Review
Treatment of Acute Lymphoblastic Leukemia

Targeted Therapy Development
Angiogenesis review

Meeting Highlights
ASCO 2008
UICC 2008
Editorial Board Profiles > 2 - 3
International Advisory Board > 5
Editorial > 6 - 7

Original Articles
° Superior Sulcus (Pancoast) tumors of the lung
  Riad Younes > 8 - 9
° Low dose Docetaxel, Carboplatin and Capecitabine in the treatment of recurrent and/or metastatic HNC: Results of a Pilot Phase II study
  Marwan Ghosn et al. > 10 - 13

Review
° Treatment of Acute Lymphoblastic Leukemia
  Sima Jeha > 14 - 19

Targeted Therapy Development
° Overview of Angiogenesis: Mechanisms and Predictors
  Zaher Otrock et al. > 20 - 24

Case Report
° Primary Meningeal Non Hodgkin Lymphoma
  Hamouda Boussen et al. > 25 - 26

Meeting reports
° ASCO 2008 Main Highlights
  Ahmad Awada > 27 - 28
° Best of ASCO in Beirut, Lebanon
  Nagi Saghir et al. > 29
° The World Cancer Declaration adopted by the UICC World Cancer Congress 2008 in Geneva
  Michel Daher > 30 - 31

News from the Arab World
° Cancer Prevention & Early Detection
° 2nd LSH Regional Meeting
° Clinical Trials in MENA
° LSMO 7
° EASO Lymphoma day
° Best of CTRC-AACR
° AMAAC Annual Conference 2009
° The Gulf Federation for Cancer Control
° COMO 8

Calendar of Events > 43 - 44

Instructions for authors > 45 - 47
Dr Marwan Ghosn
Dr Marwan Ghosn is currently the Head of Hematology & Oncology division at Clemenceau Medical Center, affiliated with Johns Hopkins International, in Beirut - Lebanon. He has previously served for more than 15 years as Head of the Hematology-Oncology Department at Hotel-Dieu de France University Hospital in Beirut. He is Professor and Program Director of the Hematology Oncology Department at Saint-Joseph University School of Medicine. He served as President of the Lebanese Society of Medical Oncology. He is an active member of several national & international scientific organizations and societies. He is author and co-author for more than 60 peer-reviewed articles. He contributed in the redaction of several chapters in books in the field of medical oncology and pharmacology. He is the Editor-in-Chief of the “Cancer Letter” edited by the Lebanese Cancer Society. Dr Ghosn has special interests in multiple areas including leadership in conducting research and clinical trials for new drugs and/or new combinations in solid tumors, and an expertise in the management of breast cancer, urologic cancers, gastrointestinal tumors and in the geriatric oncology domain. He recently acquired an expertise in the health care management and hospital management, and especially in Patient Safety issues.

Dr Sami Khatib
Dr. Sami Khatib earned his MD (1978) and the Spanish Board in Clinical Oncology (1982) from Autonomous University of Barcelona – Spain. He is a Senior Consultant in Clinical Oncology and Early Detection, and has a Diploma in Hospital Management. Dr. Sami’s areas of professional interest are in Radiation Oncology (breast and lung), Screening, and Early Detection. He is a member of Barcelona Medical Association, Barcelona Radiation Oncology Association, Spanish Oncology Association, Jordan Medical Association, American Society of Clinical Oncology, European Society for Therapeutic Radiology and Oncology, and a member of the American Society for Therapeutic Radiology and Oncology. Dr. Khatib is the Co-Author of the WHO – Pan American Health Organization Book entitled «Organization, Development, Quality Assurance and Radiation Protection in Radiology Services: Imaging and Radiation Therapy». Dr. Khatib was the Associate Director for Patients and Community Affairs at King Hussein Cancer Center (KHCC). Recently, He is the Senior Assistant Director General and the Director, Office of Cancer Planning and Public Outreach Programs at King Hussein Institute for Biotechnology and Cancer (KHIBC). Moreover, he is the Secretary General of the Arab Medical Association Against Cancer (AMAAC).
Dr Khaled Al-Saleh
Dr Khaled Al-Saleh is currently Consultant and Head of Radiation Oncology Department at Kuwait Cancer Control Center in Kuwait. He obtained his degree of M.B.B & Ch. from Alexandria, Egypt in February 1980. He obtained his Board Certificate in Radiotherapy and Oncology from Madame Curie Institute, Warsaw, Poland on November 1992. He served as Registrar at the National Cancer Centre, Tokyo, Japan in 1985 and the Middle Sex Hospital, London, from 1986 to 1989. He served as General Secretary of the Gulf Federation for Cancer Control (GFCC), since 2002. He is an Associate General Secretary of the Arab Medical Association Against Cancer (AMAAAC) and Head of Kuwait Society of Oncology since 2001. He is currently the Editor-in-Chief of the Gulf Journal of Oncology and an Associate Editor of the Pan Arab Journal of Oncology (PAJO). He is an active member of the American Association of Clinical Oncology and the International Union Against Cancer (UICC). Dr Al-Saleh is member of the Kuwait Writer Association and the Kuwait Press Association. He has published four short stories in Arabic language, has weekly articles in Al-Watan daily news paper and translated brief of oncology book in Arabic. He was also a writer of Palliative Medicine in Arabic in 2002.

Dr Jamal Khader
Dr Jamal Khader is a Consultant Radiation Oncologist at King Hussein Cancer Center (KHCC) in Amman, Jordan. He is currently the Director of the Radiation Oncology Residency Program and the Head of the Section of Thoracic Cancers and Genitourinary in the Radiation Oncology Department at KHCC. He is also acting as Director of the International Extramural Affairs Office of the Center. He is an Examiner Member of the Radiation Oncology Committee-Jordan Medical Council. Dr Khader is an active member of the American Society of Therapeutic Radiation Oncology (ASTRO), the European Society of Therapeutic Radiation (ESTRO), the Association of UICC fellows (AUF), the American Brachytherapy Society (ABS), the Jordan Oncology Society (JOS), the Jordan Medical Association (JMA), the Arab Medical Association Against Cancer (AMAAAC), the Jordanian Chapter of the Mediterranean Task Force for Cancer Control (MTCC). He was nominated as General Secretary of the Jordan Oncology Society (JOS) from 2003-2006.

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

Dr Nazar Makki
Dr Nazar Makki is graduated from Alex University in 1959. He obtained his diploma in 1961 and pursued his fellowship (Ed) in UK where he obtained his diploma in May 1965. He worked as house officer and registrar in surgery in Alex. University, Saint James Hospital (London) and Surbiton General Hospital (Surrey, UK). He was appointed as clinical demonstrator in surgery and lecturer in surgery in 1965 and as assistant Professor of Surgery in 1970 at Mosul Medical College, University of Mosul, Iraq. He was appointed as Head of the department of surgery in Mosul 1979 and Head of the department of surgery at Al-Nahrain Medical College, Al-Nahrain University (Formerly Saddam College of Medicine Saddam University 1989-1994, Baghdad). He served as Supervisor of the Arab Board of Surgery at Mosul Medical College and Saddam College of Medicine from 1981 to 2007. He joined Erbil Medical College in Iraq for the last one year. He is currently member of examinations committee for undergraduate and post graduate study and member and Chief Editor of Mosul Medical College Journal and the Iraqi Medical Association Journal in Baghdad.
AMAAC Introduction

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 Executive Board of AMAAC

Sami Khatib, M.D. (Jordan) - Secretary General
Hussein Khaled, M.D. (Egypt) - Associate Secretary General
Khaled Al Saleh, M.D. (Kuwait) - Associate Secretary General
Mouhiedin Al-Seoudi, M.D. (Syria) - Associate Secretary General

> The Officially nominated members of AMAAC

Algeria  Adda Bouncedjar, M.D.
         Kamel Bouzid, M.D.
        
Bahrain  Abdulla Ajami, M.D.
         
Egypt    Hussein Khaled, M.D.
         Sherif Omar, M.D.
         
Iraq     Abdul Mon’em Ahmed, M.D.
         Nezar Taha Maki, M.D.
         
Jordan   Jamal Khader, M.D.
         Sami Khatib, M.D.
         
Kuwait   Khaled Al Khalidi, M.D.
         Khaled Al Saleh, M.D.
         
Lebanon  Nagi El-Saghir, M.D.
         Marwan Ghosn, M.D.
         
Libya    Salah El-Fathali, M.D.
         Mufid El-Mistiri, M.D.
         
Oman     Bassim Bahrani, M.D.
         
Saudi Arabia  Asem Al Radi, M.D.
               Shawki Bazarbashi, M.D.
               
Sudan    Hussein Mohammad Hamad, M.D.
         Kamal Hamad, M.D.
         
Syria    Mouhiedin Al-Seoudi, M.D.
         Maha Manachi, M.D.
         
Tunisia  Hamouda Boussen, M.D.
         Khaled Rahhal, M.D.
         
Yemen    Arwa Awn, M.D.
         Afif Nabhi, M.D.
Matti AAPRO, MD
Director, Multidisciplinary Oncology Institute, Genolier, Switzerland
Consultant to the Scientific Director, European Institute of Oncology, Milano, Italy
Consultant, Division of Oncology, Geneva University Hospital
Geneva - Switzerland

Hoda ANTON-CULVER, PhD
Professor & Chair
Department of Epidemiology
Professor, Department of Microbiology and molecular Genetics, School of Medicine
Director, Genetic Epidemiology Research Institute
University of California
Irvine – USA

Jean-Pierre ARMAND, MD
Professor & General Director
Centre de Lutte contre le Cancer
Institut Claudius Regaud
Toulouse – France

Ahmad AWADA, MD
Head of Medical Oncology Clinic
Jules Bordet Cancer Institute
Brussels - Belgium

Patrice CARDE, MD
Chairman Lymphoma Committee
Gustave Roussy Institute
Paris - France

Franco CAVALLI, MD
Professor & President UICC
Director
Oncology Institute of Southern Switzerland
Bellinzona - Switzerland

Joe CHANG, MD
Assistant Professor of Radiation Oncology
Clinical Service Chief, Thoracic Radiation Oncology
MD Anderson Cancer Center
Houston - USA

William DALTON, MD
President and Chief Executive Officer
H.Lee Moffitt Cancer Center and Research Institute
University of South Florida
Florida - USA

Jean-Pierre DROZ, MD
Professor & Former Head of Oncology Department
Centre de Lutte contre le Cancer Leon Berard
Lyon - France

Alexander EGGERMONT, MD, PhD
Professor of Surgical Oncology
Head of Department of Surgical Oncology
Erasmus University Medical Center
Daniel den Hoed Cancer Center
Rotterdam - The Netherlands

Jean-Pierre GERARD, MD
Professor of Radiation Oncology
General Director of Antoine-Lacassagne Cancer Center
Lyon - France

Joe HARFORD, MD
Director of the Office of International Affairs
National Institute of Health
United States Department of Health and Human Services
Bethesda - USA

Alan HORWICH, MD
Professor of Radiotherapy
Section of Academic Radiotherapy and Department of Radiotherapy
The Institute of Cancer Research
London – United Kingdom

Fritz JANICKE, MD
Director Clinic & Polyclinic of Gynecology
University Medical Center Hamburg-Eppendorf
Hamburg – Germany

Sima JEHA, MD
Director of the Leukemia / Lymphoma Developmental Therapeutics
Saint Jude Children’s Research Hospital
Memphis - USA

Hagop KANTARJIAN, MD
Professor of Medicine
Chair of the Department of Leukemia
The University of Texas - MD Anderson Cancer Center
Houston - USA

Fadlo R. Khuri, MD
Professor and Chair, Department of Hematology and Medical Oncology
Roberto C. Goizueta Distinguished Chair in Cancer Research
Deputy Director, Clinical and Translational Research - Winship Cancer Institute
Emory University School of Medicine
Atlanta - USA

Jean-Francois MORERE, MD
Professor at University Paris XIII
Head of the Department of Oncology
Assistance Publique – Hôpitaux de Paris
Paris - France

Mack ROACH, MD
Professor & Chairman
 Radiation Oncology & Professor of Urology
University of California, Irvine
California - USA

Philippe ROUGIER, MD
Professor of Medical Oncology
Gastrointestinal Cancer
Liver and Pancreas Tumors
Ambroise-Pare Hospital
Boulogne - France

Yousef RUSTUM, PhD
Chairman of the Department of Cancer Biology
Roswell Park Cancer Institute
Academic Research Professor
Associate Vice Provost
University at Buffalo
New York - USA

Sandra M. SWAIN, MD
Medical Director, Washington Cancer Institute
Washington Hospital Center
Washington – USA
Clinical Research in the Arab World: Where do we stand?

