± 138.8	7	453	86.9 ± 97.2	7	312	NS

NS = nonsignificant P-value > 0.05

Significant P-value < 0.0

Ultrasonographic examination showed the following data: Peritoneal nodules were detected in 16 patients (80%) in group 1 and in 13 patients (65%) in group 2. Ovarian masses were detected in 5 patients of group 1 (25%) and 4 patients in group 2 (20%). No statistical difference were found between the studied groups (P-value >0.05)

Table 2 shows the aetiology of malignant ascites in the studied patients: Ovarian cancer had the upper hand in prevalence in both group, it was found in 13 patients (65%) and 12 patients (60%) in group 1 and 2 consequently. Pseudomyxoma peritonii represented 15% of cases (3 patients) in group 1 and 20% (4 patients) in group 2. There was no statistical significance regarding the type of tumors between the two groups (P-value > 0.05).

Table (2): Type of Tumors found in the studied patients

Variable	Group I		Group II	
	No.	%	No.	%
Gastric cancer	2	10 %	1	5 %
Gall bladder cancer	1	5 %	1	5 %
Ovarian cancer	13	65 %	12	60 %
Breast cancer	1	5 %	2	10 %
Pseudomyxoma peritoneii	3	15 %	4	20 %
Total	20	100%	20	100%

Laboratory characteristics of ascitic fluid did not show any statistically significant difference between the studied groups (P-value >0.05)

Table (3) shows the primary tumor pathology and cytological features of ascitic fluid in the studied groups: the primary tumor pathology was cystadenocarcinoma in 13 patients (65%) in group 1 and 12 patients (60%) in group 2. Adenocarcinoma in 3 patients (15%) in group 1 and 2 patients (10%) in group 2, mucinous adenocarcinoma in 3 patients (15%) in group 1 and 4 patients (20%) in group 2 and mammary duct carcinoma in a single patient (5%) in group 1 and 2 patients (10%) in group 2. There was no statistically significant difference (P-value >0.05) between the two groups.

Table (3): Primary tumor pathology and cytological features of ascitic fluid in the studied patients

Variable		Group I		Group II		P-value
		No.	%	No.	%	
Primary Pathology	Adenocarcinoma	3	15	2	10	NS
	Cystadenocarcinoma	13	65	12	60	NS
	Mammary duct carcinoma	1	5	2	10	NS
	Mucinous Adenocarcinoma	3	15	4	20	NS
Malignant cells	Sheets of malignant epithelial cells	13	65	11	55	NS
	Mucin secreting cells	7	35	9	45	NS
Mesothelial cells	Reactive	20	100	20	100	NS
	Non reactive	0	0	0	0	NS
Lymphocytes	Positive	20	100	20	100	NS
	Negative	0	0	0	0	NS
Total		20	100	20	100	

Cytological examination of ascitic fluid:

Sheets of malignant epithelial cells were detected in ascitic fluid of 13 patients (65%) of group I and 11 patients (55%) of group II while mucin secreting cells were detected in 7 patients (35%) of group I and 9 patients (45%) of group II with no statistical significant difference (P-value > 0.05). There were reactive mesothelial cells in ascitic fluid cytology of all patients of the two groups (100%). Excess Lymphocytes in ascitic fluid cytology of all patients of the two groups (100%) was detected.

Assessment of patients in the follow up schedule showed the following: Table (4) demonstrates the percent change in laboratory profile after the procedure, though serum creatinine in group 1 (35.2± 42.9) was significantly higher than group 2 (11.3± 23.6), other data did not show any statistically significant difference between the studied groups.

Table (4): Percent change in laboratory profile before and after the procedures

Variable		Group I	Group II	P-value
		Mean ± SD	Mean ± SD	
Percent change	RBCs (Before vs. After)	-0.3 ± 11.3	1.3 ± 13.0	0.673
	TLC (Before vs. After)	-8.1 ± 12.0	-5.8 ± 11.1	0.535
	Platelets (Before vs. After)	-1.8 ± 7.3	-2.1 ± 8.5	0.908
	AST (Before vs. After)	15.3 ± 28.1	2.5 ± 14.4	0.078
	ALT (Before vs. After)	3.0 ± 19.7	-0.4 ± 11.1	0.494
	Urea (Before vs. After)	89.2 ± 164.4	24.7 ± 79.0	0.122
	Creatinine (Before vs. After)	35.2 ± 42.9	11.3 ± 23.6	0.035

Adverse effects after the procedures were recorded and are shown in figure (1). Abdominal pain in 12 patients (60%) of group I and 6 patients (30%) of group II, anorexia in 6 patients (30%) of group I and 4 patients (20%) of group II, vomiting in 5 patients (25%) of group I and 4 patients (20%) of group II, fever reaching 38° C in 5 patients (25%) of group II only. When comparing group I with group II, there was a significant statistical difference regarding the presence of fever (p-value < 0.05) yet other data did not show any statistically significant difference (p-value > 0.05).

Figure-1 Adverse effects after the procedure.

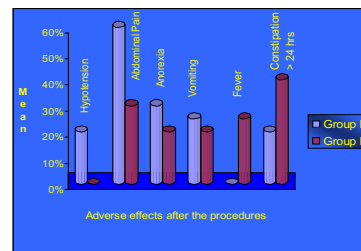


Figure 2 shows the clinical parameters used to evaluate the studied patients before and after the procedures. Body weight and abdominal girth were found to decrease after the procedures and in the next weeks but with no statistically significant difference between the two groups.

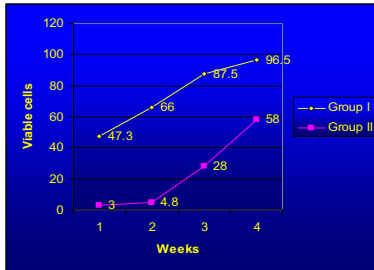
Figure-2 Follow up of viable malignant cells in ascitic fluid of the studied groups

Figure (3) shows the mean value of viable malignant cells in ascitic fluid cytology after 1 week, 2 weeks, 3 weeks and 4 weeks of the procedure. Group 2 was significantly lower than group 1 in viable malignant cell,

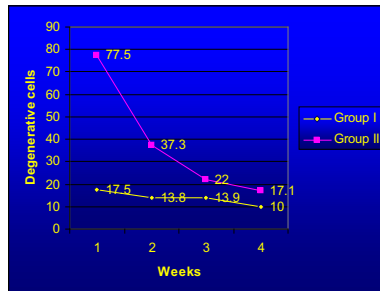
Figure-3 Follow up of degenerative cells in ascitic fluid in the studied groups

Figure (4) shows that the mean value of degenerative cells in ascitic fluid cytology after 1, 2, 3 and 4 weeks of the procedure in group 2 to be significantly higher than group 1

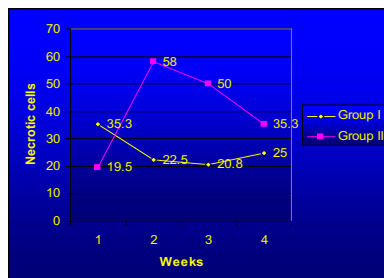
Figure-4 Follow up of necrotic cells in ascitic fluid in the studied groups

Figure (5) shows that the mean value of necrotic cells in ascitic fluid cytology after 1 week of the procedure was significantly higher in group 1 than in group 2 (P-value <0.01). while in the second and third weeks of the procedure. Group 2 was significantly higher than group 1 (P-value <0.01). The mean value of necrotic malignant cells in ascitic fluid cytology after 4 week

of the procedure was (25 ± 7.1) in group I and (35.3 ± 13.3) group II with no statistically significant difference (p-value > 0.05).

Table (5) shows the results of clinical parameters and cytology before the procedure versus 4 weeks after the procedures. All clinical parameters (body weight and abdominal girth) 4 weeks after the procedure were significantly lower in both groups than before the procedure. Regarding the cytology of ascitic fluid, in group 2, the mean value of viable malignant cells 4 weeks after the procedure was significantly lower than before the procedure (P- value <0.01). Also there was a significant change in degenerative and necrotic cells 4 weeks after the procedure (p-value <0.01). In group 1, the cytology of ascitic fluid did not show a significant change 4 weeks after the procedure.

Table (5): The results of clinical parameters and cytology before the procedures versus 4 weeks after the procedures

Variable	Group I	Group II			
		Mean ± SD	P-value	Mean ± SD	P-value
Body weight	Before	98.5 ± 14.8	0.00	103.1 ± 12.5	0.00
	After 4Ws	89.7 ± 14.3		90.6 ± 12.3	
Abdominal girth	Before	99.4 ± 19.5	0.00	98.0 ± 16.0	0.00
	After 4Ws	90.4 ± 18.1		85.8 ± 13.6	
Viable malignant cells	Before	100 ± 0.0	0.167	100 ± 0.0	0.00
	After 4Ws	96.5 ± 10.9		58 ± 26.3	
Degenerative malignant cells	After 1W	17.5 ± 8.7	1.00	77.5 ± 12.1	0.00
	After 4Ws	10 ± 0.0		17.1 ± 4.7	
Necrotic malignant cells	After 1W	35.3 ± 22.3	0.126	19.5 ± 10.5	0.00
	After 4Ws	25 ± 7.1		35.3 ± 13.3	

Significant (P-value < 0.05)

Cytomorphologic Criteria:

Cluster of cells with enlarged, variably-sized round or oval nuclei with prominent macronucleoli. Smear background is clean.

Discussion

Malignant ascites is a manifestation of advanced malignant disease that is associated with significant morbidity⁴. It is usually associated with a poor prognosis and a devastating effect on individuals' ability to function and on their quality of life. Elimination of cancer may be the only way to completely eliminate the fluid accumulation, yet it is not a realistic option. Treatment efforts therefore, focus on symptom control and supportive measures rather than definitive therapies⁵. The use of intraperitoneal drug delivery in treatment of malignant diseases confined to the peritoneal cavity is a definitive way to insure increased exposure of the tumor to antineoplastic agents leading to improved cytotoxicity⁶. Literature reports that achieving an intraperitoneal temperature of at least 41°C is desirable for optimizing drug diffusion into tissues and for maximizing the synergistic effect

with chemotherapy ², Gori et al ⁷ suggested that intraperitoneal hyperthermic perfusion chemotherapy is a feasible, well tolerated and promising alternative as consolidation therapy in patients with ovarian cancer.

The current study aimed to show the effect of intraperitoneal chemotherapy in comparison to intraperitoneal Chemohyperthermia as treatment modalities in patients with intraperitoneal malignancies. The efficacy of each treatment was assessed using viability of malignant cells in ascitic fluid cytology and effect on body weight and abdominal girth as clinical parameters for treatment success. Most of our patients had ovarian cancer, this goes in agreement with Sato et al ⁸ who reported that the most common malignancies to spread along the peritoneum are from the gastrointestinal tract and ovary.

In this work, Cisplatin was the chemotherapeutic agent of choice used intraperitoneally. Cisplatin is known to have 15 times higher concentration if given intraperitoneally than if given systemically as mentioned by Piso et al ⁹. It is one of the antineoplastic agents most frequently used in intraperitoneal Chemohyperthermia (IPCHT). The rationale for its use depends on its potential to work at high temperatures and its ability to act at any stage of malignant cell replication ⁹. Synergism between Cisplatin and hyperthermia has been shown in several clinical trials. In animal models this finding was considered to be a consequence of higher and selective uptake of the drug by the cancer cells ¹⁰.

Our results showed improvement in the quality of life in our patients after the procedures. This was shown by the significant decrease in body weight and abdominal girth after regression of ascites. Patients experienced some relief of pressure symptoms as shortness of breath, upper GIT symptoms, low back ache and fatigue. In both groups there was significant lowering of body weight and abdominal girth four weeks after the procedures. This goes in agreement with McQuellon et al, ¹¹ who reported that IPCHT is effective in preventing recurrence of ascites.

In the current study, cytological analysis of ascitic fluid showed some encouraging results. The viable malignant cells after 1, 2, 3 and 4 weeks of the procedure were significantly lower in group2 than in group 1.

In group I there was no significant difference in percentage of viable, necrotic or degenerative malignant cells before versus 4 weeks after the procedure.

However, in those patients undergoing intraperitoneal chemohyperthermia (Group II) the effects were more pronounced. This was shown by the significant difference in the percentage of viable cells over the 4 weeks as well as the percentage of

degenerative cells in ascitic fluid cytology.

At the end of the follow up period, no significant difference regarding viability of malignant cells was observed in patients undergoing intraperitoneal chemotherapy (group I) than before the procedure. However the difference was still significant in those undergoing intraperitoneal chemohyperthermia.

This could be explained by the fact that Intraperitoneal chemotherapy has an objective in the eradication of the microscopic residual disease and tiny tumor nodules that the surgeon cannot see or remove because of a diffuse involvement of small bowel peritoneum ¹²

The effects of hyperthermia on malignant tissue seem to be mediated by direct cytotoxicity and the microcirculation peculiar to neoplasms. Moreover, hyperthermia synergistically enhances the chemosensitivity of tumor cells to chemotherapy. Mechanisms of action include increased cellular accumulation and activation ¹.

In the current study the adverse effects noted within the first 48 hours after the procedures were abdominal pain, anorexia, vomiting and constipation. Slight elevation of body temperature to 38° C was a significant finding in those undergoing intraperitoneal chemohyperthermia. Most side effects were relieved by the third day after the procedures.

Deraco et al.¹³ analyzed the morbidity of chemohyperthermic treatment. The most frequent complications were ileus, renal failure, pancreatitis, bone marrow toxicity, pelvic infection.

The significant adverse effect related to the combined approach of intraperitoneal perfusion hyperthermia with chemotherapy which is ileus was not observed in our work,

There was a significant impairment of renal function indicated by some elevation of serum creatinine in patients undergoing intraperitoneal chemotherapy. This effect was not pronounced in group II of our study.

No significant adverse effects were noted on blood picture or other blood chemistry profiles in this work.

In conclusion: intraperitoneal chemohyperthermia proved to be superior on intraperitoneal chemotherapy regarding viability and degenerative effects on malignant cells. Side effects were tolerable and better quality of life was attainable. It can be a promising alternative in treatment of malignant ascites.

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Chronic Myeloid Leukemia: New Targeted Therapies

Elias Jabbour, MD and Hagop Kantarjian, MD

Abstract

Department of Leukemia
The University of Texas
M.D. Anderson Cancer
Center, Houston, Texas

Correspondence:

Elias Jabbour, MD,
Department of Leukemia,
Unit 428, The University
of Texas M.D. Anderson
Cancer Center,
1515 Holcombe Blvd,
Houston, TX 77030;
e-mail: ejabbour@
mdanderson.org

Chronic myelogenous leukemia (CML) is a progressive and often fatal hematopoietic neoplasm. The Bcr-Abl tyrosine kinase inhibitor imatinib mesylate represented a major therapeutic advance over conventional CML therapy, with more than 90% of patients obtaining complete hematologic response, and 70%–80% of patients achieving a complete cytogenetic response. Resistance to imatinib represents a clinical challenge and, is often a result of point mutations causing a conformation change in Bcr-Abl, which impair imatinib binding. Novel targeted agents designed to overcome imatinib resistance, include dasatinib (a potent dual Src and Bcr-Abl inhibitor), nilotinib (a selective potent Bcr-Abl inhibitor), bosutinib and INNO406 (both Src-Abl inhibitors), and others. Other approaches are exploring combination therapy, with agents affecting different oncogenic pathways, and immune modulation. Herein, we review some of these targeted therapies, particularly those for which clinical data are already available.