Clinical Research is continuously growing in Lebanon and in the Arab World. Indeed, there is a remarkable interest and investment of Pharmaceutical industries and International Research Groups in this field in the region. Clinical research is tackling all phases of drug development from phase I, II, III, IV and EAP trials.

ClinicalTrials.gov, a registry of federally and privately supported clinical trials conducted in the United States and around the world, currently has 62,292 trials with locations in 158 countries. However, if we analyze the figures of studies conducted in the Arab World, we notice a shy activity with 345 studies only. This number corresponds to 325 Millions inhabitants. Egypt, Saudi Arabia, Tunisia and Lebanon are the top active countries in this field. The number of Clinical trials in Europe is 100 times the number registered in the Arab world for a corresponding population of 2.4 times the Arab population only.

The analysis of the current status of clinical research in the Arab World and particularly in Lebanon is detailed below:

> The Strengths are:

• Fast recruitment rates accelerating the recruitment in clinical trials especially for rare disease.
• English-speaking of the investigators and their staffs. Some hospitals in the region have their medical records in Arabic or French and this may create some obstacles.
• High scientific level of Investigators
• Lower costs in comparison to Western Countries:

Clinical trials are, of course, necessary, but they come with a staggering price tag. On average, pharma companies are spending anywhere between $100 and $800 million per drug candidate. Given this climate, drug companies are looking for cost-saving measures. Sure, pharma companies bring in a lot of money, but they also have to spend a huge amount also.

CMSInfo, Chesam, UK, reports that national spending on clinical trials in the United States was nearly $24 billion in 2005. Results are forthcoming, but the research institute expects this number to rise $32.1 billion in 2011, growing at an average rate of 4.6% per year. The number of clinical trials performed in 2005 was 8,386. At a growth rate of 5.8%, the number of clinical trials performed in 2011 will reach more than 13,000. Research companies are predicting huge growth in this market, but it is clear that life science companies need to find a way to decrease these costs if the industry is to fund all those trials and conducting clinical trials in our region can be a cost-decreasing way.

• Relatively short distance facilitating the monitoring process for some countries like Lebanon

> The Weaknesses are:

• Deficit in the logistics, organization & infrastructure of some clinical research tools that may delay or constitute some obstacles:
  – Ethics Committee (GCP compliance, organization, etc)
  – Maintenance of medical records
  – Incomplete and/or pending Legislation at the level of the Competent Authorities
• Insufficient research team development and training. There is few recognized and specific entity for research at the sites level.
• Lack of time at the investigator>s level. The medicine is mostly highly private and competitive.
• Lack of strategies towards clinical trials at the level of Government and Health Authorities in terms of planning, motivation, investment and support.

> The Opportunities are:

• Clinical trials of new drugs are conducted at the same phase as in other parts of the globe.
• Qualified and motivated investigators (some of them are members of the International Steering Committee of the trials).
• Growing interest in clinical trials among physicians.
• Implementation in growth of Clinical Research Organization (CRO) providing services for research.
• Short timelines to get approvals.
• Patient education and opening towards new technologies and drugs. Thus, some patients are asking for new molecules and eventually enrolment in clinical trials.
• Increase in the medical tourism in the region due to the lower costs of disease management in comparison to Western Countries.
> The Threats are:

- The economic, political and insecurity climate dilute the interest and the concentration of local investigators and freeze the investment of pharmaceutical companies in this field.
- The socio-cultural background of the oriental patients about clinical trials thus the patients are refusing to “be submitted to research”. This is due to a lack or loose of trust between the patient and his treating physician. Efforts in the development and application of the law that defines the relation between the patient and the physician are crucial.

In conclusion, clinical research activity is growing despite limited current activity. We still have fantastic opportunities to occupy an advanced place. Serious and consolidated efforts have to be joined to improve our level of activity to reach a global standardized level.

Marwan Ghosn, MD, MBA / MHM

Table 1: Number of Studies Registered ClinicalTrials.gov in the Arab World

<table>
<thead>
<tr>
<th>Country</th>
<th>Number of studies Registered at <a href="http://www.clinicaltrials.gov">www.clinicaltrials.gov</a></th>
<th>Population*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Egypt</td>
<td>101</td>
<td>74,166,000</td>
</tr>
<tr>
<td>Saudi Arabia</td>
<td>55</td>
<td>24,175,000</td>
</tr>
<tr>
<td>Tunisia</td>
<td>53</td>
<td>10,215,000</td>
</tr>
<tr>
<td>Lebanon</td>
<td>51</td>
<td>4,055,000</td>
</tr>
<tr>
<td>Morocco</td>
<td>24</td>
<td>30,853,000</td>
</tr>
<tr>
<td>United Arab Emirates</td>
<td>18</td>
<td>4,248,000</td>
</tr>
<tr>
<td>Jordan</td>
<td>13</td>
<td>5,729,000</td>
</tr>
<tr>
<td>Kuwait</td>
<td>7</td>
<td>2,779,000</td>
</tr>
<tr>
<td>Algeria</td>
<td>6</td>
<td>33,351,000</td>
</tr>
<tr>
<td>Qatar</td>
<td>6</td>
<td>821,000</td>
</tr>
<tr>
<td>Sudan</td>
<td>5</td>
<td>37,707,000</td>
</tr>
<tr>
<td>Bahrain</td>
<td>2</td>
<td>739,000</td>
</tr>
<tr>
<td>Iraq</td>
<td>1</td>
<td>28,506,000</td>
</tr>
<tr>
<td>Syria</td>
<td>1</td>
<td>19,408,000</td>
</tr>
<tr>
<td>Mauritania</td>
<td>1</td>
<td>3,044,000</td>
</tr>
<tr>
<td>Oman</td>
<td>1</td>
<td>2,546,000</td>
</tr>
<tr>
<td>Yemen</td>
<td>0</td>
<td>21,732,000</td>
</tr>
<tr>
<td>Somalia</td>
<td>0</td>
<td>8,445,000</td>
</tr>
<tr>
<td>Libya</td>
<td>0</td>
<td>6,039,000</td>
</tr>
<tr>
<td>Djibouti</td>
<td>0</td>
<td>819,000</td>
</tr>
<tr>
<td>Comoros</td>
<td>0</td>
<td>818,000</td>
</tr>
<tr>
<td>Palestine</td>
<td>0</td>
<td>5,000,000</td>
</tr>
<tr>
<td>Total</td>
<td>345</td>
<td>325,195,000</td>
</tr>
</tbody>
</table>

* World Health Organization www.who.org
Superior Sulcus (Pancoast) tumors of the lung

Riad N. Younes, MD, PhD

(1) Head of the Department of Thoracic Oncology, Hospital do Câncer AC Camargo and Hospital Sirio-libanes, São Paulo, Brazil

Corresponding Author: Riad N. Younes, Head of the Department of Thoracic Oncology, Hospital do Câncer AC Camargo and Hospital Sirio-libanes, São Paulo, Brazil, Email: rnyounes@yahoo.com

Key words: NSCLC, lung cancer, pancoast, superior sulcus.

Submitted: 1 September 2008; Accepted: 14 September 2008
ISSN: 2070-254X

Introduction

Superior sulcus tumors (SST) of the lungs are relatively slow growing at the primary site, with distinctive biological behavior and associated symptoms and syndromes, when compared to other non-small cell lung cancer (NSCLC) with similar histology. Once disseminated beyond adjacent organs, however, the distribution and the pattern of metastatic foci are similar to other NSCLC. The estimated occurrence of SST ranges between 3% and 8% of all pulmonary carcinomas. SSTs arise from the pulmonary parenchyma anatomically located at or above the pulmonary superior sulcus, which marks the position of the subclavian artery on the surface of the lungs. This portion of the lung is closely surrounded by complex structures of chest wall, including C7 and T1 vertebrae, part of the first and second upper ribs, as well as the clavicles bilaterally. Along with the bony structures, the apex of the lungs are adjacent to subclavian arteries and veins, carotid trunks, superior vena cava, as well as nerve roots. This peculiar position might explain the unique symptoms related to this tumor. Pancoast described, in 1924 the typical presentation of the superior sulcus tumors, with the clinical syndrome named after him1. The direct invasion of the adjacent structures of chest wall and mediastinum accounts for the characteristic symptoms, including shoulder and upper extremity pain, as well as alterations of regional innervation (head and neck and upper limb). The peripheral position of the SSTs is associated with relatively infrequent signs or symptoms of pulmonary disease, like cough, dyspnea or hemoptysis. Clinical presentation, as well as treatment planning are closely related to the organs affected or invaded by the tumor mass. Pain and Claude Bernard – Horner syndrome are common manifestations of chest wall and nerve invasion. This study presents our experience with the treatment of superior sulcus lung tumors, as well as the long-term outcomes in our patient population. The main objective of the study is to evaluate survival rates of patients with NSCLC tumors located at the superior sulcus of the lungs, and submitted to different treatment approaches.

Methods

This is a retrospective study of all patients admitted with the diagnosis of SST of the lung, with no evidence of distant metastases, between 1990 and 2007. During that period, 19 patients were treated for NSCLC, confirmed by percutaneous fine needle aspiration (n=11) or core biopsy (n=8). Median age at diagnosis was 62 years (range: 59 to 71). Most patients were male (n=14, 73.7%), with median performance status of 90% (range: 80% to 100%). All patients had one or more of the characteristic local symptoms. Pain was the main complaint, present in 100% of the patients. Neurological alterations due to invasion of nerve roots were noted in 14 patients. Full Pancoast syndrome was observed in seven patients (36.8%). Thorough pre-treatment staging was performed, including CT scan of the chest and upper abdomen, CT or MRI of the brain as well as whole body bone scan. The last four patients were submitted to PET/CT scans (18F-FDG). After ruling out any detectable distal disease, the patients were treated. The patients were staged as follows: IIb (n=12), IIIa (n=5), and IIIb (n=2). Management included radiotherapy only (n=3), radiotherapy and chemotherapy (n=7), radiotherapy and surgery (n=4), chemotherapy followed by surgery (n=3), and chemo-radiotherapy followed by surgery (n=2). Patients candidates to surgical resection has histological evaluation of their mediastinum through mediastinoscopy. Surgical resection was considered pathologically complete in eight patients (88.8% of resected patients). En bloc chest wall resection and upper lobectomy was performed on all operated patients, associated with systematic mediastinal lymph-node dissection. Frozen section evaluation of surgical margins was routinely performed. Preoperative radiation ranged between 30 Gy and 45 Gy. Exclusive radiation therapy dose ranged between 50 Gy and 65 Gy. All chemotherapy regimens were platinum based. Follow-up included chest and upper abdomen CT scan every three months.

Statistical analyses were performed on SPSS 11.5 for windows.

Results

Overall objective response rate to radiation or chemoradiation therapy, as well as to neoadjuvant chemotherapy was 68.4%. The was no treatment-associated deaths. Thirty-day postoperative complication rate was 55.6%, with major complications seen in two patients (bleeding that required reoperation and pulmonary embolism, respectively). Median follow up was 22 months (range: 7 to 62 months). Overall median survival rate of all patients included was 34 months (95% CI: 15-53 months - Figure 1), as estimated by Kaplan-Meier method. Patients submitted to surgical resection presented with better, although not significant (p=0.129), overall survival (57% at five years), as compared to the unresected group, with a median survival of 29.2 months, and no patient surviving over five years (Figure 2). Of the patients submitted to surgical resection, five-year disease-free survival rate was 32% (median 39 months).

Discussion

Superior sulcus lung tumor is associated with apparently different prognosis, as well as biological behavior, warranting special treatment strategies. Since 1961, neoadjuvant radiotherapy, followed by surgical resection was considered the treatment of choice in operable patients. Several prognostic factors (like lymph node metastases, vascular and vertebral body invasion) were subsequently identified to help defining the patient population more likely to benefit from this aggressive approach. Unfortunately, some patients with SSTs still present with unresectable disease, with complete resection only reached in 65% to 70% of patients. Several technical modifications were introduced to increase operation rates, including vascular replacement and vertebral body resection. Neoadjuvant treatment nowadays include induction chemoradiation therapy followed by an attempt to complete resection. Most studies used a combination of drugs with a platinum compound. Patients submitted to neoadjuvant treatment with complete resection, presented with 53% five-year survival rate. Multimodality treatment, including chemoradiotherapy as well as radiotherapy and surgery, was established as the treatment of choice since late 1990’s. In patients with invasion of adjacent subclavian vessels or vertebral bodies, operative technique should include a team of vascular and...
orthopedic surgeons with experience in similar situations. On the other hand, patients with unresectable disease or unfit for complete resection, are considered for radiotherapy or combined chemoradiotherapy, with five-year survival rates ranging from 12% to 25%.

Data from the present study, where we present our experience with SSTs, confirm previous reports that demonstrated the effectiveness of aggressive approach to superior sulcus lung tumors. Initial treatment with chemotherapy and/or radiotherapy resulted in overall objective response rate (RECIST) of 68.4%. Resection was only possible in 9/17 patients, after induction therapy. Five-year survival rate of 57% for completely resected patients is encouraging. The small number of patients included in this study probably accounts for the lack of statistically significant difference between the groups of patients resected, as compared to the patients with unresected disease.

This study, although retrospective, shows that multimodality approach for patients with SSTs of the lungs should be considered as treatment of choice, mainly in specialized centers. Results of this treatment are similar to those reported by prospective studies. Thorough staging, including PET-CT evaluation, should be routinely employed in this group of patients, to avoid unnecessary major operations. 

References

Low dose Docetaxel, Carboplatin and Capecitabine in the treatment of recurrent and/or metastatic Head and Neck Cancer (HNC): Results of a Pilot Phase II study

Marwan Ghosn, MD1, 2, Colette Hanna, MD1, Fadi Farhat, MD4, Georges Chahine, MD1, Amin Haddad, MD4, Elie Nasr, MD4 and Joseph Kattan, MD1, 2.

(1) Hotel-Dieu de France University Hospital, Beirut, Lebanon, (2) Clemenceau Medical Center, Beirut, Lebanon, (3) Hammoud Medical Center, Saida, Lebanon

Key words: Head and Neck Cancer, Docetaxel, Capecitabine, Carboplatin, Cisplatin, Cetuximab, Chemotherapy.

Submitted: 25 August 2008; Accepted: 22 September 2008

ISSN: 2070-254X

Abstract

> Rationale: Platinum-based treatment is the standard of care for patients having Head and Neck Cancer (HNC). Many combination regimens were investigated adding Taxane or 5-FU to Cisplatin or Carboplatin resulting in response rates of 30% to 40%. Combination of Cetuximab these regimens produced interesting results.

> Objective: The primary objective is to assess the efficacy and toxicity of the combination of Docetaxel, Carboplatin and Cetuximab in the treatment of HNC. Results of this pilot phase II trial will serve as a feasibility study in order to assess the possibility of addition of Cetuximab to this combination.

> Patients and Methods: Between January 2002 and August 2004, patients with recurrent or metastatic HNC received the combination of: Docetaxel 25 mg/m2 on days 1 & 8, Carboplatin AUC 2 on days 1 & 8 and Capecitabine 1350 mg/m2 per day for two consecutive weeks, repeated every 21 days.

> Results: Twenty patients have been enrolled. There were 20 % of complete response (4 pts), 30 % (6 pts) of partial response resulting in an overall response rate of 50 % (IC 95%: 27.20 – 72.80 %). The median overall survival was 5.2 months. The major hematological toxicities were Grade 2 and 3 anemia in 12 patients (60 %) and 2 patients (10 %) respectively and febrile neutropenia in 2 patients (10 %). The non hematological toxicities were mainly nausea, vomiting and stomatitis.

> Conclusion: This combination showed good results with acceptable toxicity profile. It warrants to be studied in addition to Cetuximab in metastatic and recurrent Head and Neck Cancer.

Rationale

Despite surgical resection and postoperative radiotherapy, advanced carcinomas of the head and neck have a 30% rate of recurrence regionally or locally and 25% rate of distant metastasis. The five year survival rate of patients with advanced carcinomas of the head and neck is 40 %. Chemotherapy for squamous cell carcinoma of the head and neck cancer (HNC) was initially limited to palliative settings. Since the introduction of Cisplatin, HNC is considered chemosensitive because combination of this agent with 5-FU succeeded to cure some patients with advanced HNC [1, 2]. In three meta-analyses of updated individual data reported by the MACH-NC Collaborative Group, the authors concluded that chemotherapy (Platinum and 5-FU combination) showed a small significant survival benefit. Indeed, the main meta-analysis of 63 trials (10,741 patients) of locoregional treatment with or without chemotherapy yielded a pooled hazard ratio of 0.9 (95% CI 0.85-0.94, p < 0.0001) corresponding to an absolute survival benefit of 4% at 2 and 5 years in favor of chemotherapy [3]. Thus, alternative regimens with the potential to improve complete response rate, the durability of locoregional control and survival were being investigated. Docetaxel, a semisynthetic taxoid antineoplastic, was proved to be more effective than Cisplatin in inhibiting the growth of Xenografts of HNC cell lines. In preclinical models, potential synergy was noticed when adding Docetaxel to Cisplatin [4]. Single agent Docetaxel was prospectively evaluated in four phase II trials. The dose of 100 mg/m2 IV every 3 weeks was shown to be an active and generally well tolerated single-agent regimen for locally recurrent or metastatic HNC, with overall response rates ranging from 21% to 42%. In vivo, the promising single-agent activity and tolerability of Docetaxel in HNC prompted assessment of Docetaxel plus Cisplatin or plus 5-FU. Overall response rates have ranged from 33 to 42% with Cisplatin and from 24 to 27 % with 5 FU. Phase II trials with the triplet Docetaxel, Cisplatin and 5FU were reported. Different schedules were tested [5-22]. Based on the encouraging efficacy of the combination Docetaxel, Cisplatin and 5FU, this study was designed. Cisplatin is replaced by Carboplatin trying to reduce the renal toxicity of Cisplatin. 5-FU was replaced by Capecitabine allowing oral and easier administration schedule. Lower doses were chosen in attempt to reduce the toxicity of the chemotherapy and ensure better compliance to treatment. Indeed, Docetaxel given at 100 mg/m2 or 75 mg/m2, a significant toxicity in terms of neutropenia was reported in the 3-week schedule, while this was not the case with a weekly schedule including docetaxel at 35 mg/m2 and cisplatin at 25 mg/m2.

Based on the above, the study was designed on January 2002. Results of this pilot phase II trial will be used to assess the possibility of adding Cetuximab to this regimen in order to reach the best efficacy and toxicity profile.

Patients and Methods

To be included, patients had to meet all the following eligibility criteria: histologically confirmed squamous cell carcinoma of the head and neck, clinically or radiologically bidimensionnally measurable disease. In locally recurrent or metastatic disease previous chemotherapy (excluding Taxanes) as induction or as concurrent to radiotherapy for the primary tumor is allowed after a free interval of more than two years. Patients had to have a life expectancy of more than 3 months, with an Eastern Cooperative Oncology Group of 0 to 2. Additional criteria included adequate bone marrow reserve (white blood cell count [WBC]> 3500/µl, neutrophil count > 1500/µl, and platelet count > 100000/µl), adequate hepatic function (bilirubine and liver enzymes < 2 times the upper limit of normal) and a serum creatinine level < 2 times the upper limit of normal. Were excluded all the patients with prior chemotherapy for primary tumor within 2 year free interval, or
with other prior malignancies than prostate adenocarcinoma, non melanotic skin cancers and in situ cervical cancer. Additional exclusion criteria were an active cardiac disease necessitating continuous therapy renal dysfunction with creatinine clearance less than 40 ml/min, liver dysfunction defined as conjugated bilirubin > upper limit of normal and liver enzymes > 2 times upper limit of normal. Patients included should not present any evidence of neurological disturbance or cerebral metastases. Patients were evaluated in a multidisciplinary clinic for confirmation of eligibility, staging and treatment planning. Patients were staged by physical examination according to the criteria established by the American Joint committee on Cancer. Radiologic evaluation was used to document baseline disease and response to therapy in sites not fully assessable by clinical examination. The local ethics committee approved the protocol, and all patients signed informed consent.

Chemotherapy

Docetaxel (25 mg/m2) given weekly for two consecutive weeks followed by one week rest and delivered as an intravenous infusion over 60 minutes in 250 ml of normal saline. Premedication with 16 mg dexamethasone IV was given before each infusion. Followed the administration of Carboplatin at AUC=2 also given weekly for 2 consecutive weeks followed by one week rest. The AUC is calculated according to Calvert Formula and the GFR calculated or estimated according to Cockcroft and Gault formula. Carboplatin is delivered as an intravenous infusion over 60 minutes in 250 ml of normal saline. The patients received also Capecitabine at a dose of 1350mg/m2 given orally on a daily basis for two consecutive weeks followed by one week rest. Day 8 of chemotherapy was omitted in case of grade 4 hematologic toxicity (according to National Common Institute Common Toxicity Criteria). If hematologic toxicity does not recover at D21, the D1 will be held for one week. Subsequent dosages in these cases will be reduced of 20%. If toxicities reappear after the dose reduction patient will be withdrawn from the study. The first evaluation was planned after 3 cycles of treatment. Stable or responding patients continued treatment to complete 6 cycles. Additional chemotherapy cycles for stable or responding patients were left to the physician’s discretion. However the treatment was discontinued in case of unexpected toxicity, persistent hematologic toxicity despite dosage reduction and progressive disease as measured according to the World Health Organization.

Baseline and treatment evaluations

The following tests were evaluated before entry into the study : medical history, physical examination, performance status (ECOG), blood cell count and blood chemistry including bilirubin, aspartate aminotransferase, alkaline phosphatase, creatinine, ECG, CT scanners of the Head and Neck and the chest, abdominal sonography and radionuclide bone scan if indicated.

The blood cell count was repeated before each cycle of chemotherapy. An imaging study of the relevant regions was performed after every three courses of treatment. The following criteria were used in the evaluation of response. The primary endpoint was objective tumor response and the secondary endpoints were progression-free survival (PFS), overall survival (OS). Patients were accrued according to Simon’s two-stage Optimal trial design, with an assumption of P0=0.1( the level of no interest), P1=0.3 (the target activity level of interest) and both type I and type II errors of 0.1. The PFS and OS curves were analyzed according to Kaplan –Meier method. OS was measured from start of treatment to the time of death from any cause. PFS was measured from the start of treatment to the first observation of disease progression or death.

Results

> Patient Characteristics: A total of 20 patients were enrolled in this study. Patient Characteristics: A total of 20 patients were enrolled in this study. Demography and clinical characteristics are summarized in Table 1. The median age was 59 years (range, 46-80). The sex ratio was 17 / 3. Eight patients had locoregional recurrence (40%), 6 had distant metastasis (30%) and 6 had both (30%).

> Chemotherapy administration: A total of 82 cycles of chemotherapy was administered. The median number of chemotherapy cycles for the 20 patients was four, with a range of one to 9.

> Toxicity: Maximum hematologic toxicities per person are listed in Table 2. The major hematologic toxicity was anemia with 80 % of patients experience it at some grade. One episode of febrile neutropenia was observed. Severe neutropenia (grade 3) was observed in 10 % of the patients. The maximum nonhematologic toxicities are listed in Table 3. These adverse effects were mainly grade 1 or 2 and did not cause any treatment delay or withdrawal. 90% of the patients experienced fatigue and 40 % nausea and vomiting. One patient presented a grade 3 stomatitis. Surprisingly, no hand and foot toxicity was reported.