Introduction

CML is a progressive, often fatal, hematopoietic neoplasm characterized by the malignant expansion of pluripotent stem cells in the bone marrow. The disease comprises three clinically recognized phases – chronic, accelerated and blastic – although not all patients follow the classic three-phase course described.¹ The initial chronic phase is typically indolent and often asymptomatic; in half of patients the disease progresses directly from the chronic to the blastic phase.¹ The biology of CML has been extensively reviewed.^{2–5}

CML was the first neoplastic disease for which a direct chromosomal link was found. CML represents an important model for the development of targeted therapies in hematology/oncology, because a single oncogene is responsible for initiating the disease process.⁴ Cytogenetically, CML is characterized in 95% of patients by the presence of the Philadelphia chromosome (Ph), a truncated derivative of chromosome 22 that arises following translocation of genetic material between this chromosome and chromosome 9 (t[9;22][q34;q11]).⁶ The resulting fusion gene, *BCR-ABL* (Breakpoint Cluster Region – Abelson murine leukemia viral proto-oncogene) codes for an abnormal, non-membrane-bound oncoprotein (p210Bcr-Abl). The oncoprotein is a constitutively active tyrosine kinase that perturbs numerous signal transduction pathways, resulting in uncontrolled cell proliferation and reduced apoptosis, or programmed cell death.^{1, 7} Signal transduction pathways activated by Bcr-Abl may be important targets for new therapies and include Ras/Raf/mitogen activated protein kinase (MAPK),^{8–13} phosphatidylinositol 3 kinase,^{14–18} STAT5/Janus kinase,^{19–24} and Myc.^{25–28} Activation of specific signaling pathways by Bcr-Abl is mediated via Src family kinases, which may also represent a therapeutic target.^{8, 29}

The pathogenesis of evolution from chronic phase to advanced phases of CML is not fully understood.¹

Acquisition of the *BCR-ABL* fusion gene increases the propensity of the Ph-positive clone to acquire additional genetic changes. Moreover, the *BCR-ABL* gene may acquire new mutations that allow an already genetically unstable phenotype to acquire further changes. A common gene mutations in the evolution from chronic phase to blastic phase involve the p53 gene,³⁰ loss of p16, INK41/arf EXON 2,^{31, 32} and RB.¹ Mutations can also be critical in the development of treatment resistance. Acquisition and expansion of CML clones with mutations in the ATP phosphate-binding loop (P-loop) of the kinase domain may be associated with an increased risk of disease progression and early mortality in patients treated with imatinib mesylate.^{34–36}

This review describes the novel treatment strategies for patients who cannot obtain benefit from imatinib because of resistance or intolerance.

Imatinib resistance

Incidence

The incidence of primary resistance (patients who never respond to imatinib) and secondary resistance (patients who become resistant after an initial response) increases with more advanced phases of CML. For example, in a 4.5 year follow-up of patients with chronic, accelerated, or blastic phase CML (total n=300),³⁷ primary resistance occurred in 3%, 9%, and 51% of patients (failure to achieve a complete hematological response), respectively. Secondary resistance (hematologic recurrence) was noted in 22%, 32%, and 41% of patients, respectively.³⁷

The recent IRIS trial update described the discontinuation of treatment with imatinib in patients with CML.³⁸ At five years, 171 out of 553 patients (31%) had discontinued treatment with first-line imatinib. Treatment was discontinued for the following reasons: side effects (i.e. imatinib intolerance)/non-CML related deaths 6% (n=32); lack of efficacy/

progression (i.e. imatinib resistance) 11% (n=60); crossed-over to interferon-alpha/cytarabine then discontinued 3% (n=14); 'other' reasons 12% (n=65). Recently, imatinib failure has been defined based on hematologic and cytogenetic responses at set time points as well as on progression and signs of warning.³⁹ Thus, there is a medical need to overcome imatinib resistance in CML.

Mechanisms of imatinib resistance

Several mechanisms of resistance to imatinib, BCR-ABL-dependent and BCR-ABL-independent, have been identified and are discussed below.

BCR-ABL-dependent mechanisms of resistance

Gene amplification resulting in increased expression of BCR-ABL may account for a small proportion of cases resistant to imatinib.⁴⁰⁻⁴¹ BCR-ABL gene mutations are noted in 30% to 50% of patients with imatinib resistance. Clinically relevant mutations disrupt critical contact points between imatinib and Bcr-Abl or induce a transition from the inactive to the active configuration, to which imatinib is unable to bind.^{27, 30} Numerous BCR-ABL mutations have been identified. Not all mutations have the same biochemical and clinical properties: some result in a highly resistant phenotype *in vitro*; others are relatively sensitive, and resistance may be overcome by imatinib dose increase.^{8, 31-34} The T315I mutation and some mutations affecting the so-called P-loop of BCR-ABL confer a greater level of resistance to imatinib and to the novel tyrosine kinase inhibitors.^{35-36, 42}

BCR-ABL-independent mechanisms of resistance

Resistance to imatinib may result from decreased intracellular drug concentrations, either caused by drug efflux proteins,⁴³⁻⁴⁴ or by binding to plasma proteins.⁴⁵⁻⁴⁶ Clonal evolution might also contribute to imatinib resistance.⁴¹ The exact contribution of such mechanisms to resistance is unclear at present.

Recently, the role of SRC-family kinases has attracted particular interest in understanding imatinib-resistance in CML.⁴⁷⁻⁴⁹ BCR-ABL activates multiple signal transduction pathways normally associated with growth, survival, and differentiation of hematopoietic cells. Tyrosine phosphorylation is a critical step in this activation. BCR-ABL itself has a constitutively active tyrosine kinase domain. It may also initiate signalling by activating other non-receptor tyrosine kinases, including members of the SRC-family.⁵⁰⁻⁵³ Overexpression and activation of the SRC-family kinases (LYN) have been reported in imatinib-resistant CML cell lines.⁴⁸⁻⁴⁹ Blood cell lysates from imatinib-resistant patients also contained high levels of LYN protein.⁴⁸

Overcoming imatinib resistance

Several approaches have been investigated to overcome or prevent the development of resistance to imatinib. These include 1) high-dose imatinib, 2) new

more potent tyrosine kinase inhibitors, which would also be less susceptible to mutation-induced mechanisms of resistance, 3) imatinib combinations, and 4) non-tyrosine kinase inhibitors approaches. The first of the newer-generation tyrosine kinase inhibitors, dasatinib (Sprycel; BMS-354825), an orally bioavailable dual BCR-ABL and SRC inhibitor, has been recently approved by the FDA for the treatment of CML post imatinib failure. Nilotinib (Tasigna; AMN-107) is another oral more potent and selective BCR-ABL inhibitor that has been approved as well. Bosutinib and others are in advanced clinical trials. Other strategies include vaccines and investigational approaches.

High-dose imatinib

As the phase I clinical study of imatinib did not identify a maximum tolerated dose for imatinib, dose escalation beyond the standard 400 mg/d is a potential strategy for addressing some forms of suboptimal response or secondary resistance to imatinib.⁵⁴ In a study of 54 patients whose CML had met criteria for nonresponsiveness to standard-dose imatinib or had relapsed after a course of imatinib, treatment was initiated with imatinib at 600 mg/d or 800 mg/d. Among 20 patients unresponsive to standard-dose imatinib, 13 (65%) achieved a hematologic response (9 achieved a complete hematologic response); however, only 1 achieved a major cytogenetic response. Among 34 patients with cytogenetic resistance or relapse, 13 (38%) achieved a major cytogenetic response (6 complete).

The ability of higher doses of imatinib to improve responses in patients with primary or secondary imatinib resistance raises the question of whether imatinib should be initiated at a higher dose in newly diagnosed CML. Investigators from our institution compared outcome of patients with newly diagnosed CML treated with high-dose imatinib with historical matched cohorts of patients treated with standard dose.⁵⁵ Patients treated with high-dose imatinib had higher rates of complete cytogenetic response (91% vs 76%, $p=0.002$); these occurred earlier, with 88% achieving this response after 6 months of therapy vs 56% with standard dose ($p<0.00001$). The cumulative incidences of major molecular response and complete molecular response were significantly better with high dose imatinib.⁴⁰ Progression-free and transformation-free survivals were also better in the high-dose group ($p=0.02$ and 0.005) respectively.⁵⁵

The ability of higher doses of imatinib to elicit responses in patients refractory to or relapsed from previous therapy suggests that dose escalation represents a feasible second-line alternative. Dose escalation is likely to be effective in a subset of patients in whom imatinib resistance is mainly due to either BCR-ABL overexpression or BCR-ABL mutations resulting in only partial resistance,⁵⁶ and in patients who previously

achieved a prior cytogenetic response and lost it. Thus, alternative treatment options are still required.

Dasatinib

Dasatinib is a newly-approved, potent, oral multi-targeted kinase inhibitor of five critical oncogenic enzymes, Bcr-Abl, Src, c-Kit, platelet-derived growth factor receptor, and ephrin A receptor kinases.⁵⁷ It has 325-fold greater potency compared with imatinib against cells expressing wild-type Bcr-Abl, and was effective against all imatinib-resistant kinase domain mutations, with the exception of T315I.⁵⁸⁻⁵⁹ In preclinical studies, dasatinib prolonged survival of mice with Bcr-Abl-driven disease, and inhibited proliferation of Bcr-Abl-positive marrow progenitor cells from patients with imatinib-sensitive and -resistant CML.⁵⁸

Phase I study

In a phase I dose finding study, dasatinib showed efficacy in all phases of CML.⁶⁰ In chronic phase, 35 of the 40 patients (88%) treated achieved a complete hematologic response, and 16 (40%) had a major cytogenetic response (33% complete). In advanced phases, the major hematologic response (bone marrow blasts < 5%) rate was 80% (8/10) in accelerated phase (complete 50%), 77% (17/22) in myeloid blastic phase (complete 18%), and 60% (6/10) in lymphoid blastic phase/Ph-positive ALL. The overall rates of major and complete cytogenetic responses in advanced disease were 36% (15/42) and 21% (9/42), respectively.

Phase II studies

The phase II studies (SRC-ABL Tyrosine kinase inhibition Activity Research Trials [START]) included four trials evaluating the effects of single-agent dasatinib 70 mg twice daily in imatinib-resistant/intolerant patients with chronic phase-CML (START C),⁶¹ accelerated phase-CML (START A),⁶² myeloid and lymphoid blastic phase-CML (START B),⁶³ and Ph-positive ALL (START L).⁶⁴

Three hundred and eighty seven patients with chronic phase CML who had either imatinib resistance (n = 288) or intolerance (n = 99) were evaluable. After a median follow-up of 15 months, 80% of patients intolerant of imatinib achieved a major cytogenetic response (75% complete), and 52% of patients resistant to imatinib achieved a major cytogenetic response (40% complete).⁶¹ In another phase II study, patients with chronic phase CML post resistance to standard dose imatinib (400 mg to 600 mg/day) were randomized (2:1) to dasatinib 70 mg twice daily (n=101) or high-dose imatinib (n=49).⁶⁵ With a median follow-up of 15 months, 35% of patients treated with dasatinib achieved a complete cytogenetic response compared to 16% of patients treated with imatinib. The difference in response rates was most evident after failure on imatinib 600 mg daily (major cytogenetic response rates 49% versus 24%) but after failure on imatinib

400 mg a day (major cytogenetic response rates 58% versus 53%). Progression-free-survival was better with dasatinib (estimated 12-month rates 94% versus 70%; p < 0.0001). Dasatinib has also shown activity in patients with accelerated and blastic phase CML after imatinib failure. Preliminary results from the first 174 patients treated in accelerated phase showed a major hematologic response in 64% of patients (complete in 45%); major cytogenetic response was achieved in 48% of patients.⁶² The complete hematologic response rates in patients with blastic phase CML and Ph-positive ALL were 27% and 35%, respectively; the major cytogenetic response rates were 38% (31% complete) and 57% (54% complete), respectively (Table 1).⁶³⁻⁶⁴

Safety data

Pooled safety analysis of all six studies showed that dasatinib was well tolerated. Most drug-related serious adverse events were managed with dose interruptions or reductions. Myelosuppression was the most common

Table 1 : Results of Dasatinib Phase II Studies in CML And Ph-positive ALL post imatinib failure.

Disease phase	N	Hematologic response (%)		Cytogenetic response (%)	
		Major	Complete	Major	Complete
Chronic	387	91		58	49
Accelerated	174	64	45	37	28
Myeloid blastic	157	50	27	38	31
Ph-positive ALL	46	51	33	57	54
Chronic-Randomized					
Dasatinib	101	92		48	35
High-dose imatinib	49	82		33	16

CML = chronic myeloid leukemia; ALL = acute lymphoid leukemia; Ph = o Philadelphia chromosome; CHR, complete hematologic response; HR = hematologic response of table 1.

reason for dose reductions or interruptions. Grade 3 to 4 thrombocytopenia, neutropenia, and anemia were reported in 50% to 60% of patients in chronic phase. Non-hematological adverse events were mild to moderate. Pleural effusions were observed in 5% to 35%; they were severe in 3% to 15%. These are managed with treatment interruptions/dose reductions, steroids, and diuretics.

Optimizing dose and schedule

The initial phase I trial of dasatinib suggested similar response rates at total daily doses of 100 mg daily or above given in twice daily and once daily schedules. Side effects appeared to be lower with lower doses and with single dose daily schedules. Based on these observations, 662 patients with CML chronic phase post imatinib failure were randomized to 4 treatment arms: 1) dasatinib 100 mg once daily (n=166), 2) dasatinib 50 mg twice daily (n=166), 3) dasatinib 140 mg once daily (n=163), or 4) dasatinib 70 mg twice daily (n=167).⁶⁶

With a minimum follow-up of 6 months, there was no difference in efficacy in the 4 arms: complete hematologic response rates varied between 87% and 93%, major cytogenetic response rates between 54% and 59%, and complete cytogenetic response rates between 42% and 45%. However, patients receiving dasatinib 100 mg once daily had less pleural effusions ($p=0.028$), anemia ($p=0.032$), neutropenia ($p=0.035$), and thrombocytopenia ($p=0.001$) than those receiving the 3 other dose schedules.⁶⁶ In patients with advanced stage disease, dasatinib 140 mg once daily was equivalent in activity to 70 mg twice daily, and was associated with a significantly lower incidence of pleural effusion ($p=0.024$).⁶⁷

Front-line therapy

In a phase II study in newly diagnosed CML chronic phase, 24 patients received dasatinib 100 mg once daily or 50 mg twice daily. The complete cytogenetic response rates at 6 and 9 months were 73% and 95%, respectively, better than results with historical data in patients treated with standard- dose and high-dose imatinib.⁶⁸

Nilotinib

Nilotinib (AMN107, Novartis, Basel, Switzerland) is an oral administered derivative of imatinib that inhibits Bcr-Abl with a 30- to 50-fold greater potency than imatinib recently approved for the treatment of chronic and accelerated phase CML after imatinib failure.⁵⁹ Replacement of the methylpiperazinyl group of imatinib and further rational design to optimize drug-like properties led to the discovery of nilotinib, which had substantially increased binding affinity and selectivity for the Abl kinase compared with imatinib.⁶⁹ Similar to imatinib, nilotinib binds Bcr-Abl in its

inactive conformation. Nilotinib has demonstrated activity against nearly all Bcr-Abl mutants tested, although similar to dasatinib (and imatinib), nilotinib is unable to inhibit the T315I mutation.^{59, 70} Nilotinib inhibits PDGFR and Kit, but to a lower extent than dasatinib. Unlike dasatinib, it does not inhibit Src family of kinases.