Response to treatment

The best overall response rates of the 20 patients are shown in table 4. There was 4 CR (20%), 6 PR (30 %) resulting in an Overall response rate (ORR) of 50 %. The median follow up time of all 20 patients was 50 months. Disease had progressed in 95 % patients with a median PFS of 3.2 months. The median OS was 5.2 months. The Kaplan Meier curves of the PFS and OS are shown in fig 1 and fig 2.

Discussion

This phase II pilot study was conducted in an attempt to define the safety, the tolerability and effectiveness of the triplet Carboplatin, Capecitabine and Docetaxel in recurrent or metastatic head and neck cancer. This study is published at this moment in order to document scientifically the results of this pilot phase II trial and to serve as a feasibility study in order to assess the possibility of addition of Cetuximab to this combination. The sample size was reduced to 20 patients because of large difficulties of recruitment due to the reluctance of the Lebanese community to treat cancer patients with chemotherapy assuming that their condition is incurable few years ago. Efficacy of this regimen (50% ORR and 10% SD) is favorably comparable to data reported in the literature. It is noticeable that 85 % of patients included in this trial had PS of 0 or 1 which is a good prognosis factor. Toxicity profile is encouraging with specific low rate of Grade 3 / 4 toxicities. Larger conclusion cannot be withdrawn based on the small number of patients with some heterogeneity in the population (PS, previous treatment, etc). However, results are promising and toxicity profile is acceptable especially when palliation is the primary objective of the treatment.

In our study, 12 patients over 20 patients included (60%) had distant metastasis which can explain the lower median overall survival reported in this trial (5.2 months) compared to those reported in Posner et al. and Vermorken et al. trials where patients with distant metastasis were excluded. In Posner et al. study published in NEJM 2007, a total of 501 patients were randomized to receive either Docetaxel plus Platinum plus 5-FU (TPF) or Platinum and 5-FU (PF) induction chemotherapy, followed by chemoradiotherapy with weekly carboplatin therapy and radiotherapy for 5 days per week. Median overall survival was 70 months vs. 50 months in the TPF arm and PF arm respectively. [23] In Vermorken et al study published also in NEJM 2007, a total of 358 patients underwent randomization between TPF and PF. Treatment with TPF resulted in a median overall survival of 18.8 months as compared with 14.5 months in the PF group. So as compared with the standard regimen of cisplatin and 5-FU, induction chemotherapy with the addition of Docetaxel significantly improved progression free and overall survival in patients with unresectable squamous-cell carcinoma of the head and neck cancer. [24]

Phase II and III trials adding EGFR inhibition (Cetuximab, Erlotinib, etc) suggest benefit from it. Targeting EGFR in HNC is a rational approach sustained by a large body of evidence that supports the relevance of the target [25 – 33]. Results of a phase III trial comparing Cetuximab plus platinum-based chemotherapy plus 5-FU to platinum-based chemotherapy plus 5-FU alone in Head and Neck Cancer, demonstrated that the introduction of Cetuximab significantly improved survival. Median Overall survival was improved from 7.4 months in the Chemotherapy alone group to 10.1 months in the group that received chemotherapy plus Cetuximab...
(hazard ratio for death, 0.80; 95% CI, 0.94 to 0.99; p=0.04). It is noticeable that around 47% of patients had metastatic disease and 38% received prior chemotherapy. [34]

Specific attention should be made to some marker for predicting tumor response to anti-EGFR therapy such as EGFR expression, RAS mutation, etc. Thus, the addition of Cetuximab to the combination of Docetaxel, Carboplatin and Capcitabine is a valid option and warrants to be investigated in controlled and randomized trials.

Adding targeted therapy to already consolidated polychemotherapy may display very high toxicity, thus underlining the need not to use these drugs outside clinical trials. Indeed, The National Comprehensive Cancer Network (NCCN) emphasizes in its practice guidelines for the treatment of Head and Neck Cancers that participation in clinical trials is preferred for all patients with advanced Head and Neck cancer. For patients with unresectable disease, such trials testing altered fraction radiotherapy schedules, concurrent chemoradiotherapy, and novel radiosensitizers. For patients with recurrent disease not amenable to curative therapy and patients with metastatic disease, studies include trials of new agents and re-irradiation.

**References**


Tables

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Parameters</th>
<th>No. of patients</th>
<th>% of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Median age</td>
<td>59</td>
<td></td>
</tr>
<tr>
<td>Age range</td>
<td>46-80</td>
<td></td>
</tr>
<tr>
<td>Sex Ratio: Male / Female</td>
<td>17:3</td>
<td>85% / 15%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Performance status</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>PS = 0</td>
<td>7</td>
<td>35%</td>
</tr>
<tr>
<td>PS = 1</td>
<td>10</td>
<td>50%</td>
</tr>
<tr>
<td>PS = 2</td>
<td>3</td>
<td>15%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sites of failure</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Locoregional relapse</td>
<td>8</td>
<td>40%</td>
</tr>
<tr>
<td>Distant relapse</td>
<td>6</td>
<td>30%</td>
</tr>
<tr>
<td>Both</td>
<td>6</td>
<td>30%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Location of primary tumor</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Larynx</td>
<td>16</td>
<td>80</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hippopharynx</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Oral cavity</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Mandible</td>
<td>2</td>
<td>10</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Previous therapy of the primary tumor</th>
<th>No. of patients</th>
<th>% of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>4</td>
<td>20%</td>
</tr>
<tr>
<td>Surgery alone</td>
<td>6</td>
<td>30%</td>
</tr>
<tr>
<td>Surgery and RT</td>
<td>6</td>
<td>30%</td>
</tr>
<tr>
<td>CT and RT</td>
<td>2</td>
<td>10%</td>
</tr>
<tr>
<td>CT, RT and surgery</td>
<td>1</td>
<td>5%</td>
</tr>
<tr>
<td>CT alone</td>
<td>1</td>
<td>5%</td>
</tr>
</tbody>
</table>

Abbreviations: ECOG, Eastern Cooperative Group; RT, radiotherapy; CT, Chemotherapy.

Table 2: Maximum Hematologic toxicities

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>2 (10%)</td>
<td>1 (5%)</td>
<td>2 (10%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>3 (15%)</td>
<td>12 (60%)</td>
<td>1 (5%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

Table 3: Maximum non hematological toxicities

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>4 (20%)</td>
<td>2 (10%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4 (20%)</td>
<td>2 (10%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>3 (15%)</td>
<td>4 (20%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>5 (25%)</td>
<td>1 (5%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2 (10%)</td>
<td>3 (15%)</td>
<td>1 (5%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>10 (50%)</td>
<td>6 (30%)</td>
<td>2 (10%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>0 (0%)</td>
<td>1 (5%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>1 (5%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Neuroopathy</td>
<td>1 (5%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

Table 4: Response to treatment

<table>
<thead>
<tr>
<th>Best Overall Response</th>
<th>No. of patients</th>
<th>% of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>4</td>
<td>20%</td>
</tr>
<tr>
<td>PR</td>
<td>6</td>
<td>30%</td>
</tr>
<tr>
<td>ORR</td>
<td>10</td>
<td>50%</td>
</tr>
<tr>
<td>SD</td>
<td>2</td>
<td>10%</td>
</tr>
<tr>
<td>Clinical Benefit</td>
<td>12</td>
<td>60%</td>
</tr>
<tr>
<td>PD</td>
<td>8</td>
<td>40%</td>
</tr>
</tbody>
</table>

Figures

Survival (months)
Fig 1: overall survival in all patients

Progression disease free (Months)
Fig 2: progression disease free survival.
Treatment of Acute Lymphoblastic Leukemia

Sima Jeha, MD

(1) Director of the Leukemia / Lymphoma Developmental Therapeutics, Saint-Jude Children’s Research Hospital, Memphis - USA

Corresponding Author: Sima Jeha, Director of the Leukemia / Lymphoma Developmental Therapeutics, Saint-Jude Children’s Research Hospital, Memphis - USA, Email: sima.Jeha@stjude.org

Key words: Leukemia.

Submitted: 1 September 2008; Accepted: 22 September 2008.

ISSN: 2070-254X

Abstract

Acute lymphoblastic leukemia (ALL) affects both children and adults, with prevalence between the ages of 2 and 5 years. Serial clinical trials have resulted in steady improvement in the outcome of patients with ALL. Most children and over a third of adult patients are cured with widely available treatment approaches based on the use of risk-directed multiagent chemotherapy regimens and diligent supportive care. Ongoing research is now aiming at reducing long term treatment sequelaes in children and younger adults, and at improving the outcome of adults and some subgroups of children with poor prognosis. This review tracks six decades of progress in the therapy of ALL, summarizes the rational of contemporary ALL therapy, and addresses remaining challenges.

Introduction

Steady progress in the development of treatment strategies for acute lymphoblastic leukemia (ALL) started in the 1950s, when complete remissions were achieved using single chemotherapeutic agents. Significant improvement in remission duration was achieved in pediatric trials combining and cycling these agents, with the addition of central nervous system (CNS) prophylaxis. Further progress was accomplished with serial clinical trials using outcome predictors to stratify therapy. Drugs developed over 30 years ago, such as mercaptopurine, methotrexate, vincristine, corticosteroids, anthracyclines, and asparaginase, still constitute the backbone of contemporary ALL protocols resulting in long-term, event-free survival rates exceeding 80% in children, but seldom exceeding 40% in adult patients. With improved understanding of the immunology and molecular pathways involved in ALL, current risk classification typically include age, leukocyte count at diagnosis, blast cell immunophenotype and genotype, as well as early treatment response. The favorable hyperdiploidy >50 (more than 50 chromosomes) and TEL-AML1 gene fusion (with expression of ETV6-CBFA2) are present in about 50% of childhood ALL, and rarely seen in adults. On the other hand, the unfavorable Philadelphia chromosome (BCR-ABL) is present in about 25% of adults, but is not common in children. Early response to therapy, as measured by minimal residual disease (MRD) evaluation, has played an increasingly important role in risk stratification of ALL. Early and vigorous assessment of the risk of relapse in individual patients help improve outcome of patients with high-risk leukemia while minimizing long term sequelaes and enhancing the quality of life in patients at low risk of relapse. Historically, adult ALL trials included more intensive alkylating agents based chemotherapy. Recently, adult investigators are exploring pediatric protocols in the young adult population, and innovative approaches in high risk subgroups.

Principles of treatment

Accurate assessment of relapse hazard is an integral part of ALL therapy. The prognostic impact of age, and to a lesser extent, leukocyte count can be explained partly by their association with specific genetic abnormalities. For example, the poor prognosis of infants is associated with MLL rearrangement (detected in 70% to 80% of patients in this age group), and the overall favorable outcome of patients aged 1 to 9 years is related to the preponderance of cases with hyperdiploidy >50 or TEL-AML1 fusion. However, primary genetic features do not entirely account for treatment outcome. While up to 15% of patients with hyperdiploidy >50 or TEL-AML1 fusion suffer recurrences of their leukemia, a substantial proportion of the patients with the t(9;22) and BCR-ABL fusion who are 1 to 9 years old and have low leukocyte counts at diagnosis may be cured with intensive chemotherapy alone. Among patients with MLL-AF4 fusion, infants and adults have a worse prognosis than children. Individual variability in the pharmacokinetics and pharmacodynamics of many antileukemic agents might partially explain the heterogeneity in treatment response among patients with specific genetic abnormalities and the difference in outcome by age group. Multiple genetic polymorphisms have been associated with relapse risk, acute toxicity, and late effects. The prime example of optimizing therapy based on germline genetic status is the use of polymorphisms of thiopurine methyltransferase (TPMT), an enzyme that catalyzes the methylation of thiopurines such as mercaptopurine and thioguanine, to guide treatment. Some drugs affect outcome when administered concomitantly with ALL therapy. Drugs that induce cytochrome P450 enzymes (e.g. phenobarbital and phenytoin), significantly increase the systemic clearance of several antileukemic agents and may adversely affect treatment outcome. On the other hand, drugs that inhibit cytochrome P450 enzymes (e.g. azole antifungal and macrolide antibiotics), potentiate the effects of vincristine, anthracyclines and etoposide resulting in increased toxicity. Response to therapy is determined by several factors including the leukemic cell biologic features, the pharmacogenetics of the patient, the treatment regimens administered, and compliance to therapy. The degree of reduction of the leukemic cell clone early during remission induction therapy has greater prognostic strength than any other individual biological or host related feature. Assessing MRD by flow-cytometric detection of aberrant immunophenotypes or analysis by polymerase chain reaction (PCR) of clonal antigen-receptor gene rearrangements, provides a level of sensitivity and specificity that cannot be attained by traditional morphological assessment of treatment response. There is strong concordance between the assessment of MRD by flow cytometry and by PCR methods. Over 95% of patients can be followed by flow cytometry which is a simple and rapid method. PCR method could be reserved for the few patients whose leukemic cells lack a suitable immunophenotype.

Phases of therapy

With the exception of mature B-cell ALL cases, which are treated with short-term intensive chemotherapy (including high-dose methotrexate, cytarabine, and cyclophosphamide), therapy for ALL typically consists of a brief remission-induction phase followed by intensification (or consolidation) therapy to eliminate residual disease, and then prolonged continuation treatment to maintain remission.
All patients also require treatment directed to the CNS early in the clinical course to prevent relapse due to leukemic cells sequestered in this site.4 Contemporary pediatric protocols stratify therapy based on risk groups defined by age, leukocyte count, immunophenotype, leukemic genotype, and response to early remission induction therapy.5-12 The standard or lower risk category includes patients between 1 and 10 years of age with an initial leukocyte count less than 50 x 10^9/L, and the remaining patients are considered higher risk. Additional features used by some investigators to stratify patients as lower risk include hyperdiploidy > 50 (DNA index > 1.16) and trisomy of chromosomes 4 and 10. Conversely, other characteristics, such as T-cell phenotype, adverse cytogenetic translocations [t(9;22) and t(4;11)], overt CNS leukemia at diagnosis, and slow early response to induction chemotherapy, have been used to stratify patients as high risk.

**Remission induction**

Remission induction therapy aims at eradicating leukemic cell burden and restoring normal hematopoiesis. This treatment phase typically lasts 4 to 6 weeks, and includes the administration of a glucocorticoid (prednisone or dexamethasone), vincristine, and at least a third drug (asparaginase or anthracycline, or both). A two-drug remission induction regimen of weekly vincristine and daily prednisone results in remission in 80% to 90% of children with ALL.26,27 Addition of a third agent, such as asparaginase or an anthracycline, increases the remission rate to approximately 95%.28,29 In addition to improving remission rates, intensified induction regimen also prolong remission duration.29,30 A three-drug induction regimen appears sufficient for most standard-risk cases, provided they receive intensified postremission therapy.31 The benefit in long-term survival of using 4 or more drugs during induction is widely accepted in higher risk patients but less clear in lower risk patients.32 Addition of a tyrosine kinase inhibitor has greatly improved the remission induction rate, duration of disease-free survival and quality of life of patients with Philadelphia positive (Ph+) ALL.33-35 Based on reports of more potent in-vitro antileukemic activity and better CNS penetration,36-39 dexamethasone has replaced prednisone in some induction and many continuation regimens.12,40-42 However, the biologically equivalent doses between dexamethasone and prednisone are not known, and one study suggested that prednisone can yield results comparable to dexamethasone, provided higher dose is used (i.e. 60 mg/m2/day).43 Dexamethasone given at higher dose was associated with increased incidence of hyperglycemia, hypertension, myopathy, bony morbidity, severe behavioral changes and infectious complications.44 As with glucocorticoids, the pharmacodynamics of asparaginase differ by formulation.45 The native E. coli asparaginase has been the most commonly used preparation. Polyethylene glycol-conjugated asparaginase, a long-acting and less allergenic form, is progressively replacing the native product and is being increasingly administered intravenously instead of intramuscularly.46 Asparaginase derived from Erwinia chrysanthemi, has a short half-life and its use is currently limited to patients who are allergic to the E coli formulations. The dose schedule for asparaginase should take into account the variability in the pharmacokinetic profile and potency among the different preparations.

The rapidity of response to induction therapy, as measured by clearance of peripheral and bone marrow blasts, is an important predictor of outcome.4,5 although intensification of postinduction therapy can improve the adverse prognosis of slow early responders.47 With modern chemotherapy and supportive care, 97% to 99% of children can be expected to attain complete morphological remission (i.e. < 5% blasts in bone marrow) at the end of remission induction; those who do not have poor outcome.48,49 Hence, most investigators offer these patients the option of allogeneic hematopoietic stem cell transplantation at the end of extended induction treatment.50 We and others have found that patients with 1% blasts identified by MRD studies had an outcome as poor as those with induction failure and the patients may also be candidates for allogeneic transplantation following intensification therapy to reduce MRD prior to transplant.51,52

**Consolidation (Intensification)**

Following remission induction, consolidation (or intensification) is given to eradicate drug-resistant residual leukemic cells. Therapy is tailored to the leukemia subtype and risk-group. Intensifying asparaginase therapy during the early phase of treatment improved results of Dana Farber Cancer Institute (DFCI) studies.53 adding doxorubicin to asparaginase favorably influenced the outcome of high-risk patients, particularly those with T-cell disease.54,55 Significant improvement was also reported in the outcome of patients receiving early intensification consisting of intermediate-dose or high-dose antimetabolite therapy.55-58 Delayed intensification, pioneered by the Berlin-Frankfurt-Münster (BFM) consortium, consists of using drugs similar to those used in remission induction therapy after a three months period of a less intensive, interim maintenance chemotherapy.5 The Children’s Cancer Group (CCG) confirmed the efficacy of delayed re-induction therapy in low-risk cases.59 and showed that double-delayed intensification with a second re-induction at week 32 of treatment, improved outcome in patients with intermediate-risk disease.60 An augmented intensification regimen consisting of the administration of additional doses of vincristine and asparaginase during the myelosuppression period following delayed intensification, and sequential escalating-dose parental methotrexate followed by asparaginase (Capizzi methotrexate), improved the outcome of high-risk patients whose disease had responded slowly to initial multiagent induction therapy.47

**Continuation (Maintenance)**

Continuation or maintenance phase consists of 2 to 2.5 years of low intensity metronomic chemotherapy designed to eradicate any residual leukemic cell burden. Weekly low-dose methotrexate and daily oral mercaptopurine form the backbone of most continuation regimens. Adjusting chemotherapy doses to maintain neutrophil counts between 0.5 and 1.5 x 10^9/L has been associated with a better clinical outcome.4,61 Overzealous use of mercaptopurine, to the extent that neutropenia necessitates chemotherapy interruption, reduces overall dose intensity and is counterproductive.62 It is generally recommended to give mercaptopurine at bedtime to patients with an empty stomach,63 and to avoid taken it together with milk or milk products which contain xanthine oxidase, an enzyme that can degrade the drug.64 About 10% of the population inherit one wild-type gene encoding TMPT and one nonfunctional variant allele, resulting in intermediate enzyme activity, while 1 in 300 people inherits two nonfunctional variant alleles and are completely deficient of this inactivating enzyme.65,66 Patients with heterozygous and especially homozygous deficiency of TPMT are at high risk of severe myelosuppression. Identification of these patients allows to selectively guide reductions in mercaptopurine dosage without modifying the dose of methotrexate.23,67 Patients with TPMT deficiency are also at greater risk of developing therapy-related acute myeloid leukemia and radiation-induced brain tumors, in the context of intensive thiopurine therapy.23,68-70 Substituting thioguanine for mercaptopurine during continuation therapy was associated with a high incidence of profound thrombocytopenia and hepatic veno-occlusive disease.71-73 Thioguanine use has therefore been limited to short pulses administered during consolidation therapy in some trials, while mercaptopurine is selected for prolonged administration.

Many groups add regular pulses of vincristine and corticosteroids to this regimen although the benefit of these pulses in the context of contemporary therapy has not been established.74 The optimal duration of therapy remains unknown. Attempts to shorten therapy duration from 24 months to 12 or 18 months have resulted in a significant increase in relapses.75 Many studies extend treatment for boys to 3 years because of their generally poorer outcome compared with girls,76,77 although the benefit of this approach remains to be demonstrated. Several studies showed no advantage to prolonging treatment beyond 3 years.78,79

**CNS directed therapy**

The importance of therapy directed to the CNS was first demonstrated by investigators at St. Jude Children’s Research Hospital in the 1960s, when the incidence of CNS leukemia as an initial site of relapse became progressively more common as more effective chemotherapeutic regimens resulted in longer duration of hematologic remissions. This was attributed to the CNS acting as a pharmacologic sanctuary, poorly penetrated by conventional doses of systemically administered chemotherapeutic agents.3,80,81 Radiation therapy was the first modality successfully used to prevent CNS relapse.82 The effectiveness of 2400 cGy cranial radiation as preventive therapy was offset by substantial late effects in long-term survivors, including learning disabilities, multiple endocrinopathy, and an increased risk of second malignancies. Subsequent trials demonstrated that, in the context of intensive systemic and intrathecal therapy, cranial irradiation can...
be reduced 5.83 or even omitted altogether. 5.8,83,84

Because cranial irradiation can cause many acute and late complications (eg, second cancers, neurocognitive deficits, endocrine disorders and growth impairment), it has been largely replaced by intensive intrathecal treatment and systemic chemotherapy. Propylactic cranial irradiation (12-18 Gy) given to patients with ALL who have an increased risk of CNS relapse restricts CNS relapse to 3-8% of patients. Patients with high-risk genetic features, T-cell immunophenotype, large leukemic burden, poor response to remission induction treatment, and leukemic cells in the cerebrospinal fluid (CSF) even from iatrogenic introduction from a traumatic lumbar puncture at diagnosis, are at increased risk of CNS relapse and require more intense CNS-directed therapy.85,86 Special care should be taken to minimize traumatic lumbar punctures, to deliver intrathecal therapy optimally, and to intensify systemic and intrathecal therapy in high-risk cases.87 Studies have successfully used triple intrathecal therapy or intrathecal methotrexate alone.72 Systematically administered agents including high dose methotrexate,88-90 dexamethasone,91 and asparaginase91 may contribute to prevention of CNS relapse.

Allogeneic hematopoietic stem-cell transplantation

Comparisons between allogeneic hematopoietic stem-cell transplantation and intensive chemotherapy have yielded inconsistent results due to the small numbers of patients studied and differences in case selection criteria.92,93 Allogeneic transplantation during initial complete remission may improve outcome of patients with poor response to initial induction chemotherapy,99,22 early hematologic relapse, or T-cell ALL with poor early response or hematologic relapse.15,35,94 The benefit of allogeneic hematopoietic stem-cell transplantation in infants with t(4;11) ALL remains controversial.17,95-97 Matched unrelated-donor or cord blood transplantation has yielded outcomes comparable to those obtained with matched related-donor transplantation, and should be considered reasonable alternatives if a matched donor is not available.98,99 Autologous transplantation has failed to improve outcome in ALL.92 With improving prospects for effective targeted therapy, the need for allogeneic transplantation should be continuously re-evaluated.

Challenging age groups

As cure rates approach 90% in children aged 1 to 9 year old, the following age groups still present challenges that need to be addressed with more innovative approaches.