Phase I study

In a phase I dose escalation study, nilotinib showed anti-CML activity in 119 patients (17 chronic phase, 56 accelerated phase [10 with clonal evolution only], 24 myeloid blastic phase, and 22 lymphoid blastic phase/Ph-positive ALL) with imatinib-resistant CML.⁷¹ Patients received nilotinib at dosages ranging from 50 mg to 1200 mg/day. Hematological responses were seen in 72% of patients in accelerated phase and in 38% of patients in blastic phase. Cytogenetic response rates ranged from 27% in lymphoid and myeloid blastic phase, to 48% in accelerated phase, and 53% in chronic phase. Nilotinib dosage was escalated up to 1200 mg/d with good tolerance, and the maximum tolerated dose was estimated at 600 mg twice daily. Hematologic and cytogenetic responses were similar in patients with or without mutations, and in patients with p-loop or other mutations. The two patients with a T315I mutation did not respond to nilotinib.⁷¹

Phase II studies

The efficacy of nilotinib was confirmed in 3 ongoing phase II studies in imatinib-resistant or -intolerant patients with CML in chronic, accelerated, and blastic phases. Two hundred eighty-two patients with chronic phase post imatinib failure were treated with nilotinib 400 mg twice daily. The complete hematologic response rate was 74%, the major cytogenetic response rate 52%, and the complete cytogenetic response rate 34%. The estimated one-year survival rate was 95%. Side effects were modest, including Grade 3-4 myelosuppression in 20% to 30%; no pleural effusions were observed. Response rates were similar in patients with imatinib resistance versus intolerance and in patients with or without mutations.⁷² The activity of nilotinib in CML accelerated and blastic phase post imatinib failure was also encouraging, although response rates were lower and response durations shorter (Table 2).⁷³⁻⁷⁴

Among 64 patients in accelerated phase, the hematologic response rate was 59% and the major cytogenetic rate 36%. Among 161 patients in blastic phase, the complete hematologic response rate was 33% (Complete hematologic response rate 21%). Among 41 patients with Ph-positive ALL, the complete hematologic response rate was 24%.⁷⁴

Safety data

In all 3 phase II studies, nilotinib was well tolerated. The rate of Grade 3-4 neutropenia was 28% and of thrombocytopenia 29% in chronic phase. Non-hematologic side effects were infrequent and usually

Table 2 : Results of Nilotinib Phase II Studies in CML and Ph-positive ALL Post Imatinib Failure

Disease	N	CHR	% Response	
			Major	Complete
CML Chronic	280	74	52	34
CML Accelerated	64	25	36	22
CML Blastic	120	21	NR	NR
Ph-positive ALL	41	24	NR	NR

CHR = complete hematologic response; CML = chronic myeloid leukemia; ALL = acute lymphoid leukemia;

Ph = Philadelphia chromosome of table 2.

Table 3 : Results of Bosutinib Phase I/II Study in Chronic Phase-CML Post Imatinib Failure

Response in chronic phase (N=48)	Percent
Complete hematologic response	84
Cytogenetic response	81
Major	52
Complete	33

Grade 1-2. These included fatigue, pruritus, headache, muscle spasms, and gastro-intestinal disturbances. Nilotinib was not associated with the common toxic effects seen with imatinib such as fluid retention, edema, cramps, and weight gain, or with pleural effusions. Nilotinib prolonged the QTcF interval in rare patients.

Front-line therapy

In preliminary results from 14 patients with newly diagnosed CML treated with nilotinib 400 mg twice daily,⁷⁵ a major cytogenetic response was observed in all patients at 3 months (complete in 13 and partial in 1); the complete cytogenetic response rate was 100% in all evaluable patients at 6 months (n=13) and 9 months (n=11). Major molecular response rates at 6 and 9 months were significantly higher with nilotinib compared with historical data with standard-dose and high-dose imatinib.⁷³

Bosutinib (SKI-606)

Bosutinib (SKI606), an orally available dual Src/Abl inhibitor, is 30 to 200 times more potent than imatinib. It has minimal inhibitory activity against C-Kit and PDGFR (therefore expected to produce less myelosuppression and pleural effusions). In a phase I/II study of 69 patients with CML treated post imatinib failure, the complete hematologic response rate among 48 patients in chronic phase was 84%, and the cytogenetic response rate 81%, (major 52%, complete 33%) (Table 3).⁷⁶ The median follow-up on study was short. Grade 3-4 toxicities were minimal including skin rashes in 6% and thrombocytopenia in 6%. Mild to moderate diarrhea was common at the phase II dose of 500 mg orally daily.

INNO-406

INNO-406 is an orally available, dual Abl/Lyn kinase inhibitor that is up to 55-times more potent than imatinib in Bcr-Abl cell lines. INNO-406 demonstrated specific Src kinase activity against Lyn kinase. In an ongoing phase I study, INNO-406 was well tolerated in patients at dose ranges of 60 mg daily to 240 mg twice daily. Encouraging activity was noted in imatinib-resistant and nilotinib-intolerant patients, with 6 out of 14 patients (43%) showing evidence of response.⁷⁷

Non ATP binding tyrosine kinase inhibitors MK0457 is an aurora kinase inhibitor with selective inhibitory activity against T315I mutant CML. In a preliminary experience involving 11 patients with CML advanced phases and T315I mutations, MK0457 given at 8 – 32 mg/m² hourly for 5 days induced responses in 5 patients: 2 complete cytogenetic responses, and 3 partial-minor cytogenetic responses.⁷⁸ Other aurora kinase inhibitors with potential activity against T315I mutant CML include AT9283 and KW2449.

Other therapeutic approaches

Other approaches are being developed for patients who develop resistance to imatinib. Two orally administered farnesyl transferase inhibitors (tipifarnib, R115777; and lonafarnib, SCH66336) have shown clinical activity both as single agents and in combinations with imatinib in heavily pre-treated patients with advanced phase disease.⁷⁹⁻⁸² Decitabine (5-aza-2'-deoxycytidine) administered to 35 patients with imatinib resistant CML induced hematologic response in 23 patients (66%; 34% CHR) and cytogenetic response in 16 (46%).⁸³⁻⁸⁴ Homoharringtonine may have an additive or synergistic effect with imatinib. In preliminary data of a study administering subcutaneous homoharringtonine to 5 evaluable patients with CML in chronic phase who had failed imatinib therapy, all achieved a hematologic response, and 3 patients achieved a cytogenetic response.⁸⁵

Conclusion

For patients with CML, imatinib represented a significant breakthrough in first-line treatment. Resistance to imatinib monotherapy has emerged as an important clinical challenge. The recent availability of highly potent tyrosine kinase inhibitors, dasatinib and nilotinib, has further broadened the treatment armamentarium against CML. With the advent of novel agents and the combination of tyrosine kinase inhibitors, farnesyl transferase inhibitors, and possibly compounds with other mechanisms of actions, both conventional and targeted, the treatment prospects of patients with CML are very hopeful.

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The Role of Novel Antiangiogenic Drugs in Advanced Renal Cell Carcinoma

Toni K. Choueiri, M.D.

Dana-Farber Cancer Institute, Brigham and Women's Hospital, and Harvard Medical School.

Abstract

Over the last few years, renal cell carcinoma (RCC) has become a cancer model for targeted antiangiogenic agents based on the growing understanding of distinct molecular pathways in this disease. Clear cell RCC, the most common histologic subtype in RCC, is characterized by the inactivation of the von Hippel-Lindau (VHL) tumor suppressor gene, which results in the dysregulation of hypoxia response genes, including an overproduction of vascular endothelial growth factor (VEGF) and other growth factors that promote tumor angiogenesis, progression, and metastasis. In advanced RCC, substantial clinical activity has been reported with VEGF blockade employing several approaches including antibodies and small-molecule VEGF receptor inhibitors. Two small-molecule VEGF receptor (VEGFR) inhibitors, sunitinib and sorafenib, have recently been approved by the USA Food and Drug Administration for the treatment of advanced RCC. In this review, we summarize the relevant biology and initial findings of this recent set of groundbreaking trials using targeted molecular approaches for the management of metastatic RCC. Many trials are still ongoing with the goal of defining the optimal sequence and combination.

Keywords: *Renal Cell Carcinoma (RCC), Vascular Endothelial Growth Factor (VEGF), von Hippel-Lindau (VHL), bevacizumab, sunitinib, sorafenib, axitinib, pazopanib.*

Molecular pathways and possible targets in RCC.

A limited subset of patients with metastatic renal cell carcinoma (RCC) will experience benefit from cytokines. Objective response rates are in the range of 10-15% with a durable complete response rate less than 10% (1). A growing understanding of the underlying molecular biology of RCC has established tumor angiogenesis as a relevant therapeutic target in clear cell RCC, the most common RCC histological subtype (90% of all metastatic RCC (2)). The pathogenesis of clear cell RCC was elucidated by the discovery of the von Hippel-Lindau (VHL) gene in the familial cancer syndrome which overall represents 5% or less of all kidney cancer cases (3). VHL is a tumor suppressor gene in which biallelic gene inactivation promotes tumorigenesis. One allele is inactivated through a deletion (also known as loss of heterozygosity) observed in over 90% of sporadic clear cell RCC (4, 5). The remaining VHL allele can be inactivated either through a gene mutation (~50% of clear cell RCC (6, 7) or through gene silencing by methylation of the CpG rich DNA region (~10% of cases 8, 9). VHL, under normal conditions, encodes a protein (referred to as p-VHL) that targets hypoxia-inducible factor (HIF) for proteolysis. 10, 11 However, when VHL is inactivated, a defective p-VHL is produced and HIF is not subject to proteolysis. HIF is able then to induce the transcription of a variety of genes that play an essential role in tumor progression. 12. Transcription genes include VEGF (12, 13) platelet derived growth factor (PDGF) 14, transforming growth factor alpha (TGF-alpha) (15), basic fibroblast growth factor (bFGF) 16, carbonic anhydrase IX (CAIX or G250) 17, erythropoietin 18 and many others (19).

Among these growth factors, VEGF is probably the most important direct mediator of tumor angiogenesis through promotion of proliferation, migration and survival of endothelial cells (20). Inhibitors targeting the VEGF signaling pathway have undergone extensive clinical testing in clear cell RCC.

Clinical studies of VEGF-targeted therapy for RCC

Anti-VEGF Antibody (bevacizumab)

Bevacizumab is a recombinant monoclonal antibody which binds and neutralizes all biologically isoforms of VEGF. 21 This monoclonal antibody is 93% of human and 7% of murine origin. In preclinical models of RCC, murine anti-VEGF antibodies demonstrated antitumoral *activity in vitro* and *in vivo* in renal tumor angiogenesis model systems (22, 21). Initial phase I trials with bevacizumab involved patients with advanced cancer and concluded that bevacizumab can be safely administered intravenously at doses up to 10-mg/kg. Moreover, some patients with RCC showed significant tumor shrinkage (23, 24).

A randomized phase II trial in metastatic clear cell RCC patients who failed interleukin-2, was the first to provide a proof-of-concept of the importance of targeting angiogenesis in RCC. Yang et al randomized 116 patients to receive placebo, low dose (3 mg/kg) or high dose (10 mg/kg) bevacizumab given intravenously every 2 weeks. 25 At a median follow up of 27 months, there were four partial responses (10%), all in the high-dose bevacizumab arm. An intent-to-treat analysis demonstrated a significant prolongation of time to progression (TTP) in the high dose bevacizumab arm compared to placebo (4.8 vs. 2.5 months; $p <$

Correspondence: Toni K. Choueiri, M.D., Dana-Farber Cancer Institute, 44 Binney St, Boston, MA 02115. E-mail: Toni_Choueiri@dfci.harvard.edu

0.001 by log rank test). Toxic effects were minimal and reversible, with 21% grade 3 hypertension and 64% proteinuria (without renal failure) the primary treatment associated toxic effects. 26 Follow-up has demonstrated no further toxic side effects, including four patients who have continued on therapy without progression for as long as five years 26.

Data from the Yang et al trial have suggested that although bevacizumab delayed progression, it might best be combined with tumoricidal therapy to optimize results, and several trials were conducted to test this hypothesis. Two large Phase III trials, an intergroup US trial and a European trial comparing this agent with subcutaneous interferon-alpha, a generally accepted valid comparison arm at that time for patients with metastatic RCC, have recently been completed. The European trial has just been presented at the 43rd annual meeting of the American Society of Clinical Oncology. Between June 2004 and October 2006, 649 patients were randomized to receive interferon-alpha alone with placebo or bevacizumab. Patients treated on the bevacizumab arm had higher response rate (30% vs. 13%, $p < 0.0001$) and TTP (10.2 vs. 5.4 months, $p < 0.0001$). Estimated overall survival (OS) was also higher in the bevacizumab-containing treatment arm but did not reach the predefined level of statistical significance. The benefit from bevacizumab was across all analyzed subgroups. The incidence of grade 3 and 4 adverse events for the bevacizumab/Interferon-alpha arm was significantly higher than the placebo-containing arm (60% vs. 45%, respectively) but was overall manageable and included fatigue (23%), proteinuria (6.5%) and hypertension (4%). 27. No unexpected safety events were observed.

Trials in combination with high-dose IL-2 are also underway. The rationale for this combination lies in the fact that murine models suggest that VEGF inhibition may overcome immunotherapy resistance and enhance IL-2 antitumor effect. 28,29 Bevacizumab 10 mg/kg IV every 2 weeks is being tested with standard high and low-dose IL-2 regimens in several centers such as Cleveland Clinic and Dana-Farber/Harvard Cancer Center.

Bevacizumab has been further investigated in combination with an anti-epidermal growth factor receptor (EGFR) strategy. TGF-alpha is VHL-regulated growth factor for RCC, with biologic effect through interaction with the EGFR 30 15. Pre-clinical investigation in human RCC xenograft models of bevacizumab and erlotinib, a small molecule EGFR inhibitor, have demonstrated potential benefit of combination therapy on tumor growth inhibition 31. A clinical phase II trial in metastatic RCC with bevacizumab 10mg/kg IV every 2 weeks in combination with erlotinib 150 mg daily reported

an impressive 25% objective response rate and 60% survival at 18 months 32. Severe toxicities included rash (13%), diarrhea (13%) and hypertension (8%). However, a recently completed randomized phase II trial of bevacizumab with or without erlotinib in untreated, metastatic RCC (n=100) reported a lack of difference between the treatment arms in progression-free survival and response rates (33).