Infants

> Infant

ALL comprises about 2% of total ALL cases (4% of childhood ALL). Whereas the outcome of the 15-20% infants with MLL germline ALL is comparable to that of older children with ALL, those with very young age (< 6 months), high initial leukocyte count (WBC > 300 x 109/L), MLL rearrangement, and a poor early response to therapy have a dismal prognosis with less than 20% survival rates.17 95,100,101 The use of hematopoietic stem-cell transplantation in infants is controversial. Studies suggesting that the use of hematopoietic stem-cell transplantation contributed to a favorable outcome in infant ALL did not have a control arm in which patients only received chemotherapy and the data were not corrected for waiting time to hematopoietic stem-cell transplantation.97,98 Moreover, in one of these studies total body irradiation was used and led to substantial late effects in infants.98 Data from a large retrospective intergroup analysis did not show differences between infant MLL rearranged cases who did or did not receive hematopoietic stem-cell transplantation.17

> Adolescents and young adults

Older adolescents and young adults (AYA) 16-21 years receive treatment from either pediatric or adult oncologists depending on referral pattern. Overall, the number of patients in this age range comprise a relatively small percentage of either pediatric or adult ALL trial populations, and they are often analyzed together with patients 10-15 years old in pediatric series, or those patients 20-30 years and older in adult clinical trials. Several retrospective analyses have demonstrated significantly better survival for AYA patients treated on pediatric cooperative group studies (event free survival 60-65%) compared with survival of patients from the same age group who were treated on adult cooperative group trials (event free survival 30-40%). Pediatric protocols generally include more intensive use of nonmyelosuppressive agents (glucocorticoids, asparaginase, and vincristine), earlier and more intense CNS directed therapy, and more prolonged maintenance. Differences in adherence to protocol therapy among pediatric or adult medical oncologists and the patients they treat may also contribute to the discrepancy in survival. To understand the actual basis for this difference in outcome, several investigators and consortia are using common regimens to treat patients aged 1-50 years.

> Older adults

Despite improvements in the achievement of complete remission and progress in the supportive care of adults with ALL, the majority of patients eventually relapse, and the overall survival is only 30-40%. The Philadelphia chromosome (Ph+) resulting in the BCR-ABL fusion gene is the most common cytogenetic abnormality in adults with ALL, and is detected in approximately 50% of patients with B-precursor cell ALL who are over 60 years old. Elderly patients cannot tolerate intensive treatment, and trials including older adults have provisions for dose reductions in this age group. The incorporation of molecularly targeted therapy using the ABL tyrosine kinase inhibitor, imatinib mesylate, has begun to change the therapeutic landscape and outcome.33 Ongoing trials are incorporating newer kinase inhibitors to overcome resistance. Addition of rituximab to the hyper-CVAD regimen appear to improve outcome in CD20+ patients, compared to CD20+ ALL on hyper-CVAD alone.102

Relapse

Therapeutic options for refractory ALL are limited. Most relapses occur during treatment or within the first 2 years after its completion, although relapses have been reported as late as 10 years after initial ALL diagnosis.103 The most common site of relapse is the bone marrow. Relapse in extramedullary sites, such as the CNS and testes, has decreased to less than 5% and 2% respectively.104 Leukemia relapse occasionally occurs at other sites. Patients presenting with an isolated extramedullary relapse often have MRD in the bone marrow.105 Patients with isolated bone marrow relapse generally fare worse than those with combined bone marrow and extramedullary relapse.105 Factors indicating an especially poor prognosis are short initial remission and T-cell immunophenotype. Other adverse factors include t(9;22). The presence of minimal residual disease at the end of second remission induction is also a strong adverse prognostic indicator.106,107 Salvage regimens are mostly based on different combinations of the same agents used in frontline therapy, and are associated with significant morbidity and dismal long term survival rates in most cases. Patients with early or multiple relapses and heavy prior chemotherapy exposure, have an expected median survival of 9 to 10 weeks even when multiantigen chemotherapy is used. While chemotherapy may secure a prolonged second remission in children with ALL who experience late relapse (defined as more than 6 months after cessation of therapy), allogeneic hematopoietic stem cell transplantation is the treatment of choice for patients who experience hematologic relapse during therapy or shortly thereafter and for those with T-cell ALL. Patients with late-onset isolated CNS relapse who had not received cranial irradiation as initial CNS-directed therapy have a very high remission retrieval rate, with long-term prognosis approaching that of newly diagnosed patients in those who had a long initial remission before the CNS event.92,108,109

Future directions

Current therapy for patients with ALL has become increasingly dependent upon patient and disease-specific characteristics. Expanding the application of pharmacogenomics, a science which aims to define the genetic determinants of drug effects, will allow further individualized therapy in the future. While optimizing the use of old drugs continues through serial studies, new formulations of existing agents are being tested to improve the efficacy and reduce the toxicity of the parent compounds. Such modifications include improving drug transport and delivery, or altering the molecular structure to improve the therapeutic index. Ongoing trials are studying the benefit of the two novel nucleoside analogs, clofarabine and nelarabine, in high risk ALL and T-cell ALL respectively. In addition to refining leukemia classification, studies of global gene expression help identify potential molecular targets for therapy. It remains to be determined whether the success in targeting BCR-ABL with tyrosine kinase inhibitors will translate to other
pathways including NOTCH and FLT3. The challenge is to combine our current knowledge with technology to design effective risk-targeted therapies based on biological features of leukemic cells, host genetics, and early response to therapy. The dramatic increase that has occurred in the cure rate for children with ALL will be difficult to replicate in older patients without considerable additional research. In order to raise the survival rate of adolescents and adults with ALL, researchers will need a more thorough understanding of the biology of this form of leukemia, including the role that genes play in therapies.

References

Pan Arab Journal of Oncology  

| Page 1 | Issue 3 | September 08 | www.amaac.info |


Overview of Angiogenesis: Mechanisms and Predictors

Zaheer K. Otrock MD¹, Ali Shamseddine MD², Hassan A. Hatoum MD², Ali Bazarbachi MD, PhD².

¹Department of Pathology and Laboratory Medicine, ²Department of Internal Medicine, American University of Beirut Medical Center

Corresponding Author: Ali Shamseddine MD, Department of Internal Medicine, American University of Beirut-Medical Center, PO Box 113-6044, Beirut 1107 2802, Lebanon; E-mail: as04@aub.edu.lb

and

Ali Bazarbachi, MD, PhD, Department of Internal Medicine, American University of Beirut-Medical Center, PO Box 113-6044, Beirut, Lebanon; E-mail: bazarbac@aub.edu.lb

Key words: Angiogenesis.

Submitted: 4 September 2008; Accepted: 20 September 2008.

ISSN: 2070-254X

Introduction

Angiogenesis is an important biological process not only under physiological conditions but in a variety of diseases including cancer [Risau 1997]. It is the sprouting of new blood vessels from the pre-existing ones. This process is important for the growth of new blood vessels during fetal development and tissue repair; however, uncontrolled angiogenesis promotes neoplastic diseases and other disorders. Under these conditions, angiogenesis is a highly regulated process, i.e. turned on for brief periods and then completely inhibited [Folkman and Shing, 1992].

After the primary vascular plexus is formed, more endothelial cells (ECs) are generated, which can form new capillaries by sprouting or by splitting from their vessel of origin in a process termed angiogenesis [Risau 1997]. Angiogenesis depends on the balance between different molecules released by the host and tumor cells, and consists of a series of steps, including separation of ECs from pericytes and the basement membrane, invasion and migration across basement membranes, and eventually resulting with the extension into the tumor body [Carmeliet 2000; Hanahan and Folkman, 1996]. Specific angiogenic molecules can initiate this process. Specific inhibitory molecules can stop it. Numerous inducers of angiogenesis have been identified, including the members of the vascular endothelial growth factor (VEGF) family, angiopoietins, transforming growth factors (TGF), platelet-derived growth factor, tumor necrosis factor-alpha (TNF-alpha), interleukins, and the members of the fibroblast growth factor (FGF) family [Papetti and Herman, 2002; Presta et al., 2005]. In addition, many factors control and influence angiogenesis including soluble growth factors, membrane-bounded proteins, cell-matrix and cell-cell interactions, and many interacting systems [Papetti and Herman, 2002].

In this manuscript, we give an overview of important mediators and molecular mechanisms in angiogenesis. Predictors of angiogenesis like hypoxia inducible factor-1 (HIF-1), mast cell density as a surrogate for microvessel density [Acikalin et al., 2005], and CD34, have been actively investigated recently for their potential role as prognostic factors in tumor recurrence, aggressiveness and resistance to chemotherapy. Nevertheless, inhibitors to these molecules are being investigated in different malignancies and different settings. Direct and indirect inhibitors exist. Some of these inhibitors are already in the clinical use like CCI 779, an mTOR inhibitor responsible for indirect inhibition of HIF-1 alpha [Mellilo 2007]. Further understanding of the tumor microenvironment will lead to development of more effective and more specific targeted therapy consequently leading to better clinical outcomes. In order to facilitate this understanding, we shed light on the role of each of vascular endothelial growth factors and receptors, matrix metalloproteinases system, and plasminogen activator/plasmin system in angiogenesis.

Vascular endothelial growth factors

One of the most specific and crucial regulators of angiogenesis is vascular endothelial growth factor (VEGF) [Gupta and Zhang, 2005]. The VEGF family comprises seven secreted glycoproteins that are designated VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, placental growth factor (PIGF) and VEGF-F [Ferrara et al., 2003; Houck et al., 1991; Suto et al., 2005]. Vascular endothelial growth factor-A (VEGF-A; also referred to as VEGF) is the best characterized and the most studied of the VEGF family members. It is a tumor-secreted cytokine with grave importance in both normal and tumor-associated angiogenesis [Rini and Small, 2005]. VEGF-A exerts its biologic effect through interaction with cell-surface receptors. These are transmembrane protein tyrosine kinase receptors and they include VEGF receptor-1 (VEGFR-1) and VEGFR-2, selectively expressed on vascular ECs, and the neuropilin receptors (NP-1 and NP-2), expressed on neurons and vascular endothelium [Dvorak 2002]. Upon binding of VEGF-A to the extracellular domain of the receptor, a cascade of downstream proteins are activated after the dimerization and autophosphorylation of the intracellular receptor tyrosine kinases. VEGF-R2 appears to be the major receptor responsible for mediating the proangiogenic effects of VEGF-A [Ferrara et al., 2003; Cross et al., 2003]. VEGFR-3 preferentially binds VEGF-C and VEGF-D. VEGFR-3 is up-regulated on blood vascular ECs in pathologic conditions such as in vascular tumors and in the periphery of solid tumors [Partanen et al., 1999]. VEGFR-3 expression was correlated with transient lymphangiogenesis in wound healing and was up-regulated in blood vessel endothelium in chronic inflammatory wounds [Paavonen et al., 2000]. Thus, VEGFR-3 is believed to play various roles in cardiovascular development and remodeling of primary vascular networks during embryogenesis and enhancing lymphangiogenesis in adulthood.

VEGF-A is the most potent pro-angiogenic protein described to date. It induces proliferation, sprouting and tube formation of ECs [Ferrara et al., 2003]. In addition, it causes vasodilatation by inducing the endothelial nitric oxide synthase and so increasing nitric oxide production [Hood et al., 1998]. VEGF-A binds many receptors on hematopoietic stem cells (HSCs), monocytes, osteoblasts and neurons [Ferrara et al., 2003]. In vivo, VEGF-A expression has been shown to be associated with significant steps in angiogenesis and physiologic vasculogenesis [Jakeman et al., 1993; Shweiki et al., 1993]. In mice, deletion of the VEGF-A gene is lethal, resulting in vascular defects and cardiovascular abnormalities [Carmeliet et al., 1996]. VEGF-A affects an important number of angiogenic processes including...
wound healing, ovulation, maintenance of blood pressure, menstruation and pregnancy [Brown et al, 1992]. In humans, VEGF-A is expressed in practically all solid tumors studied as well as in some hematological malignancies [Ferrara et al, 2003]. Recently, VEGFR-2 (specifically VEGF-A) was over-expressed in patients with distant metastases of pulmonary adenocarcinoma [Nishi et al, 2005].

Matrix Metalloproteinases System in Angiogenesis

The degradation of the basement membranes is an essential requirement for the formation of new vessels. Matrix metalloproteinases (MMPs) are a family of proteolytic enzymes that degrade various components of the ECM. They can be divided into two structurally distinct groups, namely secreted MMPs and membrane-type MMPs (MT-MMPs) [Pepper 2001]. The secreted MMPs include collagenases (MMP-1, MMP-8, and MMP-13), stromelysins (MMP-3, MMP-10, and MMP-11), gelatinases (gelatinase A or MMP-2; gelatinase B or MMP-9) and other MMPs [Pepper 2001].