Small molecule VEGF receptor inhibitors

Small molecule tyrosine kinase inhibitors represent another mechanism for targeting the VEGF pathway. In addition to inhibiting VEGFR, these "promiscuous" agents target other receptors in the split kinase domain family of receptor tyrosine kinases, including PDGFR. 34, 35 PDGF potentiates tumor growth via multiple processes including autocrine and paracrine stimulation of cancer cells and perivascular cells. 36-38

Sunitinib

Sunitinib is a potent and selective inhibitor of VEGFR and PDGFR 39. In vitro assays with sunitinib have demonstrated inhibition of ligand-dependent VEGFR-2 and PDGFR-B phosphorylation as well as inhibition of VEGF-induced proliferation of endothelial cells and PDGF-induced proliferation of mouse fibroblast cells. 40 In vivo experiments demonstrated inhibition of receptor phosphorylation resulting in growth inhibition of various implanted solid tumors 41-44. Several phase I trials have been conducted with sunitinib. 45-49 Dose-limiting toxicity included fatigue, gastrointestinal toxicity, cytopenias and skin toxicity, which were reversible upon discontinuation of treatment. These trials identified 50-mg daily dose given on a 4-weeks on/2-weeks off schedule as the recommended phase II dose.

Two multicenter uncontrolled phase II trials of sunitinib in metastatic RCC have been conducted. Both trials enrolled cytokine-refractory patients. The first trial included 63 patients with all histologic subtypes and demonstrated an objective response rate of 40% and stable disease for greater than 3 months in an additional 27% of patients. 50 The second trial included 106 patients and restricted eligibility to clear cell RCC and required both prior nephrectomy and RECIST-defined progression after prior cytokine therapy. This trial reported one complete and 40 partial responses (objective response rate 39%). Toxicity in these trials, most commonly grade 1 or 2, included asthenia, nausea, diarrhea, stomatitis and cytopenias. 51 Sunitinib was USA FDA-approved for the treatment of advanced RCC in January 2006.

Based on the aforementioned two uncontrolled clinical trials, a landmark multicenter phase III trial of sunitinib versus IFN-alfa was recently reported. 750 patients with previously untreated, metastatic renal-cell

carcinoma in a multicenter were randomized to receive either repeated 6-week cycles of sunitinib or IFN- α (at a dose of 9 MU given subcutaneously three times weekly). The primary end point was progression-free survival. Secondary end points included the objective response rate, overall survival, patient-reported outcomes, and safety. Median PFS was significantly longer in the sunitinib group (11 months) than in the IFN- α group (5 months), corresponding to a hazard ratio of 0.42 (95% confidence interval, 0.32 to 0.54; $P < 0.001$). Sunitinib was also associated with a higher objective response rate (31% vs. 6%) and better quality of life than did patients in the IFN- α group ($P < 0.001$ for both comparisons). The proportion of patients with grade 3 or 4 treatment-related fatigue was significantly higher in the group treated with IFN- α , whereas diarrhea was more frequent in the sunitinib group. 52 The fatigue could be attributed in part to the possible hypothyroidism associated with sunitinib, as shown in later reports (53). This study introduced sunitinib as a standard of care in untreated advanced RCC patients. An update of this study presented at the recent 2007 ASCO meeting reaffirmed superior efficacy of sunitinib compared to IFN- α in first-line treatment of advanced RCC (54).

Sunitinib in bevacizumab-refractory RCC

Given the distinct mechanism of small molecule agents such as sunitinib and the extended spectrum against VHL-mediated targets relevant to RCC (e.g. PDGF) compared to a VEGF ligand-binding agent such as bevacizumab, there is biologic rationale for investigating sunitinib in bevacizumab-refractory patients. A multicenter trial of sunitinib in bevacizumab-refractory patients (only in abstract format) showed a PR of 16% and a TTP of 6 months, suggesting that there might be a rationale for continued targeting of the VEGF signaling pathway (55).

Other possible sunitinib combinations and schedules

The existing dose and schedule for Sunitinib in RCC has been 50 mg daily for the first 4 weeks of repeated 6-week cycles (4/2 schedule) based on prior pre-clinical and phase I trials. A multicenter phase II study was designed to determine the efficacy and safety of single-agent sunitinib when administered in a continuous 37.5 mg/day regimen. One-hundred and seven patients were randomized to AM or PM dosing. Response rate was 20%, lower than responses seen with the 4/2 schedule but the PFS of 9 months was comparable to the 4/2 schedule. Toxicities and efficacy was not different based on the AM or PM dosing and similar overall to the toxicities seen with the 4/2 schedule.

An ongoing larger study (The Renal EFFECT trial) will equally randomize 474 untreated, metastatic clear cell RCC patients to continuous dosing of sunitinib

monotherapy, standard monotherapy (4 weeks on/2 weeks off) or the combination of sunitinib and IFN- α . An initial non-randomized component in 25 patients will establish the safety of the combination arm. This multicenter, open-label trial will have a primary endpoint of time to disease progression.

The safety of combination sunitinib and bevacizumab will be established in a standard phase I dose escalation trial. The rationale being that additive or synergistic VEGF blockade may be achieved with combination sunitinib/ bevacizumab therapy. In fact, increases in plasma VEGF levels have been documented in patients during sunitinib exposure and elevated VEGF levels produced during sunitinib exposure may drive tumor growth during the 2 weeks off period. Co-administration of a VEGF-binding agent such as bevacizumab may address this concern. A large randomized phase II of sunitinib +/- bevacizumab is planned.

Sorafenib

Sorafenib is an orally active, bi-aryl urea molecule with VEGFR/PDGFR inhibition that targets tumor cell proliferation and tumor angiogenesis (56). Sorafenib was initially developed as an inhibitor to the serine threonine kinase Raf-1 that plays an important role in tumorigenesis 57. Ras mutations in RCC are not common, although activation of the MAPK pathway has been demonstrated in 50% of human RCC tumors in one series. 58 Sorafenib significantly inhibited tumor growth in xenograft models in a dose-dependent fashion 59, 60 and has undergone evaluation in multiple simultaneous phase I trials in refractory solid tumors. 61-63, 64 These trials employed standard dose escalation schemas from 50-mg sorafenib daily to 800 mg BID utilizing on different schedules. All trials identified hand-foot skin reaction as the prominent dose-limiting toxicity and identified 400 mg BID of continuously dosed sorafenib as the maximal tolerated dose for phase II trials.

A phase II randomized discontinuation study with sorafenib has been reported in 202 patients with metastatic RCC. Tumor shrinkage was observed in 144 patients (71%) and a progression-free survival (PFS) advantage of 23 versus 6 weeks ($p = 0.0001$) was demonstrated in the randomized cohort of 65 patients. 65 Hypertension, hand-foot skin reactions (HFS) and fatigue were the major severe toxicities. These data prompted a subsequent 903 patient, placebo-controlled, randomized trial of sorafenib in cytokine refractory RCC. This trial reported a PFS advantage in the treatment arm of 24 versus 12 weeks ($p < .000001$) 66, despite a low (10%) RECIST-defined response rate. The PFS benefit was demonstrated across all prognostic subgroups. All grade toxicities mainly included HFS reactions (30% with sorafenib vs. 7% with placebo), rash/desquamation (40% vs. 16%, respectively), hypertension reactions (8% vs. 1%, respectively) and

fatigue (37% vs. 28%, respectively). Grade 3 and/or 4 toxicities consisted of the same reactions mentioned above but were all < 6%. The first interim analysis of overall survival (before cross-over) showed that sorafenib reduced the risk of death, as compared with placebo (P=0.02), although this benefit was not statistically significant according to the O'Brien-Fleming threshold. An updated report from the 2007 ASCO meeting continued to show a PFS advantage independent of VEGF levels. Overall Survival results were confounded due to cross-over. 67

Based on the studies mentioned above, the Food and Drug Administration approved sorafenib for the treatment of patients with advanced renal cell carcinoma in December 2005. Unlike sunitinib, this agent does not appear to have a superior activity to interferon-alpha in the front-line setting. A recently reported randomized phase II trial at the 2007 ASCO meeting showed a median PFS was 5.7 months vs. 5.6 months) for sorafenib vs. interferon-alpha, respectively. Nevertheless, quality of life measures and overall tumor shrinkage were greater with sorafenib (68).

Sorafenib is now undergoing extensive investigation in RCC. For example, a trial of sorafenib and bevacizumab is investigating the safety of this combination. A single arm phase II will investigate sorafenib in metastatic RCC patients failing prior bevacizumab or sunitinib will test the utility of this agent in patients resistant to other VEGF-targeted therapy. Two phase II trials with sorafenib with interferon were recently reported PFS ranging from 6.5 to 10 months.^{79, 80} Sorafenib combination therapy will be tested in a multi-arm randomized trial of 2-drug combinations utilizing sorafenib and other novel agents including bevacizumab and CCI-779, an mTOR inhibitor. This trial, conducted through the Eastern Cooperative Oncology Group (ECOG), will evaluate progression-free survival to select a regimen(s) for further investigation.

Axitinib (AG013736)

Axitinib is a substituted imidazole derivative that inhibits the tyrosine kinase portion of all VEGF receptors and PDGF receptor beta at low nanomolar concentrations (Investigator's Brochure, December 2002). In vitro data demonstrated endothelial cell regression preceded by loss of vessel patency and blood flow with two days of treatment with axitinib. 69 A multicenter phase I trial of axitinib was conducted in 36 patients with refractory solid tumors, including 6 RCC patients 70. Hypertension was the predominant toxicity, with 22 patients experiencing hypertension of any grade and 11 of these patients demonstrating grade 3 hypertension. The maximum tolerated and recommended phase II dose was 5 mg BID in the fasted state 70.

A phase II trial of axitinib at 5 mg twice daily was conducted in 52 cytokine refractory RCC patients. With a median follow-up of one year, a 46% objective response rate was reported with 74% of patients experiencing some degree of tumor shrinkage 71. Further, therapy was well tolerated with hypertension, diarrhea, fatigue and proteinuria noted as common toxicities. Median time to progression has not been reached at a median follow-up of more than 12 months. A phase II trial of axitinib in metastatic RCC patients refractory to prior sorafenib treatment completed accrual and was recently reported. 72 The trial included 62 patients and showed a response rate of 21% and a median PFS of 7.4 months. Interestingly, tumor control was also seen in a subset of 14 patients who received prior sunitinib, indicating perhaps a lack of clinical cross-resistance of these different VEGF-targeted agents.

Pazopanib (GW786034)

Pazopanib is a potent, oral multi-target receptor tyrosine kinase inhibitor of VEGFR-1, -2, -3, PDGFR- and - and c-kit. In preclinical experiments, pazopanib demonstrated significant inhibitory effect in cell proliferation and inhibition of VEGF-induced VEGFR-2 phosphorylation in mouse lungs. 73 Phase I trials showed that 800mg once daily was the recommended dose. 74 Grade 3 and/or 4 side effects were minimal and included nausea, emesis, fatigue, and hypertension. Prolonged disease stabilization/minor responses have been observed in 12 of the 52 patients with a variety of advanced cancers. Specifically, of the ten patients with metastatic RCC enrolled, five patients had evidence of tumor shrinkage. The interim results of a multicenter, international phase II trial utilizing a randomized discontinuation design were reported at the last ASCO meeting by Hutson et al. 75 This trial randomized 225 metastatic RCC patients with cytokine naïve and refractory (failed 1 prior cytokine or bevacizumab-containing regimen) to receive oral pazopanib 800 mg once daily. Based on the robust clinical activity from the first 60 patients, the independent data monitoring committee recommended that randomization be discontinued and the study continued as an open-label single arm study. At week 12, response rate was 27% and disease control (response+ stable disease) was 73% by independent review. Grade 3 or higher toxicities included mainly liver tests abnormalities (14%), hyponatremia (8%), hypertension (8%), fatigue (4%), and diarrhea (3%). A phase III study with pazopanib in advanced RCC patients has completed enrollment and the results are eagerly awaited.

Unanswered questions in the field

Metastatic RCC now has the fortunate circumstance of multiple agents with an anti-tumor effect emerging simultaneously. Decisions regarding the use of these agents in terms of initial and subsequent therapy are

not firmly established as the above-mentioned agents have not been directly compared. Definitive statements regarding relative efficacy or toxicity are sometimes hard to make. The clinical trials noted above employed different methodologies, patient eligibility and response criteria. Thus, several critical questions appear.

1. What is the ideal initial VEGF-targeted anti-angiogenic agent(s)?

Sunitinib is the only antiangiogenic agent that showed superior activity compared to IFN-alpha in untreated RCC patients. Bevacizumab showed superior activity when combined to the “old standard” interferon-alpha

Table 1 : Summary of clinical results with selected anti-angiogenesis agents in metastatic RCC

Agent(s)	Trial design	Clinical activity	Toxicities
Ligand binding agent			
Bevacizumab ^{25, 27, 32, 33}	Randomized, placebo-controlled phase II trial; 100% pretreated pts	10% RR (WHO criteria) Delay of TTP vs. placebo (2.5 vs.4.9 months; p < 0.001)	Hypertension, proteinuria
	Single arm phase II (with erlotinib) 32% pretreated pts	25% RR (RECIST criteria)	Rash, hypertension, proteinuria
	Randomized phase II (+/-erlotinib) trial in untreated patients	No difference in PFS between both arms	Rash, hypertension, proteinuria
	Randomized phase III (IFN-a +/- bevacizumab) trial in untreated patients	30% RR vs. 13% for IFN-a (p<0.0001) PFS of 10.2 vs. 5.2 months for IFN-a (p,0.0001)	Fatigue, hypertension, proteinuria
Small molecule VEGFR and PDGFR inhibitor			
Sunitinib ⁵⁰⁻⁵²	Single arm phase II (2 trials) 100% cytokine-refractory	40% RR (RECIST criteria)	Fatigue, nausea, diarrhea, stomatitis, cytopenias
	Randomized phase III trial in untreated patients vs. IFN-a	31% RR vs. 6% with IFN-a (p<0.001) PFS of 11 vs. 5 months with IFN-a (p<0.001)	Fatigue, cytopenia, rash, diarrhea
Sorafenib ^{65, 66, 68}	Randomized discontinuation phase II	PFS advantage vs. placebo (23 versus 6 weeks; p = 0.0001)	Hand-foot syndrome, rash, fatigue, hypertension
	Randomized, placebo controlled phase III trial 100% pretreated	10% RR (RECIST criteria) PFS advantage vs. placebo (5.5 vs. 2.8 months; p< 0.000001)	Hand-foot syndrome, rash, fatigue, diarrhea, hypertension
	Randomized phase II in untreated patients	No PFS advantage over IFN-a	Hand-foot syndrome, rash, fatigue, diarrhea, hypertension
Axitinib ^{71, 72}	Single arm phase II 100% pretreated	46% RR (RECIST criteria)	Hypertension, proteinuria, diarrhea, fatigue
	Phase II in patients refractory to sorafenib	21% RR (RECIST criteria), PFS of 7.4 months	Fatigue, hypertension, Hand-Foot syndrome

VEGF : Vascular Endothelial Growth Factor

WHO : World Health Organization defines objective response as a 50% or greater reduction in the sum of the bidimensional measurement of tumors.

TTP : Time To Progression

PFS : Progression Free Survival

RR, Response Rate

RECIST : Response Evaluation Criteria In Solid Tumors defines objective response as a 30% or greater reduction in the sum of the unidimensional measurement of tumors.

IFN-a : Interferon-Alpha

and the use of bevacizumab alone in this setting is unclear. However, overall survival data is lacking for both sunitinib and bevacizumab. One should remember that patients who progressed on initial antiangiogenic therapy have the option to receive several other active drugs in this disease masking a survival benefit from the initial agent. It should also be remembered that high-dose IL-2 remains the only therapy that is associated with a potential cure, despite that only 5% of patients will have the fortune to achieve long-term survival. Barriers to IL-2 therapy additionally include severe toxicities, the selection of the appropriate patient and the absolute need for experienced centers for such therapy. Investigation of cytokines plus VEGF-targeted agents is ongoing to provide insight into additive or synergistic clinical effects.

The agents noted above, while similar, are not identical in mechanism, toxicity or tumor response rates. Thus, it is possible that one or more of these agents may have activity in a patient refractory to previous VEGF-targeted therapy as previously mentioned (55, 72). Ongoing clinical trials will define the tolerability and clinical utility of these agents in a refractory setting. Data from these trials in aggregate may provide insight into an optimal sequence of drugs, although specific additional trials will be required for definitive data. Further, clinical trials combining VEGF-targeted approaches are underway to investigate additive or synergistic effects. Whether combination or sequencing of these drugs produces optimal results is at present unknown.

2. Can these agents be used in the adjuvant setting?

At present, there is no standard effective therapy for localized RCC after nephrectomy, regardless of recurrence risk. Antiangiogenic agents may work best in a minimal disease setting and exploration of these agents in adjuvant clinical trials in RCC is expected. An ECOG-lead intergroup trial is open to accrual and randomizes RCC patients who are at high risk for recurrence after nephrectomy to one year of treatment with placebo, sorafenib or sunitinib with a primary endpoint of disease-free survival. Additionally, the SORCE trial lead by the Medical Research Council (MRC) in Europe will randomize over 1,800 high-risk RCC patients after nephrectomy to placebo therapy x 3 years, sorafenib x 3 years or sorafenib x 1 year followed by placebo x 2 years. This trial will test both the utility of sorafenib in this setting and the optimal duration of use. It should be noted, however, that treatment of patients outside of a clinical trial is inappropriate given lack of clinical data and potentially serious toxicities.

3. What is the role of cytoreductive nephrectomy in the era of anti-VEGF agents?

Two randomized phase 3 clinical trials showed a survival benefit for cytoreductive nephrectomy in patients receiving interferon-alpha therapy. ⁷⁶ Whether this applies to anti-VEGF therapy is unknown. However,

many physicians have embraced the paradigm of nephrectomy regardless of the therapy used. Moreover, most reported trials with anti-VEGF agents required nephrectomy as an inclusion criteria, and in theory the benefit from these anti-angiogenic agents pertains to nephrectomized patients. Patients who are unable to undergo nephrectomy can however be given anti-VEGF agents short of other therapies and can be considered for nephrectomy later. This “neoadjuvant” hypothesis is also being tested in clinical trials.

4. What other recent non-VEGF drugs are active in RCC?

The mammalian target of rapamycin (mTOR) pathway (phosphoinositide 3-kinase/Akt pathway) has a central role in the regulation of cell growth and increasing evidence suggests its dysregulation in kidney cancer. Receiving input from multiple signals, including growth factors, hormones, nutrients, and other factors, this pathway stimulates protein synthesis by phosphorylating key translation regulators such as ribosomal S6 kinase ⁷⁷. Hence, use of inhibitors of the pathway represents a new strategy for the targeted treatment of RCC, and mTOR inhibitors have already shown promising clinical efficacy with low toxicity profiles in patients with metastatic RCC. A phase III trial with an mTOR inhibitor, temsirolimus, was conducted in patients with poor-risk metastatic RCC based on encouraging activity in this risk group in a previous smaller trial (81). Patients were randomized to receive interferon, temsirolimus (given intravenous once weekly) or the combination of both therapies. This trial showed a significant overall survival of 10.9 months in patients receiving temsirolimus alone compared to 7.3 months in patients with interferon alone ($p=0.0069$) ⁷⁸. Given the mechanism of action of mTOR inhibitors and VEGF pathway-targeted agents, mTOR inhibitors may prove useful if administered in combination or after resistance to VEGF inhibitors. Future trials will test this hypothesis as well as the use of temsirolimus (and other mTOR inhibitors) in unselected RCC populations.

5. Can we select patients with VEGF-targeted drugs?

Attempts to predict outcome in patients with metastatic renal cell carcinoma (RCC) have conventionally been based on pre-therapy clinical factors such as performance status, disease-free interval, number of metastatic sites, and several laboratory variables. These factors were developed before the era of vascular endothelial growth factor (VEGF)-targeted therapy. Recent analysis from trials with anti-VEGF agents is finding that these factors continue to be of major importance in patient prognostication as reported recently by Choueiri et al (82). Additionally, several serum and molecular markers, many of which relate to

certain alterations of the VHL pathway, are currently being investigated. Responses to VEGF-targeted agents seem to be related to a greater modulation of serum VEGF and soluble VEGF receptors levels. 84 The impact VHL gene status on response VEGF-targeted therapy was tested in a large cohort reported by Choueiri et al during the last ASCO meeting (83). VHL gene status (inactivated by mutation or promoter methylation vs. wild-type VHL gene) and was not found to predict a higher response rate to these agents. However, a subset of VHL mutations that predict a “loss of function” of the VHL gene seem to have the best response to these agents. Future prognostic models will incorporate molecular markers with clinical variables to refine prognosis and prediction in metastatic clear cell RCC patients treated with novel VEGF-targeted agents. These models, if externally and prospectively validated, will culminate in rationally selecting patients for specific VEGF-directed therapeutics.

Conclusion

Advances in the molecular genetics of RCC have led to several promising trials of VEGF-targeted molecular therapies for patients with advanced disease. These trials have shown encouraging results with respect to a delay in the time to progression and response rates that have been, in many cases, much greater than have previously been observed with immunotherapy. The side effects have been unique, as expected, given the novel mechanism of action, but overall manageable. Two VEGF-targeted agents (sorafenib and sunitinib) have been approved in the U.S.A. by the Food and Drug Administration in the treatment of advanced RCC. The ultimate role of these and other agents has not been fully defined, but it is likely that they will be incorporated into multimodal treatment protocols for patients with advanced RCC. Future trials will focus on many issues such as the optimal combination and sequence as well as patient selection based on clinical and molecular features. These recent advances provide us with hope and passion into the future of the field of oncology.

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Conservative surgery with preservation of fertility in gynecologic malignancy

Denis Querleu

Abstract

Gynecological malignancies may affect women in their reproductive age. As a consequence, loss of fertility is a concern for those women who have not fulfilled their desire for maternity. On the other hand, it has been recognized for years that subsequent pregnancy does not adversely affect the outcome of patients managed for cancer, and that the majority of drugs currently used for the treatment of gynaecological malignancies do not impair ovarian function. On the contrary, the dose of pelvic radiation therapy required to control pelvic malignant conditions definitively inhibits the reproductive and hormonal function of the ovaries, and impairs the ability of the uterus to maintain a viable pregnancy.

As a consequence, preservation of fertility in the management of gynaecologic malignancies requires the maintenance of at least the uterus and one ovary without radiation therapy, if possible without inducing pelvic adhesions impairing fertility, although the latter can be overcome using assisted reproductive technologies. Conservative surgery is defined as surgery with complete staging and preservation of at least the uterine corpus and at least part of one ovary.

Department of Surgery,
Claudius Regaud Cancer
Center, Toulouse, France
Querleu.Denis@claudius
regaud.fr

Carcinoma of the uterine cervix

surgeons that are not at ease with radical vaginal procedures. The laparoscopic variant, that mimics the abdominal operation, has also been described [12-13]. In addition, less than radical surgery, involving simple trachelectomy, may be accepted in selected cases of early cervical cancer with negative nodes [14], although this cannot be accepted as a standard.

Oncological outcome

A case-control study comparing conservative versus radical management has provided evidence of the safety of the concept [15]. Central as well as lateropelvic or distant metastases have been described [16-17]. An ovarian recurrence has been reported [18].

The most recent information about long term oncological results has been orally presented in 2006 by the author [19]. A combination of databases of 7 major centers in Canada, Germany, United States, and France totalled 532 patients. Incidentally, duration of surgery was 232 minutes and hospital stay averaged 4.7 days in this large collaborative series. 1% and 1.4% intraoperative and 5.6% and 15.3% postoperative complications were secondary to lymph node dissection and trachelectomy, respectively. 32 patients had some adjuvant therapy impairing fertility as a result of positive nodes or margins. In the remaining 500 patients, 18 recurrences were observed, 7 of them were central recurrences. Six patients died of disease. No influence of pathologic subtype was found, that means that adenocarcinoma is an acceptable indication. LVSI and tumor diameter were strongly related to the risk of recurrence. Tumor diameter is available in 189 patients. Two patients out of 22 presenting with tumors larger than 2 centimeters recurred, compared to 4 out of 167 in patients with tumors less than 2 centimeters ($p < .001$). Information on peritumoral lymph vascular space invasion (LVSI) is available in 403 patients. A significant proportion (11 out of 99, 11%) of patients with LVSI recurred, compared

to 4 out of 304 patients without LVSI ($p < .001$).

This large series provides a clear information available for a safe selection of patients : only patients with node negative, less than 2 centimeters squamous cell or adenocarcinoma of the uterine cervix, without LVSI. Others pathologic subtypes are excluded. Patients with polypoid tumors larger than 2 centimeters with a narrow implantation base on the cervix, far from the endocervical canal may be accepted. The presence of LVSI is a strong argument against the indication.

Obstetrical outcome

Although Dargent's operation is reserved to young women with a real desire of childbearing, some patients do not really desire pregnancy. Preserving at least the option of future childbearing may be the only goal of the operation. Infertility related to the reduction of cervical function does exist but is becoming less frequent as a result of a trend towards strict selection of patients allowing to preserve a 10 mm endocervix [20]. Patients presenting with evidence of impaired fertility may be included as long as the infertility factor is curable. Assisted reproductive techniques including in vitro fertilization, intrauterine insemination, and ovarian stimulation have been used after radical trachelectomy [21].

Pregnancies occur in approximately half of patients. There is a definite risk of premature birth or late abortion that is only partially prevented by permanent isthmic cerclage and additional cervical closure during pregnancy. Early reports by the Lyon team and others [21] found an average 17% of second trimester loss. This can be overcome only by maintaining 10 mm of endocervix [20, 22].

Preoperative workup and selection of patients

Selection of patients is crucial to ensure oncological safety and prevent second trimester abortions and

premature deliveries. Specific preoperative workup is made of MRI and cone biopsy. MRI allows to precisely assess the maximum diameter of the tumor, selecting with a few exceptions patients with tumors less or equal to 2 centimeters. Localization of the upper limit of the tumor is another essential information, that helps to predict the requirements for endocervical resection and estimate the length of remaining endocervix.

A majority of patients are referred after diagnostic cone biopsy. Careful review of the report and whenever necessary review of slides is mandatory. Special attention is given to the identification of lymph-vascular space invasion. The adverse prognosis attached to the presence of LVSI is important enough to advise preoperative cone biopsy in all cases, although repeat multiple biopsies may help to rule out this prognostic factor, that is considered by many authors as a contra-indication to conservative surgery and an indication for adjuvant external radiation therapy.

Another issue is the required upper margin. As much of the endocervix should be retained in order to avoid impairing fertility, and to improve the obstetrical outcome. On the other side, a 8 mm clear pathologic margin is theoretically required for squamous cell cancer, as observed in vulvar cancers [23]. There is obviously a trade-off between fertility preservation and oncological safety that also affects patient selection : location of the upper endocervical limit of the tumor must be compatible with the dual requirement of sufficient clear margin and sufficient remaining endocervix.

Finally, aggressive pathologic subtypes such as neuroendocrine carcinomas are absolute contra-indication. Overall, after a careful selection process, up to 40% of patients presenting with cervical cancer under the age of 40 might still be candidate to conservative management [24].

Other fertility preserving options

Neoadjuvant chemotherapy followed by simple conization has been proposed [25-27]. Although investigational, the option is the only one available for patients with tumors larger than 2 centimeters.

Epithelial ovarian cancer (EOC)

Conservative treatment of at least a part of one ovary and the uterus in order to preserve fertility in young patients can be proposed in selected patients with EOC. However, the results and limits of such treatment remain unclear. Only three studies involving a large number of patients have been published on the results of conservative management of EOC [28-30]. The largest and the only one to include a centralized pathologic review of the ovarian tumor by the same pathologist is the French study [30]. 34 patients of this study fulfilled all inclusion criteria. Thirty had

stage IA disease (G1 n=13; G2 n=14 and G3 n=3); 3 stage IC and 1 stage IIA. Ten patients received postoperative chemotherapy. Eleven patients recurred : ten patients had invasive disease and one had borderline recurrence. Among the 10 patients with invasive recurrence, initial stage and grade were: stage IA G1 n=1; stage IA G2 n=4; stage IA G3 n=1 and stage \geq IC n=4. Overall, all patients with stage > IA recurred. Ten pregnancies were observed in 9 patients. The conclusion is that conservative management is safe in stage IA grade 1 patients, can be discussed in stage IA grade 2 and in selected small volume stage IA grade 3 patients, but that stages IC and over must be excluded. Comprehensive staging including peritoneal cytology, peritoneal biopsies, omentectomy, systematic bilateral pelvic and aortic lymph node dissection, and dilatation and curettage, is mandatory to correctly stage candidate patients and exclude occult advanced stage disease. Pathological examination by a pathologist experienced in ovarian malignancy is mandatory.

As far as the affected ovary is concerned, unilateral salpingo-oophorectomy is advised as a standard. Technique is straightforward, although the need for an oncologically safe removal, without any rupture or morcellation and consequent contamination of the peritoneal cavity or abdominal wall must be stressed. In this regard, laparoscopic technique or small transverse incisions may adversely affect the outcome if they lead to faulty technique and contamination of the abdominal wall. On the other hand, laparoscopic surgery is adapted to the reassessment of apparent stage I diagnosed during primary surgery [31]. Laparoscopic surgery by an experienced surgeon allows careful examination of the contralateral ovary, is an adapted tool to rule out peritoneal growth, and has been found to be a safe technique to perform advanced staging operation such as omentectomy and pelvic/aortic lymph node dissection [32].

However, some reports of pregnancy after chemotherapy for advanced ovarian cancer are available in the literature [33]. Anecdotically, pregnancies have been reported in patients previous managed by normothermic or hyperthermic intraperitoneal chemotherapy [34].