The role of several MMPs has been characterized in ECs and in the context of angiogenesis. In particular, gelatinases A and B, MMP-2 and MMP-9, play an important role in the angiogenic response as demonstrated in ECs as well as in vivo animal models deficient in these proteases [Genis et al, 2006]. Thus, MMP-9 is critical for the angiogenic switch required during tumorigenesis as shown in a model of pancreatic cancer; MMP-9 acts by releasing VEGF from the proteoglycan matrix [Bergers et al, 2000]. The role of other MMPs in angiogenesis may depend on the tissue/organ from which ECs are derived. In this regard, it has been shown recently that MT3-MMP is preferentially required for the formation of new capillaries by endometrial ECs [Plaisier et al, 2004]. Recently it has become apparent that inhibition of MMP activity is essential for vessel stabilization during the resolution phase of angiogenesis; unchecked proteolysis results in regression of newly formed vessels [Kraling et al, 1999; Zhu et al, 2000].

MT1-MMP, the first matrix metalloproteinase identified that was anchored to the cell membrane instead of being soluble, seems to be a key player in the angiogenic response. MT1-MMP was identified as the fibrinolysin responsible for degrading and remodeling the fibrin matrix often deposited during vascular injury [Hiraoka et al, 1998]. The generation of MT1-MMP-deficient mice has supported the requirement of MT1-MMP for angiogenesis. MT1-MMP-deficient mice exhibit severe skeletal deformities which lead to death by 3-16 weeks of age [Holmbeck et al, 1999; Zhu et al, 2000]. MT1-MMP participates in several of the steps of the angiogenic response including degradation of the ECM and endothelial invasion [Hiraoka et al, 1998; Chun et al, 2004; Oblander et al, 2005], endothelial migration [Galvez et al, 2001; Galvez et al, 2002], and formation of capillary tubes [Galvez et al, 2001; Langlois et al, 2004; Robinet et al, 2005].

Plasminogen Activator/Plasmin System in Angiogenesis

Plasmin is a broad-spectrum protease which is presumed to hydrolyse many extracellular proteins, most notably fibrin. Urokinase-type plasminogen activator (uPA) and tissue plasminogen activator (tPA) are serine proteases that mainly activate plasminogen; plasminogen is their specific substrate. uPA is a serine protease and binds to a specific glycosylphosphatidylinositol-anchored cell surface receptor (uPA receptor-uPAR) [Pepper 2001].

Assessing the role of the individual components of the PA/plasmin system in angiogenesis in vivo was made possible by the generation of mice deficient in these components [Carmeliet and Collen, 2000]. Plasminogen activator inhibitor type-1 (PAI-1) is considered one of the key regulators of tumor invasion, metastasis, as well as cancer-related angiogenesis [Chorostowska-Wynimko et al, 2004]. Hypoxia which is a chief stimulus for angiogenesis was reported to increase uPAR [Kroon et al, 2000] and PAI-1 [Uchiyama et al, 2000] in ECs. In vivo, several studies have demonstrated a necessity for the PA/plasmin system in angiogenesis and tumor cell invasion [Bajou et al, 1998; Heymans et al, 1999].

Anti-angiogenesis: a medical revolution in therapeutic approach

In the last decade, there has been a tremendous advancement in the treatment of many malignancies using anti-angiogenic medications. This has impacted on the outcome and survival of cancer patients.

Among the most effective anti-angiogenic medications introduced into the armamentarium of cancer treatment are Bevacizumab and selected tyrosine kinase inhibitors (TKIs). Bevacizumab (Avastin) is a recombinant, humanized monoclonal antibody against VEGF that is used to inhibit VEGF function in vascular endothelial cells and thereby inhibit tumour angiogenesis. The addition of bevacizumab to irinotecan or oxaliplatin in metastatic colorectal cancer significantly increased median progression-free survival and overall survival in most randomized clinical trials. Overall survival advantage due to bevacizumab was 4.7 months when used as first-line therapy in phase III trials in metastatic colorectal carcinoma [McCormack and Keam, 2008]. In metastatic renal cell carcinoma (RCC), bevacizumab resulted in a significantly longer progression-free survival when compared to the traditional treatment of IFN-α (10.2 versus 5.4 months) [Escudier et al, 2007]. In addition to their role as kinase inhibitors, TKIs have an anti-angiogenic effect. For instance, Sunitinib and Sorafenib have a significant activity in RCC through their anti-angiogenic properties. Sunitinib, an oral TKI, resulted in a median progression-free survival of 11 month which was significantly longer than that in the interferon alfa treatment group (5 months) [Motzer et al, 2007].

Angiogenesis: Clinical significance and predictors

One of the most important and independent predictors of survival in cancer patients is angiogenesis [Weidner et al, 1999]. This has been noticed in a variety of malignancies like breast, lung, bladder, prostate and skin cancers [Weidner et al, 1999; Bosari et al, 1992; Weidner et al, 1993; Macchiariini et al, 1992; Srivastava et al, 1988; Beatrice et al, 1998; Williams et al, 1994]. Angiogenesis has been correlated not only with survival, but rather with distant metastasis and chemotherapy resistance. Microvessel density, for instance has been proven to be a very significant factor in predicting tumour recurrence and time to recurrence in colorectal cancer [Engel et al, 1996]. Tanigawa et al. reported a strong association between vascularity and overall survival in 133 patients with colorectal adenocarcinoma [Tanigawa et al, 1997]. In another study on the same type of colorectal cancers, Zheng et al reported a strong correlation between microvessel density on one hand and stage and tumour grade on the other hand [Sasaki et al, 2001]. Based on these facts, it is crucial to look for predictors of angiogenesis and finding potential inhibitors for these molecules. Since microvessel density is a reliable means for evaluation of the severity of angiogenesis, several markers have been introduced into the diagnostics. Different endothelial cell markers, such as CD31, CD34 and von Willebrand factor were used for evaluating neovascularisation. Monoclonal antibodies were developed in order to detect these markers in tumor tissues [Singhal et al, 2005]. In addition to PDGF, bFGF, and IL-8 are considered to play a major role in the angiogenic process. Basic fibroblast growth factor (bFGF) which originates from extracellular matrix under the effect of proteolytic enzyme increases the expression of other proteolytic molecules leading to preangiogenic and increase tumor growth [Cox et al, 2000]. Similarly there is evidence that ILS was associated with increased microvessel density in NSCLC and eventually with a worse outcome [Yuan et al, 2000].

Several other growth factors also play a role in the development of tumoral blood supply. For instance a newly discovered cytokine produced by mesenchymal cells known as hepatocyte growth factor exerts its effect on epithelial and endothelial cells and thereby inhibit tumour angiogenesis. The addition of bevacizumab to interferon alpha treatment group (5 months) [Motzer et al, 2007].

HIF-1 α: a marker and a target

Among the aforementioned factors, HIF-1 seems to be the major player with avid evidence on its significant role in angiogenesis in different cancers in humans. This role has been persued since the 1990’s.
Gene transcription was shown to directly regulate VEGF expression in hypoxia and this induction of HIF-1α gene transcription was shown to directly regulate VEGF expression in xenograft tumors [Maxwell et al., 1997]. Since malignant cells have hypoxic conditions HIF-1α is overexpressed in these cells which leads to VEGF and SDF-1 (stromal–derived growth factor 1 protein that are known to induce angiogenesis [SchOFeld and Ratcliffe, 2005; Semenza 2003]. HIF-1α accumulation in hypoxic conditions is mainly due to inhibition of 26S proteosome-mediated HIF-1α degradation during hypoxia [SchOFeld and Ratcliffe, 2005]. Degradation of HIF-1α could be inhibited by decreased binding of mutated VHL to protein to as in renal cell carcinoma condition leading to its accumulation and increased neovascularization [Blancher et al., 2001]. This increase in HIF-1α expression has been documented by histochemical analysis of tissue biopsies of different human cancers [Semenza 2003]. In addition to VEGF-1 and SDF-1, HIF-1α controls the expression of other growth factors responsible for angiogenesis; these include ANGPT1, ANGPT2, PLGF and FGDF-B [Ravi et al., 2000]. Increased HIF-1α leads to increase in insulin like growth factor 2 (IGF-2) resulting in enhancing IGF-1 receptor tyrosine kinase and activation of PI3K and MAP kinase pathways responsible for cell survival and proliferation [Fukada et al., 2002]. At the animal level using mice models, tumor neovascularization was found to be impaired in HIF-1α–deficient endothelial [Tang et al., 2004].

HIF-1α and therapeutic options

Inhibitors of HIF-1α could be either selective or non selective with most of the inhibitors being non-selective ones [Rapisarda and Melillo, 2008]. Examples of direct inhibitors include Chetamine which is known to block recruitment of coactivator P300/CBP [Kung et al., 2004], echinomycin [Kong et al., 2005] and synthetic polyamides [Olenyuk et al, 2004] which directly inhibits binding of HIF-1α to DNA. There are new efforts for targeting the dimerization of HIF-1α to HIF-1β.

Indirect HIF-1α inhibitors on the other hand are numerous and target pathways involved in activating HIF-1α as an end point [Rapisarda and Melillo, 2008]. Among these are Hsp90 inhibitors which downregulate HIF-1α. Microtubule inhibitors like methoxyestradiol (2ME2), which in addition to downregulating HIF-1α inhibits dimerization of microtubule [Melillo 2007]. Topoisomerase I inhibitors like topotecan, due to their small size are able to act as inhibitors of the HIF-1α at mytemecnomic daily doses the fact which lead the NCI to run a prospective trial on the use of topoisomerase I inhibitors in metastatic cancers as a HIF-1α expression inhibitors. Histone deacetylase inhibitors and tyrosine kinase receptor inhibitors are known to produce HIF-1α inhibition, though the efficacy of the former as HIF-1α therapeutic inhibitor is still controversial [Melillo 2007]. On the other hand, the efficacy of tyrosine kinase inhibitors in treating malignancies is well known and is greatly attributed to HIF-1α inhibition [Rapisarda and Melillo, 2008]. mTOR inhibitors like CCI 779 which is already in clinical use of RCC affects indirectly HIF-1α expression as well [Melillo 2007]. Combination of HIF-1α inhibitors with other antiangiogenic factors, chemotherapy and radiotherapy is to be further investigated in order to determine its efficacy.

Angiogenesis: Radiologic Biomarkers and Future perspective

Sustained angiogenesis is one of the pathophysiological processes in solid tumors that are targeted by different agents [Hanahan and Weinberg, 2000; Gibbs 2000]. Effect of therapeutic agents used in malignancy includes either cytolyis or cytostasis; targeted therapy includes mainly cytostasis maintaining same tumor size though less activity leading to response which is difficult to assess when using traditional CT scan and MRI [Harwit et al., 2004; Johnson et al., 2004]. PET and dynamic contrast enhanced MRI (DCE-MRI) can do better evaluation by measuring microscopic characteristics [O’Connor et al., 2008]. Measurement in Hounfield units (HU) using contrast CT scan by calculating the perfusion score through subtracting the post-contrast CT data from the pre-contrast one was proven in Hounfield units (HU) using contrast CT scan by calculating the perfusion score through subtracting the post-contrast CT data from the pre-contrast one was proven in [O’Connor et al., 2008]. In addition to PET, PET-CT scan and contrast-enhanced MRI are the most common tools for assessing antitumor therapy. PET-CT scan has been shown to have high specificity and sensitivity for the detection of small areas of tumor tissue [Rapisarda and Melillo, 2008]. PET scanning is used in detecting the tumor vasculature in order to measure tumor density and calculate the increase in degree of enhancement and SUV in (18F) FDG PET are very helpful in assessing tumor response, not only through traditional size measurement but rather through assessing vascularity which reflects tumor viability and activity [O’Connor et al., 2008]. In spite of these promising results to assess response by using the above biomarkers, yet criteria for their use as radiological features should be refined through phase III trials. The question whether new agents targeting tumor vasculature could be developed to enhance radiological features in order to assess response to antiangiogenesis remains open to be answered.

References

16. Partanen TA, Allitao K, Miittinnen M. Lack of lymphatic vascular specificity


Primary meningeal non Hodgkin lymphoma. Case report and literature review

Boussen H1, Allani B1, Kefi M2, Abdelkefi A3, Gouider E4, Ben Othman T4.