Germ cell tumors of the ovary [35]

Germ cell tumors are rare, but preferentially occur in adolescent or young females. As they are usually curable with fertility preservation at all stages of disease including stage III, fertility preservation is a mainstay of surgical management. This also holds in the setting of residual masses after chemotherapy, that may be benign. Preoperative diagnosis is essential, and involves a routine performance of specific markers in all young women that present with a pelvic mass. Elevated alpha-fetoprotein for the diagnostic of yolk sac tumors and human chorionic gonadotrophin for

the diagnosis of choriocarcinoma are diagnostic of an ovarian germ cell tumor. Ca-125, lactate dehydrogenase, placental alkaline phosphatase are less sensitive and less specific. Diagnostic of malignant transformation of mature teratomas is more difficult, and based on size and squamous cell carcinoma marker of apparently benign dermoid cysts. Diagnostic of non secreting dysgerminomas and immature teratomas is only obtained at final pathology. Thus, conservative management is advisable in young patients even in the case of advanced disease with peritoneal implants. Frozen section is not reliable enough to decide a hasty radical surgery. Unilateral salpingo-oophorectomy is safe, but is too radical if the tumor is benign. Cystectomy may thus be acceptable [36].

Most patients, but those with stage I dysgerminomas or low grade immature teratomas, will received platinum and etoposide based chemotherapy, with or without bleomycin. Fertility is not impaired after chemotherapy for germ cell tumor of the ovary[37].

Borderline ovarian tumors

As the majority of borderline ovarian tumors (BOT) is observed in patients of reproductive age, fertility is a major issue in young female patients presenting with suspicious adnexal masses. It must be stressed that BOT are not precursors of ovarian cancer, and recurrence as a malignant tumor is observed in only 2% of cases [38-39]. BOT are almost invariably controlled by surgical management, and the use of chemotherapy is limited to the unfrequent occurrence of invasive peritoneal implants. Recurrence is possible, but can still be controlled by repeat surgery [40-41]. Prognosis is excellent, with 97-98% long term survival in early stages, 92% in advanced stage serous BOT. Advanced stage mucinous BOT carry a worse prognosis, but the difficulties of differential diagnosis with invasive adenocarcinoma might account for the apparent difference in prognosis.

In general, definitive pathology by an experienced pathologist is required for the diagnosis of BOT, in order to rule out invasive disease, and identify micropapillary serous BOT that carry a worse prognosis and are classified by some authors as “low-grade carcinomas” rather than BOT. When a doubt persists at the time of surgery and frozen section, conservative management then referral to an oncological team including experienced surgeons and pathologists is advised.

The mainstay of management of BOT in young female patients is conservative surgery. Total hysterectomy and bilateral salpingo-oophorectomy is no longer advocated in young patients, whatever the stage. Unilateral salpingo-oophorectomy is standard. Cystectomy only is accepted when the tumor is bilateral or develops on a remaining ovary. When a BOT is diagnosed after cystectomy of an apparent benign

ovarian cyst, complementary salpingo-oophorectomy is indicated only in multifocal or large tumors, and/or when complete removal has not been clearly obtained. Conservative surgical management of advanced stage BOT is acceptable after extensive discussion and informed consent of a patient eagerly desiring children [42].

Surgical staging is based on careful macroscopic examination of the contralateral ovary and peritoneum. Biopsy of the contralateral ovary is not advised as it may induce adhesions without improving the detection of implants compared to visual examination of the ovary. Removal and pathological examination of any extraovarian growth is mandatory to completely manage the disease and detect invasive implants. Node dissection is not standard. Omentectomy, and appendectomy in mucinous tumors, is part of surgical staging and management. However, the low yield of restaging surgery in incompletely staged patients does not justify routine reoperation for the only purpose of random biopsies [43].

Recurrence rate is definitely higher after conservative surgery : 7 % of patients experience recurrence, most frequently on the contralateral ovary, after unilateral salpingo-oophorectomy. Recurrences on the affected ovary are observed in patients managed by cystectomy only, accounting for an overall recurrence rate of 23 % [41]. Repeat fertility preserving surgery is acceptable [39]. Fertility-inducing methods, including ovarian stimulation, have been shown not to impair the outcome [44]. However, most authors advise limitation of the number of stimulation cycles.

Sex cord stromal tumors

Sex cord stromal tumors may occasionally carry a malignant evolution. The majority of unilateral sex cord stromal tumors can be managed conservatively in patients of reproductive age, as the survival for patients who underwent unilateral salpingo-oophorectomy is similar to patients who were managed by hysterectomy [45]. Standard staging is similar to BOT. The need for lymph node dissection is not clearly established, as the yield of lymph node dissection is quite low at the time of primary management, while late node recurrences account for a significant proportion of long-term recurrences [46]. However, radical surgery and chemotherapy are indicated in advanced stage disease.

Uterine sarcomas

It is widely accepted that uterine sarcomas requires upfront surgical management including total hysterectomy. In addition, low grade endometrial stromal sarcomas are hormone dependent, that means that bilateral oophorectomy is an essential feature of surgical management. Even though carcinosarcomas are managed as adenocarcinomas, they are assimilated to grade 3 adenocarcinomas, and therefore cannot be managed conservatively.

Exceptions to the rule are few. Low grade uterine sarcomas found after myomectomy in young patients have been managed conservatively after extensive imaging and counseling [47]. Mullerian adenosarcomas presenting as polyps may also be managed conservatively under the same restrictions.

On the other hand, preferential management of vaginal and cervical rhabdomyosarcomas in children is definitely conservative, based on chemotherapy completed by surgery or radiation therapy only in those girls who do not achieve complete remission [48].

Conclusion

Preservation or intentional sacrifice of fertility is an essential part of counselling at the time of management of primary gynaecologic malignancy in a potentially fertile patient. Upfront radical surgery is not acceptable without informed consent and full exploration of the possibilities of fertility preserving policies. Gynecologic surgeons and gynecologic oncologists must be aware of all the available techniques. They also must be aware that upfront hysterectomy and/or bilateral salpingo-oophorectomy is faulty in adolescent or young female patients who could be safely managed using conservative techniques. Careful preoperative workup of any uterine or ovarian mass is the best prevention of unexpected findings and difficult decisions at the time of surgery. In the case of unexpected suspicious ovarian tumors in young patients, comprehensive staging, and conclusion of the operation awaiting the results of definitive pathology is standard. The limitations of frozen section as a diagnostic test between BOT and invasive ovarian tumors must be known [49].

On the other hand, conservative management seems reasonable only in patients currently or potentially desiring pregnancy. The minimal additional risk of recurrence involved by the conservation of uterus and ovary is not acceptable when pregnancy is not at stake.

Patients managed with fertility preservation deserve active follow up. Special consideration must be given to the need of annual ultrasound examination of retained ovaries (BOT or ovarian cancer patients), or Pap smears and MRI in radical trachelectomy patients. Patients with a stable partner should be advised to attempt pregnancy, considering the cumulative risk of recurrence with time. Any infertility factor must be corrected using available techniques, including ovarian stimulation which is not contraindicated even after BOT. Exceptions to the general rule are high risk conditions, including advanced germ cell tumors that may need additional chemotherapy, knowing that the confounding effect of pregnancy on the levels of markers is a follow up issue.

It is not clear whether radical surgery is indicated after completion of the desire of pregnancy. It is reasonable

to advise total hysterectomy and contralateral oophorectomy in the case of invasive ovarian cancer. In other conditions, such as BOT or conservatively managed cervical cancers, the final decision will be taken with the patient, taking into consideration the risk and curability of recurrence, the accuracy of follow-up in the detection of recurrences, and psychological considerations.

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Pediatric hematology oncology in Lebanon: A historical perspective

Miguel R. Abboud MD*, Peter Noun MD**, Ibrahim Dabbous MD*

*Children's Cancer Center of Lebanon and the Division of Pediatric Hematology Oncology, American University of Beirut Medical Center, Beirut, Lebanon.,

**Attending Pediatric Hematologist Oncologist, Rafic Hariri University Hospital and Lebanese Hospital, Beirut, Lebanon.

Corresponding Author: Dr. Miguel R. Abboud, Medical Director, Children's Cancer Center of Lebanon, American University of Beirut Medical Center
Email: abboudm@aub.edu.lb

Lebanon is a small country located in the Eastern Mediterranean; the current population is estimated at around 4 million inhabitants 25% of who are under 18 years of age. The county has been the scene of much turmoil over the past few years. Despite all odds Lebanon has a well developed system of medical education and care, including one of the oldest existing pediatric hematology-oncology programs in the Middle East. The program started at the American University of Beirut Medical Center (AUBMC).

Dr. Salim Firzli was trained in pediatric hematology in Michigan under Wolf Zulzer. In 1957 he returned to Lebanon as a member of the department of pediatrics at the AUBMC and established the first division of pediatric hematology in the country and perhaps the Middle East. Among his achievements was the diagnosis of the first case of sickle cell disease in Lebanon by hemoglobin electrophoresis, using equipment he had set up. Dr. Firzli also established the use of laboratory tests for the diagnosis of hemophilia and the oversaw the institution of care for patients with malignancies.

Dr. Ibrahim Dabbous joined the faculty of the department of pediatrics in 1966 after training at the University of Washington, Seattle and Northwestern in Chicago.

At that time protocol based care for children with malignancies was started and a comprehensive service for children with hematologic disorders was developed. A large number of children with thalassemia were followed at AUBMC as well children with sickle cell disease and other hematologic disorders. During the late sixties and early seventies the demographic features of sickle cell disease were described (1) and a program of chronic transfusion and chelation with desferioxamine for patients with thalassemia was developed. Eventually cutting edge research led to the identification of the mutations responsible for thalassemia in Lebanon (2,3).

Concomitant developments in this period, which preceded the Lebanese Civil War were the establishment of bone marrow transplantation for immunologic deficiencies in and the establishment of a radiation oncology department at AUBMC.

At the same time Dr. Farid Khouri established a state of the art diagnostic service at AUBMC which include cytogenetics and immune phenotyping of leukemias and lymphomas (4,5). The work of the division and

services continued to develop up till the time of the civil war. During the war the division provided care to a large number of children with blood diseases and cancer with good outcomes despite the obvious difficulties and very limited resources. It is important to note a hematology oncology service was also started at Hotel Dieu de France (HDF), the other teaching hospital in Lebanon at time, then under the leadership of Dr Najib Taleb. While not exclusive to children, the service at HDF provided care to large number of children and adolescents with pediatric malignancies and blood disorders (6)

The Lebanese civil war lasted 15 years during which services were maintained both at AUBMC and HDF due to the efforts of committed professional. Retrospective analysis of the treatment of pediatric ALL in Lebanese children covering this period showed very good results, which are all more impressive considering the difficulties encountered by investigators at that time (7). The war ended in 1991 and the post war period of reconstruction witnessed a flowering in the academic and medical sectors and a substantial improvement in the care of children with malignancies and blood disorders. The number of pediatric hematologist-oncologists increased to a total of 15 most of who were trained in US or France. They are now organized in the Lebanese Pediatric Hematology Oncology Club under the aegis of the Lebanese Pediatric Society.

During this period a number of specialized centers were started. The first of these was the Chronic Care Center which provides diagnostic services and comprehensive care to children with thalassemia in collaboration with governmental funding agencies and through private fund raising. The CCC developed an extensive transfusion and chelation service that serves over 500 children and adults with thalassemia. This center has become a focus of active research in thalassemia and was active in enacting a law of premarital screening that has been responsible for significant decrease in the number new cases of thalassemia born in the country (8).

In 2002 the Children's Cancer Center of Lebanon (CCCL) was established as an affiliate of St Jude Children's Research Hospital (SJCRH) at the AUBMC. The center has over the past 5 years provided care to 470 newly diagnosed cases of cancer in children and provided consultation services to over 1000 patients Lebanon and the region. In collaboration with the International Outreach Program at St. Jude the Center developed protocols, trained professionals and

established a state of the art diagnostic laboratory. This facility currently provides flow cytometry and molecular testing to any patient diagnosed in Lebanon with all expenses paid by the CCCL Foundation. The center also established a limb salvage program, a pediatric stem cell transplant service and a comprehensive sickle cell program. Furthermore a 3 year a fellowship and a nurse training program were established. It is the aim of these programs to train specialist for, Lebanon and countries in the region.

Through collaboration with the Lebanese Ministry of Health and independent fund raising and support from SJCRH the center is able to provide services to all patients regardless of their ability to pay. In addition to this the Center provides patients treated at other centers with medications, diagnostic tests and procedures such limb salvage. Currently 7 hospitals in Lebanon have active pediatric hematology oncology services and two centers provide stem cell transplantation to children. Thus, at this time all children diagnosed with cancer and hemoglobinopathies in Lebanon have access to advanced diagnostic and treatment facilities

The development of research has followed that of the clinical services. Lebanese investigators have been very active as evidenced by the increasing number of publications in the various areas of pediatric hematology-oncology. The next steps should be development of a cohesive and active collaborative group for clinical research and the establishment of a core of basic researchers interested in problems of pediatric hematology and oncology.

Despite the above achievements significant problems remain in the several areas. The most pressing problem at this time is funding. Efforts by private fundraising and the Lebanese Ministry of Health have led to improved coverage for children with cancer and

hemoglobinopathies. Funding for advanced procedures such as allogeneic stem cell transplants is still problematic. In another domain funding for hemophilia care is also still less than desired. In these two areas two international agreements were reached, the first to provide help with SCT in hemoglobinopathies, with Mediterranean Institute of Hematology in Italy, and the second for twining between the Lebanese Hemophilia Society with the University of Geneva. Nonetheless support is still needed to improve care for patients with hemophilia and to provide SCT for children in whom this is a potentially curative option. The problem of funding will be exacerbated if the current political crises in the country persist. It is hoped that currently active public-private partnerships will weather the storm with the support of the private donors, the Lebanese Ministry of Health and international partners.

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Palliative Care in the Hospital Setting

Miguel R. Abboud MD, Manal Azzi MS, Samar Muwakkit MD

Children's Cancer Center
of Lebanon
American University of
Beirut Medical Center
Beirut Lebanon

Author for
Correspondence:
Miguel R. Abboud, MD,
Professor of Pediatrics,
Children's Cancer Center
of Lebanon, American
University of Beirut
Medical Center, PO
BOX 11-0236, Beirut,
LEBANON
E-mail:
abboudm@aub.edu.lb

Introduction

Few situations are as complex and demanding as the end of life care for children and their families. In developed countries high level palliative care is now a standard. Sustained effort was focused on this area and in the US the Institute of Medicine of The National Academy of Science conducted an extensive survey of the issue (1). This landmark report identified significant areas where improvement was needed and in particular the need for more research and the development of new models of care in this area. The World Health Organization has also published two expert reports on palliative care (2, 3) but very few research reports have come from countries with limited resources.

The treatment of childhood cancer is one of the great success stories of modern medicine. The high success rate is the result of well designed clinical trials in childhood cancer and the efforts of health care workers in tertiary care centers. Nonetheless in the best of circumstances about 25% of children diagnosed with cancer eventually die of their disease. Thus the development of palliative care programs along with community outreach and education must be a priority for tertiary care centers. These programs need to be geared to the total care of patients whose disease is not responsive to curative treatment. In this setting control of pain and other symptoms as well as psychological, social and spiritual support are of paramount importance.

The problems surrounding end of life care are a major concern for practitioners caring for children with cancer all over the world. The issue however acquires an added dimension of complexity in countries where resources are limited and end of life care often is seen to compete with curative care for cancer patients. This is further compounded by the absence of community based organizations that are instrumental in supporting patients and families at the end of life, thus complementing the tertiary center in providing adequate care, while relieving the pressure from and sparing the resources of, the often overloaded centers. An additional obstacle to adequate palliative care is, in many countries, the absence of a legal framework that supports parent, patient and physician decision making at the end of life (4).

The Children's Cancer Center of Lebanon at the American University of Beirut Medical Center was founded in 2002 as an affiliate of the St Jude Children's Research Hospital. Since its founding, the Center has provided care to over 400 children with cancer and a large number of children with hematological disorders.

All newly diagnosed cases were treated on modern protocol based therapy and a few patients treated elsewhere were accepted for care. We have developed a multidisciplinary team approach for handling end of life care, relying primarily on the tertiary care center staff, volunteers and facilities. In the discussion below we will address common problems experienced in the end of life care of children with cancer and illustrate the issues with examples from our clinical practice.

Problems experienced at the end of life in pediatric cancer patients

Case Presentation 1

Zein, a 4 year old boy diagnosed with metastatic neuroblastoma. Certain features of his disease defined him to be at high risk for recurrence and this was discussed with the family early on. He underwent high dose chemotherapy and hematopoietic stem cell transplant successfully but was found to have a bone marrow recurrence 6 months later. At that time the parents met with the attending physician, psychologist, primary nurse and one of the volunteers at the Center to whom they were close. After they were informed of the results, the option of second line therapy was discussed and family opted for no therapy as there was possibility of a cure and the child was symptom free. Two months later he developed pain and was started on oral morphine sulfate and then fentanyl patches. As the pain worsened and he developed raccoon eyes he was hospitalized for IV morphine. At this time a second meeting was held with family in which they asked that a central line be placed and that palliative chemotherapy be started after they reviewed all potential toxicity. He received one cycle of chemotherapy and had a prompt response of bony pain and a clearing of the discoloration around his eyes. He then went on 4 more cycles of chemotherapy as an outpatient and remained pain free for 5 months with no significant toxicity due to chemotherapy and no hospitalizations. At the time of this writing he was still alive and active but plans were being made with the family to face the eventual disease recurrence.

Discussion

Once a child is diagnosed with cancer in most centers efforts are made to support the family and provide hope for an eventual cure, which is the case for the majority of patients. It is however important to keep in mind that palliative care is an integral part of the care plan for every patient with different degrees of emphasis according to the clinical scenario. For example we believe in earlier and more active intervention in patients with diseases that have a high risk treatment

failure such as brain stem gliomas and neuroblastoma with poor risk features. Clear and frank discussions with the family early on for allow better planning to address problems as they arise. Regardless of initial risk features the course of a particular child and the response to therapy is often difficult to predict (5). The path of patient to death after treatment failure is also unpredictable and this needs to be taken into account when care plans are formulated and in discussions with families. It is important to know that recent data shows that parents first recognize that a child has no realistic chance of cure 3 months after the pediatric oncologist. Earlier recognition would perhaps be associated with better integration of palliative care and allow more time for families to plan (6). Furthermore, parents recognize two goals as part of the end of life therapy of their children: life extending therapy and maximizing quality of life (5). Studies have shown that parents maintain these dual goals concurrently and thus they should be integrated in any plan for end of life palliative care. This was clearly what Zein's parents had in mind when they opted for palliative chemotherapy after they studied the potential risks and benefits of the proposed regimen.

Case Presentation 2

Reem was 14 year old girl with osteogenic sarcoma of the right distal femur. She received chemotherapy and underwent limb salvage surgery. At the time of surgery a poor tumor response was found, that is a bad prognostic factor. The patient and family were informed of this and arrangements were made for the addition of new chemotherapeutic agents to her regimen. Six months after the end of chemotherapy she was found to have a solitary lung metastatic nodule. This was surgically removed but three months later two more nodules were detected. They were surgically removed and salvage chemotherapy was started. After 3 cycles of chemotherapy she was found to have multiple lung nodules and a large mass that was unresectable. After discussions with the patient and family a decision was made to stop chemotherapy and to care for the patient at home. She became progressively dyspneic and oxygen was started at home. The parents were told that should the need arise or if they did not feel comfortable at home that they could come to the hospital at anytime. Oral morphine and later fentanyl patches were also started. She complained of fatigue, shortens of breath and pain. Home visits were made by one of the center's physicians and she continued to come to the center to attend special school classes and to receive blood transfusions. Six days before her death the family called and said that they could not cope with the situation at home and the increasing pain and dyspnea. She was admitted to the hospital started on p.r.n. IV morphine every 3 hours. The house staff were concerned about using high doses of opioid for several reasons. After discussions with the house staff and family the patient

was started on a continuous morphine drip. An initial CBC and electrolyte panel was obtained as well as a chest CT to look for pneumonia or a pleural effusion. No further laboratory studies were obtained. Her pain and dyspnea were controlled and she died peacefully with the family around her 5 days later.

Discussion

This case illustrates several of the problems faced in the care of children who have failed cancer therapy. In a study by Wolfe and colleagues conducted a landmark study of the symptoms experienced by children at the end of life and their treatment (7). The most common symptoms causing suffering were as in our patients fatigue, dyspnea and pain. In addition patients experienced loss of appetite, nausea vomiting and constipation. An important finding of this study was that these symptoms were often not treated successfully. In our patient fatigue it was most likely due to hypoxia and anemia. Other factors such as insomnia may also have contributed. We opted to manage her fatigue by maintaining an adequate hemoglobin and oxygenation. In this setting it is also important to review the patient's drug therapy to identify any drugs or drug interactions that contribute to fatigue.

Pain management was also a significant problem in this patient. There are several obstacles to pain management at the end of life. Our patient was initially well managed with oral round the clock oral morphine and later a fentanyl patch. Upon admission to the hospital she was seen by the general pediatric team and p.r.n. morphine started. This way of administering morphine or other opioids is ineffective in this setting. Under dosing of opioids is often the result of ignorance of pain management protocols and the irrational fear of addiction among practitioners. An additional obstacle to pain management at end of life is the fear of many practitioners that opioids may hasten the death of patients. While there is little evidence that appropriate opioid use at the end of life hastens death (1, 8, 9), this issue has gained added urgency as the debate rages around euthanasia. At a recent conference in Lebanon the view that starting a morphine drip could be considered "passive euthanasia" was voiced. This was opposed by Father Charbel Chlela a Maronite Catholic theologian on the grounds that the good derived from relieving pain at the end of life far outweighs any unintended bad results. This view was supported by a Moslem Qadi and a large number of oncologists but opposed by a legal representative of the Lebanese government. Thus, further debate is needed to establish a legal frame work that will cover what is current practice in many centers in Lebanon (4). In this context it is important to note that practitioners taking care of children with life threatening conditions should receive special training about the use of medications for the relief of pain in the end of life setting.

The reader is referred to several excellent reviews on this issue (5, 11, 12).

The management of dyspnea at the end of life can be a challenge. In our case the cause was obviously the pulmonary metastasis and the uncomfortable feeling was relieved by systemic opioids. We however considered a superimposed pneumonia which could be treated with antibiotics or a pleural effusion that could be drained. Other causes of dyspnea at the end of life include cardiac failure and pulmonary toxicity due to chemotherapy. In a patient with dyspnea all of these possible causes need to be critically evaluated and managed.

Two other important issues are raised in this case; the first is the issue of daily activities and schooling and the second is the location of care for a dying patient is. Quality of life is very important for children and their families at the end of life. We have created a school within the Center that is staffed by volunteer teachers. The school is well attended and several children like the case above insisted on continued attendance despite a very poor prognosis. Concerning location of care studies in the US estimate that about half of children with cancer die at home (7). There have been studies that claim that this may have beneficial effects on family functioning but the situation is far from clear. Where all resources are available is not clear what leads certain families to chose end of life care at home or in the hospital or to allow hospice care for the dying child. Given our limited resources for home care we have opted to give families a choice of being at home or in the hospital at the end of life. With time more families have chosen to stay home and recently many of the children have died at home. We have made it always clear that, as in the case presented above, the Center's door is always open to the family and patient and the staff is available for consultation and advice. We are currently preparing to survey the families of children who died in order to improve our services.

Conclusions

The problems faced by the dying child and the family are complex and require a multidisciplinary team approach. Management of the dying child may be carried out in the home or hospital but significant resources are needed. Hospice care is not available in many parts of the developing world. In Lebanon hospice would be a welcome addition and complement care offered at our center and other pediatric oncology programs. This is important for optimization of care and better utilization of resources. Significant involvement

of health care practitioners and the community as well as the development of the legal framework governing the delivery of care at the end of life are required. These and other issues are addressed in two recent reviews (5, 13).

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Development of new technologies in oncology: do the advantages justify the cost?

A perspective from within the industry Pierre Dodion, Executive Director, Pfizer Inc., New York, USA
 Pierre. F. Dodion@pfizer.com

Pharmaceutical companies, whether publicly traded or privately owned, have the objective, like in any business segment, to be profitable. But pharmaceutical companies fully measure the very particular nature of their business, i.e. the improvement of human health and the quality of patients quality of life which may of course translate in several aspects such as alleviating symptoms, prolonging life, curing or preventing a disease,... In reality the two objectives (profit and patients welfare) go intimately together. It is unlikely that a pharmaceutical company that would market medicines of limited interest for the patients would stay successful in the long run. Conversely and in particular in oncology, the most successful companies from the economical perspective are those that have been able to develop and commercialize true advances for the patients. Beyond these general considerations, we have then to decide what a significant interest or advance is and what will be the price the society is willing to pay to stimulate innovation and to allow the company to sustain financial stability. — There is no simple way to define what a significant advance in oncology is. A 25-30% relative improvement in survival or progression-free survival versus the standard of care is commonly accepted for regulatory approval (Johnson). However, while this may correspond to an improvement of survival by several months in the adjuvant setting, it may also represent, for refractory cancers, a minimal survival advantage of a few weeks with some toxicity — which may not constitute a big advance; however, the same survival advantage with limited or no toxicity may represent such a significant advance. Finally, for some patients, even a short survival advantage with toxicity may be important. In the US, for example, advocates have asked that patients with certain diseases could continue receiving drugs of unproven benefit (Okie). In reality, the various stakeholders — regulators, oncologists, patients, payers and others — have different views about what represents a significant advance. That decision is currently pretty much in the hands of regulators, clinical investigators and the pharmaceutical industry. The commonly accepted advance in survival or progression-free survival could require adjustments in a broader discussion involving all stakeholders on a more regular basis.

The other side of the equation is price. The price of new medications is often perceived as excessive. There are however certain economical facts that cannot be ignored (Scherer). The development cost of a new drug is currently around 1 Billion dollars and there is no indication that regulatory and clinical requirements will decrease in the future; on the contrary, many recommend additional studies in particular in the domain of safety (Psaty). Furthermore, a development program is by no means successful in all cases; the failure rate remains around 50% en at the stage of phase III clinical trials. Failure rates are of course much higher at earlier stages of development. Revenues from successful drugs have of course to be used to support these unsuccessful developments. The average net cost of a drug development (encompassing the successful and unsuccessful developments) is in fact much higher than 1 Billion dollars. How can one conclude on these considerations? It all comes down to the concept of value: considering its cost, does a given medication bring added value to the patient and to society (Cutler)? The value concept encompasses benefits, safety considerations, price and other considerations (including subjective ones). Customers are actually reasoning in terms of value in many acts of every day life; as an example, some customers prefer to buy a standard car, others prefer to buy a more luxury and costly car, because despite its higher price, it represents value for the buyer. In the domain of health care, the interaction is more complex than the standard one between a buyer and a seller. In particular, the patient does not choose to be sick; in addition, he is rarely aware of the true price of a medication; on the other side, payers and providers may not have a full understanding of the benefit of a medication, as they are not exposed themselves to the disease. In other words, no single partner is in a position to truly assess the value of a medication, It can be anticipated that the debate around cost of new medications will continue and may even increase in the future, especially at light of finite resources. Progress in this challenging domain could be achieved by bringing more often all stakeholders to the table of the discussion — not just the pharma industry and payers and by shifting the discussion from price to value.

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Editor Disclaimer

Health Economics and cost effectiveness studies have been incorporated in the treatment algorithm

decisions in the developed countries and in some developing countries where medical services were mainly supported by governmental bodies. Point of views from private and governmental institutions, patients, industries and third party payers are developed. We would like to share with our readers and different stakeholders of the medical community their opinions.

Perspectives from the regulatory bodies, patients, institutions and industry are welcomed and will be published in upcoming numbers of the PAJO. This article is a first comment that we republish today because it serves the discussion which is actually going on especially with the development of new expensive treatments. As usual the opinions expressed are solely those of the author.

God Heals

Remember when you heard the words -
and your mind went blank - you were in another world

God heals

Remember in your darkest hours -
when all that surrounds you is pain and sorrow

God heals

Remember friends' prayers - your family's encouragement
glimmers of hope from everyday angels

God heals

Quiet...you can hear Him now -
always there - yet never this close

God heals

It's just another day -
yet everything has changed - and you hear yourself say

God heals

Birds are singing -
the sky is a beautiful blue - flowers are blooming...

God heals

Truths that you knew as a child -
awakened again with new understanding

God heals

Remember when others can't -
that life is a gift - each day to treasure

God Has Healed



Announcing the Birth of the Arab Society of Gynecologic Oncology (ASGO)

In the early 1970s, a group of physicians in the United States of America realized that the care of women with gynecologic cancers was fractionated, delivered by various teams with no direct collaboration and lacking research direction. These physicians decided that the patients' outcome could be significantly improved if their care was governed by guidelines and policies that were established by a professional body of experts. Accordingly, the Society of Gynecologic Oncology (SGO) was founded and fellowship training programs in gynecologic oncology were established in a number of medical centers and universities. This initiative turned to be one of the best measures taken to improve the care of women with gynecologic cancers. Over the past three decades, a number of professional international, regional and local societies were formed, prompted by the need to spread this movement around the world and encouraged by the success of the SGO.

In the Arab countries, there are many established professional societies that have targeted general fields in medicine. The field of gynecologic oncology has been so far without representation. After discussions with a number of society leaders and specialists, a group of volunteers met in Dubai in December 2006 and included gynecologic, medical and radiation oncologist from various countries of the Arab World. The attendees agreed on the need to form a regional society for gynecologic oncology. It was decided to affiliate with existing societies rather than create yet another group that may suffer from poor membership and representation. The group established communication and discussions with the Arab Medical Association Against Cancer and the Arab Association of Obstetrics and Gynecology Societies. It was agreed with their leadership that the new gynecologic society will represent both groups and address the educational and research needs of gynecologic oncology for both groups.

The Arab Society of Gynecologic Oncology was officially registered in October 2007. The Bylaws have been completed and summarized below.

The goals for which the Society is formed are as follows:

- (a) To improve the care of patients with gynecologic cancer in the Arab Countries;
- (b) To advance knowledge and raise standards of practice in gynecologic oncology;
- (c) To encourage regional research in gynecologic oncology;

The Society will strive to achieve its goals through the following means

It will seek collaboration with the mother association Arab Medical Association Against Cancer, with the Arab Association of Obstetrics and Gynecology Societies, the International Gynecologic Cancer Society (IGCS) as well as other professional medical societies, local and international, in order to:

- o Develop multidisciplinary curricula for education and training of professionals
- o Review, discuss and disseminate among its constituency internationally accepted clinical guidelines covering all aspects of gynecologic cancer

It will make its knowledge and data available to policy makers, governmental agencies or organizations in the MiddleEast that are involved in medical care, in order to:

- o Address the magnitude of the problems related to gynecologic cancer in the region and its impact on public health
- o Educate the public and increase their awareness regarding the risk factors, signs, symptoms and management strategies of gynecologic cancer
- o Positively impact health policies by introducing important and effective cancer screening modalities

It will promote networking and active communication among its members as well as other of the medical and scientific community in order to:

- o Disseminate knowledge acquired from new research completed locally as well as internationally
- o Develop a think tank to review, modify and apply internationally adopted clinical guidelines
- o Promote collaboration in clinical as well as translational research

Membership is open to gynecologic oncologists, medical oncologists, radiation oncologists, pathologists and basic scientists who provide care to women with gynecologic and/or are involved indirectly in advancing the field of gynecologic oncology. An annual membership will be charged to all members to cover the costs of the administrative activities.

The first council members include: Adnan R Munkarah as President (Saudi Arabia); Muhieddined Seoud as Vice President (Lebanon); Isam Lataifeh as treasurer (Jordan); Saad Ghazal-Aswad as Secretary (United Arab Emirates); Mostafa El-Sorafi (Egypt), Medhat Faris (Oman) and Ismail Al-Badawi (Saudi Arabia) as members at large.

For interested individuals, feel free to contact us at the following email addresses:

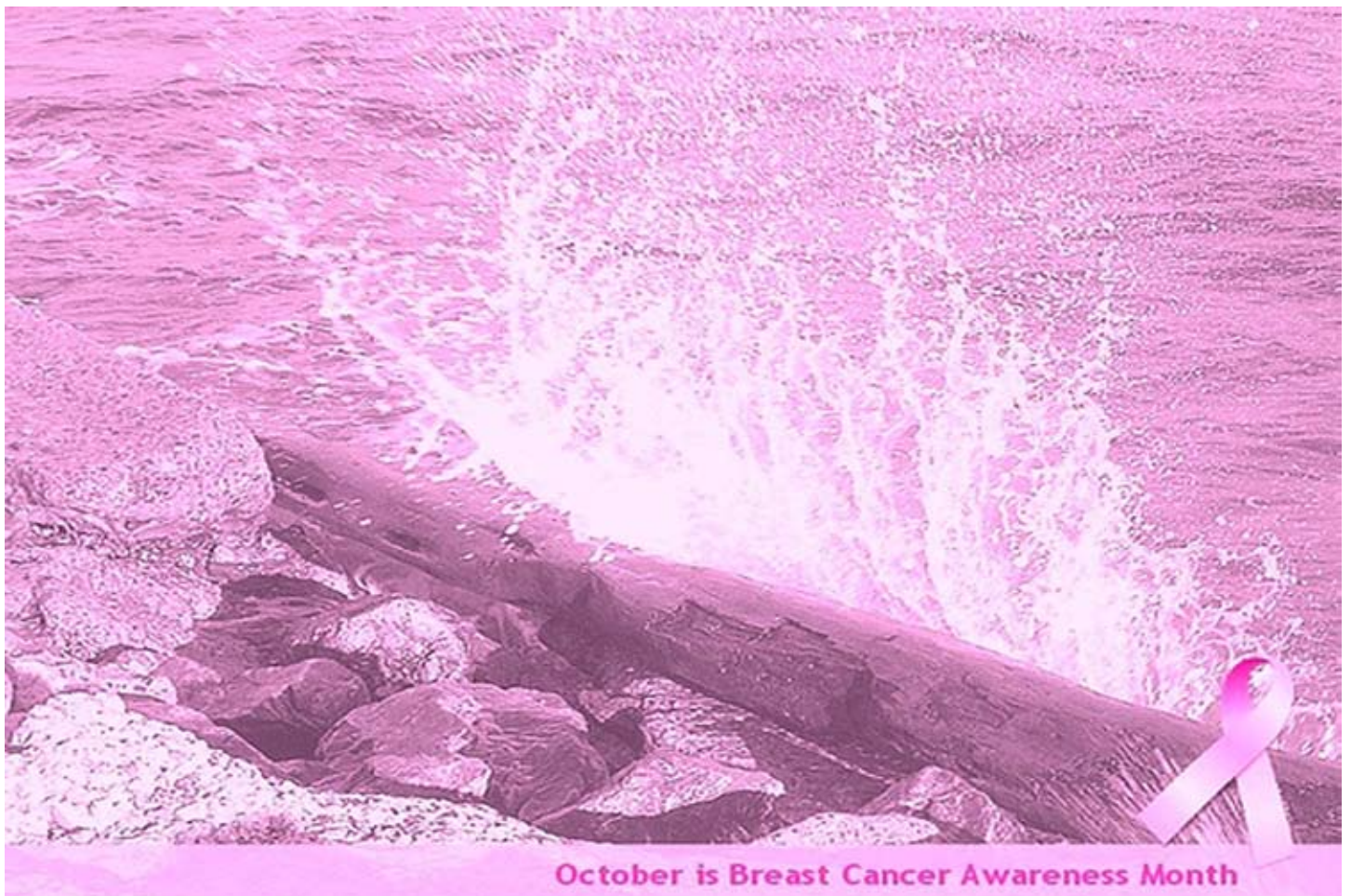
Adnan R Munkarah : amunkarah@kfshrc.edu.sa, Chairman, Department of Obstetrics &Gynecology, King Faisal Specialist Hospital & Research Center. Muhieddined Seoud : mike@aub.edu.lb, Saad Ghazal-Aswad saadaswad@yahoo.com

Raising Breast Cancer Awareness in the Middle East

The U.S.-Middle East Partnership for Breast Cancer Awareness and Research organized a one week trip from October 20-26, 2007 to the United Arab Emirates, Saudi Arabia, Kuwait, and Jordan aiming to promote breast cancer awareness and early detection.

The First Lady Laura Bush met with governmental officials, leaders of medical and educational institutions and prominent women's-rights activists. In Abu Dhabi, Ms. Bush met breast cancer survivors at the Pink Majlis at Sheikh Khalifa Medical City, where breast cancer patients can come to talk freely about a subject that has been considered too embarrassing and frightening to mention and are educated about the disease. In Dubai, she met with Her Highness Shaikha Fatima Bint Mubarak, Chairwoman of the General Women's Union and Chairperson of the National Higher Committee for Anti-Breast Cancer Campaign. She helped the launch the "Making It Our Business: Breast Cancer Awareness" program. Eleven companies, both American and Emirati, signed on as charter members, pledging to educate their employees, families, and customers about breast cancer. In Riyadh, Saudi Arabia, Ms. Bush visited the Abdul-Latif Cancer Screening Center, which has just installed state-of-the-art facilities. In Jordan, she met the King Hussein's two daughters, who have been very active in the King Hussein Cancer Center (KHCC), which is very well known for pediatric oncology. At the KHCC, Ms. Bush announced that the U.S.-Middle East Partnership will expand to Morocco, the Palestinian territories, and Egypt next year.

The U.S.-Middle East Partnership for Breast Cancer Awareness and Research, organized by the State Department's Office of Public Diplomacy and Public Affairs and the Middle East Partnership Initiative on June 12, 2006, unite the Susan G. Komen Foundation with MD Anderson Cancer Center, Johns Hopkins Medicine, the United Arab Emirates and Saudi Arabia. These partners are collaborating to develop awareness campaigns suited to each country, to increase research, training and community outreach efforts and to help women build the knowledge and the confidence they need to be in charge of their own health.



Training and Educational activities of SEMCO - ICEDOC

SEMCO, The South & East Mediterranean College of Oncology, is an alliance to AMAAC which is working to unite Arabs together against Cancer.

SEMCO was founded in collaboration with ICEDOC, The International Campaign for Establishment and Development of Oncology Centers. The ICEDOC's Experts in cancer without Borders is the main corpus of ICEDOC. It offers free consultation and advice to authorities, colleagues and cancer patients on volunteer basis.

Course Name	Date	Place	Responsible
ASCO – SEMCO course and conference	5 – 6 April, 2007	Cairo Egypt	Pr. Hussein Khaled
SEMCO-ESMO- EASO-ACOD conference	5 – 7 December, 2007	Alexandria Egypt	Pr. F.Abdel Gawad, Pr. Nashaat Loutfy, Pr. Alaa Kandil, Dr. Yousri Rostom, Dr. Tamer Refaat
SEMCO-ASCO advanced course	26 – 28 March, 2008	Cairo Egypt	Pr. Atef Yousef SEMCO & Ain Shams Dr. Atef Badran
S E M C O - A S C O Multidisciplinary Management Course MCMC course	20 - 22 November, 2008	Izmir Turkey	Pr. Munir Kinay Colleagues from Izmir & Turkey
Breast Cancer Symposium- SEMCO Conference	First week of February, 2009	Cairo Egypt	Pr. Shahla Masood, USA
SEMCO-ASCO Advanced course and meting on Integrated Oncology Palliative care.	26 - 27 March, 2009	Cairo Egypt	Pr. Hussein Khaled
ICEDOC's Experts in Cancer without Borders contributions & SEMCO			
Contribution in The ASCO MCMC course	1 - 3 July, 2007	Shanghai, China	Professor Heinz Zwierzina ,Austria
Contribution in the INCTR Cancer Control workshop	22 August, 2007	Dar Esalam Tanzania	Pr. Prasanna Kumar, India
ICEDOC expert mission	1 st trimester 2008	West Africa	
ASCO MCMC course in collaboration with ICEDOC Volunteer Expert mission	6 March 2008	Nairobi Kenya	Dr. Twilab Ngoma.

Please feel free to suggest, to propose and to leadICEDOC & SEMCO belongs to all!
Your ICEDOC & SEMCO are too grateful for all of you valuable contribution and advice.

Contacts:

worldcooperation@gmail.com

ahmedelzawawy@hotmail.com

www.icedoc.org

Gulf Countries Oncology Activities

<p>Activities of The Kuwait Oncology Society</p> <p>Management of Superficial Bladder Cancer Screening and Early Detection of Breast Cancer Molecular Biology Symposium Lung Cancer: Carcinogenesis & Management Symposium on Heredity & Cancer</p>	<p>November 2007 December 2007 November 2007 April 2008 April 2008</p>
<p>Activities of The United Arab Emirates</p> <p>Breast cancer First National Campaign in UAE Introductory Oncology Course</p>	<p>22 October 2007 24 November 2007</p>
<p>Activities of The Kingdom of Bahrain</p> <p>Advanced Course on Breast Cancer for Oncologists</p>	<p>8 November 2007</p>

Riad Amer, MD, President
 Mobile: 0599393332
 riadamer@yahoo.com

Abdel Razak Salhab, MD
 Vice-President & Genral Secretary
 Mobile: 0599031060
 salhabpna@yahoo.com

Foad Sabatin, MD
 President of the Scientific Committee
 Mobile: 0546850029
 falereidi@pol.net

Husni Makboul, MD
 Treasurer
 Mobile: 0599206114
 husnimaq@najah.edu

Ayman Al Dirk, MD
 President of the social commiittee
 Mobile: 0599764227
 Ayman_darak@hotmail.com

**The First Oncology Conference
 Palestinian Oncology Society
 16 -18 April 2008
 Palestinianoncologists@yahoo.com**

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 from 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

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 external 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 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.

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.

Editorials and Comments and Controversies

The Editor-in-Chief may solicit an Editorial to accompany an accepted manuscript. Editorials unrelated to a specific article should be submitted to the Comments and Controversies section. 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.

Case Reports / Correspondence / Special Articles letters to the Editor

The letter 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 requirements

All manuscripts should be submitted directly to the Editor-in-Chief by e-mail (mghosn.hdf@usj.edu.lb ; editorinchief.pajo@yahoo.com) and by sending the article on a CD and a soft copy.

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 Editors' decision, along with the reviewers' comments, as appropriate, via e-mail. Proprietary names will not be published in article titles or abstracts; accepted manuscript titles and abstracts will be modified to contain the generic name only.

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. Editors' disclosures are published annually, whereas reviewers' disclosures are held in confidence.

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, middle initial, 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. 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, methods, or similar heading), (3) results, and (4) conclusion. Authors may use design instead of patients and methods in abstracts of review articles. Proprietary or trade names may not be used in the title or abstract. 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:
2. Knox S, Hoppe RT, Maloney D, et al: Treatment of cutaneous T-cell lymphoma with chimeric anti-CD4 monoclonal antibody. *Blood* 87:893-899, 1996 Journal article in press (manuscript has been accepted for publication):
3. Scadden DT, Schenkein DP, Bernstein Z, et al: Combined immunotoxin and chemotherapy for AIDS-related non-Hodgkin's lymphoma. *Cancer (in press) Supplement*:
4. Brusamolino E, Orlandi E, Morra E, et al: Analysis of long-term results and prognostic factors among 138 patients with advanced Hodgkin's disease treated with the alternating MOPP/ABVD chemotherapy. *Ann Oncol* 5:S53-S57, 1994 (suppl 2) Book with a single author:
5. Woodruff R: *Symptom Control in Advanced Cancer*. Victoria, Australia, Asperula Pty Ltd, 1997, pp 65-69 Book with multiple authors:
6. Iverson C, Flanagan A, Fontanarosa PB, et al: *American Medical Association Manual of Style (ed 9)*. Baltimore, MD, Williams & Wilkins, 1998 Chapter in a multiauthored book with editors:
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13. Miller BA, Ries CAG, Hankey BF, et al (eds): *Cancer Statistics Review: 1973-1989*. Bethesda, MD, National Cancer Institute, NIH publication No. 92-2789, 1992 ASCO Educational Book:
14. Benson AB 3rd: Present and future role of prognostic and predictive markers for patients with colorectal cancer. *Am Soc Clin Oncol Ed Book* 187-190, 2006

Figures

Figures must be cited in the order they appear in the text using Arabic numerals. Figure legends should appear within the document in a separate section just before the references. Figure legends are required for all article types. Figure legends must not exceed 55 words per figure and should be written below the figure. Images may be embedded in word or Power Point files.

Tables

Tables must be cited in the order in which they appear in the text using Arabic numerals. The table's legend may include any pertinent notes and must include definitions of all abbreviations and acronyms that have been used in the table. Tables submitted with multiple parts will be renumbered. Legends must not exceed 55 words per table and should be written above the figure.

Appendices/Acknowledgments

Appendices and acknowledgments longer will appear in the print version of the article.

Language

Appropriate use of the English language is required for publication in the Journal.

Post-acceptance Information

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Corresponding authors must provide unique e-mail addresses for each contributing author at manuscript submission. Upon acceptance of the manuscript, each author will receive an e-mail invitation to sign a statement confirming that the manuscript contains no material for which publication would violate any copyright or other personal or proprietary right of any person or entity. Manuscripts will not be published until each author has completed the form.

Page Proofs

Corresponding authors will receive proofs and must carefully review them for data and typesetting errors. Corrections to proofs must be returned by e-mail, fax, or mail within 2 weeks. The corresponding author is responsible for collecting and submitting all author corrections into a single submission. Publication may be delayed if proofs are not returned by the publisher's deadline. The Editor-in-Chief must approve all major alterations, which may delay publication of the manuscript.

For any suggestions and comments or any correspondence please send your emails to : editorinchief.pajo@yahoo.com