(1) Department of medical oncology, Institut Salah Azaiz, (2) Institute of Neurology, (3) Bone Marrow Transplant Department, (4) Department of Hematologic Biology, Aziza Othmana Hospital, Tunis, Tunisia.

Corresponding Author: Pr Boussen Hamouda, Department of medical oncology, Institut Salah Azaiz - Tunis, Tunisia, E-mail: sarroura2000@yahoo.fr

Key words: Lymphoma, meningeal, primary, CSF, B, immunophenotyping, chemotherapy, intrathecal.

Submitted: 8 September 2008; Accepted: 22 September 2008.

ISSN: 2070-254X

Abstract

Primary meningeal lymphoma is rare. We report a case of a 56 year-old immunocompetent man presented with 3 month’s history of right lombosciatalgia, and progressive right leg weakness. MRI show a lesion in the foraminal area of L4. Patient was operated by laminectomy and histological exam was negative. Cytologic exam of CSF with immunophenotyping diagnosed a B high grade lymphoma. He received chemotherapy by R-ACVBP and high dose methotrexate associated to cerebral radiotherapy. With a follow-up of 22 months, this patient remains alive in complete remission.

Introduction

Central Nervous System primary lymphoma’s (CNSPLs) are rare extranodal localisations affecting brain, leptomeninges, spinal cord or eyes, representing 2.7% of intracranial neoplasms in US from 1995 to 1999 (1). According to diagnosis criteria, they remain confined to CNS and affect brain, meninges, spinal cord and eyes(2). Leptomeningeal primary lymphoma with no associated cerebral lesions is uncommon representing 7% of CNSPLs (2). We report a new case with a literature review.

Observation

A 56 year-old caucasian man with previous history since 9 years of moderate hypertension and without history of osteoarticular trauma presented with 3 month’s history of right lombosciatalgia, and progressive right leg weakness. On examination, the patient had a distal amyotrophia associated with a diffuse lower right leg weakness(2/5) without sensory level. Electromyogram suggest a radicular lesion if the L4, L5 and S1 territory. Lumbar MRI revealed corporéal tassement of L4. Patient was operated by laminectomy and histological exam was negative. Fifteen days after this surgery, there is an increase of the leg deficit and extension to the left contralateral limb. Examination show a distal and proximal deficit of the legs, more pronounced in the right side with a radicular L5 topography. Dorso-lumbar myeloscan show a discal hernia paramedian and foraminal of L4-L5 in the right side with caudal migration in 16 mm generating a conflict with the right root of L5 and a retromarginal posterior hernia L4-L5 left in conflict with the left root of L5. Few days after, appear a right peripheral facial paralysis. Cytologic examination of CSF show the presence of 15 white cells probably lymphocytic, an increased proteinorrachia at 2.15g/l and a normal glucorrachia. Cerebro-mullar MRI show postlaminectomy lesions at the level of L4-L5 associated to a postero lateral left discal discale and enhancement of gadolinium in the root of right L5.

Discussion

Primary leptomeningeal lymphoma is a rare disease revealed usually by signs of increased intracranial pressure, confusion, dysarthria, hearing loss or paraparesis and lumbosacral symptoms as we observed in our case(2). For our patient, symptoms are dominated by lombosciatalgia and uni then bilateral paraparesis, followed by a peripheral right facial palsy and positive diagnosis was based on the presence in the CSF of a monoclonal B high-grade proliferation. We retain the diagnosis of PLML considering the positive CSF cytology and the negative work-up for any extra-CNS disease, this strict definition differentiate well the “true” PLML from primary cerebral lymphomas with meningeal involvement.
and systemic lymphomas complicated by lymphomatous meningitis in concordance with the criteria proposed by Lachance et al(6). Our observation is close to the 9 cases reported by this author in 1991 presenting a neoplastic lymphomatous meningitis without parenchymal central nervous system nor systemic tumour at the time of presentation or throughout the course of their disease (6). Considering the Lachance criteria’s PLML is probably a very rare disease with less than 100 cases reported in the literature.

Positive diagnosis is based on CSF cytology that does not consistently detect malignant cells in patients with PCNSL, abnormal in only 26 to 31% of cases, but repeated samples increase its sensitivity(3). In a study about 96 patients reported by Balmaceda et al, CSF initial CSF cytology study was positive in only 15% of cases(4). CDR III PCR as a routine diagnostic technique seems to be applicable even on CSF samples with low cell counts with a sensitivity and specificity of 54% and 97% (5). PLML are usually of B diffuse large cell lymphoma, the most common worldwide type of systemic lymphoma and more rarely low-grade or T-cell types (7). Our patient, presented a high grade B lymphoma based on CSF/immunophenotyping examination.

References

ASCO 2008 Main Highlights

A. AWADA, MD, PhD

(1) Jules Bordet Institute, Université Libre de Bruxelles - Belgium

✉ Corresponding Author: Ahmad Awada, MD. Head of Medical Oncology Clinic, Jules Bordet Cancer Institute, Brussels, Belgium, email: ahmad.awada@bordet.be

Submitted: 15 August 2008; Accepted: 15 August 2008.

ISSN: 2070-254X

Early Breast cancer

> Hormonal therapy in premenopausal pts:
  * Ovarian suppression + Tam = OS + anastrozole (new option)
  * Zoledronic acid significantly improves DFS compared to endocrine therapy alone
> Ten vs 5 years adj. Tam: no clear answer but combining results suggest Tam>5 years reduces recurrence over the next few years
> Gemcitabine did not add benefit to adj. EC > Paclitaxel
> Elderly patients (≥ 65 years): adj. CMF/AC > capecitabine
> Vit D deficiency is associated with an increased risk of distant recurrence and death

Colorectal cancer

> Adjuvant bevacizumab + Folfox is well tolerated
> Adjuvant FOLFIRI after R0 stage IV liver mets: don’t work
> mCRC: no need to insist on oxaliplatin (intermittent !)
> Anti EGFR Mob + bevacizumab + chemotherapy: less effective and more toxic!
> Mutated k-ras tumors are resistant to Mob targeting EGFR

Metastatic Breast cancer

> HER-2/neu negative tumors:
  * Gefitinib + anastrozole demonstrated prolonged PFS and greater CB compared to anastrozole alone (see also Osborne, SABC2007)
  * Avado trial: doct + beva vs doct + placebo > clear benefit but less impressive than paclit + beva (E2100)
> HER-2/neu positive tumors:
  * Evidence supporting continuing trastuzumab (or other anti-HER2) post-progression confirmed
  * Trastuzumab + CT > trastuzumab alone as first line
  * Trastuzumab-resistant tumors: lapatinib, HK1-272, pertuzumab, tanespimycin, bevacizumab, pazopanib

Non-colorectal cancer

> Metastatic pancreatic cancers:
  * Gemci + erlotinib + beva > promising but who benefits (role of erlotinib ?)
  * Gemcitabine refractory: oxaliplatin might matter
> Final results of adjuvant gemcitabine: confirmation of early results
> Unresectable localized pancreatic cancer: radiation + gemci is useful for a subset of pts (which one ?)
> Sorafenib is effective in HBV related HCC and in Asian patients
> Gastric cancer: Docet + CDDP = CDDP + 5FU but toxicity profiles differ

Gynecologic cancer

> Recurrent cervical cancer:
  * Cisplatin + paclitaxel or vinorelbine or gemcit or topotecan are equivalent
  * CDDP + topotecan > CDDP (RR, TTP, OS)
  * CDDP + paclitaxel > CDDP (RR, TTP)
> Ovarian cancer: CBDCA + paclitaxel = standard of care
> BRCA deficient ovarian cancer: AZD2281, a PARP inhibitor is active (RR: 46%)

Genito-urinary cancer

> Bladder preservation should not be offered outside a clinical trial for pts with localized transitional cell carcinoma (SWOG0129)
> No evidence to support or refute the use of adjuvant therapy in high-risk bladder cancer pts
> Sunitinib demonstrates a survival benefit when compared to IFN in untreated pts with metastatic renal cancer
> Everolimus (RAD001) is the new standard of care for renal cancer pts who progress on VEGFR-TKIs
Prostate cancer / testis

> Testis : RT = 1 cycle of CBDOCA (AUC7) for stage I seminoma
> Prostate :
  `*Angiogenesis may be an important target in prostate cancer`
  `*Abiraterone (inhibitor of androgen synthesis) : clinical activity in pretreated pts (chemo. or androgen blockade)`
  `*Saraplatin is an active agent`

Head & Neck cancer

> Paccagnella study : TPF induction > CT/RT results support this approach
> TPF + Cetuximab is safe (role of 5-FU ?)
> HPV is a causative factor in ~50% OP SCCHN with improved prognosis

Bone tumors and soft-tissue sarcomas

> Bone tumors :
  `*Giant cell tumors : role for denosumab (RR : 87%)`
  `*Ewing’s sarcoma : q2wCT > q3wk`
  `- Activity of an IGFR-R inhibitor (CP-751871)`
> Soft-tissue sarcomas
  `*Ifos less effective for LMS and liposarcoma`
  `*LMS : Gemci = gemcit/docet (french study)`
  `*HPS/SFT : Temozolomide + beva. Active (RR : 79%)`
> GIST
  `*IGF-R is a potential target`
  `*Sorafenib and IPI-504 (HSP-90 inhibitor) have some activity as 3rd line therapy (RR : 14%)`

Melanoma

> Stage II melanoma : adj. ganglioside GM2-KLH-QS21 vaccination is inferior to observation !
> Sentinel lymph node biopsy improves survival among SEER patients in particular in thin and intermediate thickness lesions
> Promising agents :
  `*Axitinib an inhibitor of VEGFR (ORR 19%)`
  `*Second generation, GM-CSF encoding oncolytic viruses (ORR: 26%)`
  `*IFNα2b + anti-CTLA4 : ORR 19%`
> Imatinib may be an useful agent in mutated kit mucosal and acral melanomas

Lung cancer

> IALT : - Efficacy of adj. CT for the first 5 years
  `- Diminished benefit > 5 years (unexplained CT-related mortality)`
  `- ERCC1 continues to be predictive for CT benefits`
> Preoperative CDDP+gemci in early stage NSCLC : promising
> Maintenance Pemetrexed prolong PFS and OS. Superior activity in non-squamous histology
> Flex trial : - CDDP + NVB + Cetuximab > CDDP + NVB (EGFR +)
  `- Role of EGFR FISH & K-ras mutation in efficacy ?`
> IGFR is a potential new target and CP-751.871 seems to be exquisitely active in squamous histology
> SCLC : CDDP + topotecan or irinotecan are not superior but could be alternative to CDDP + etoposide
> Gene signature may refine prognosis but need further validation

Supportive Care

**Oral Mucositis**

> Recombinant human intestinal trefoil factor (rhITF) in mucositis
> Trefoil factor: peptide produced by GI tract.
> Formulation: oral spray
> Patients, n = 99, with symptomatic mucositis, grade >= 2, at first cycle, were given rhITF in 2nd cycle of same treatment.
> Mucositis rhITF vs placebo: 9% vs 48,5% , p< 0.001

<table>
<thead>
<tr>
<th>BV +/- irinotecan in recurrent GBM</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=82)</td>
</tr>
<tr>
<td>Median OS</td>
</tr>
<tr>
<td>PFS 6 mos (%)</td>
</tr>
<tr>
<td>O R R (%)</td>
</tr>
</tbody>
</table>

**Melanoma**

> Stage II melanoma : adj. ganglioside GM2-KLH-QS21 vaccination is inferior to observation !
> Sentinel lymph node biopsy improves survival among SEER patients in particular in thin and intermediate thickness lesions
> Promising agents :
  `*Axitinib an inhibitor of VEGFR (ORR 19%)`
  `*Second generation, GM-CSF encoding oncolytic viruses (ORR: 26%)`
  `*IFNα2b + anti-CTLA4 : ORR 19%`
> Imatinib may be an useful agent in mutated kit mucosal and acral melanomas

**Lung cancer**

> IALT : - Efficacy of adj. CT for the first 5 years
  `- Diminished benefit > 5 years (unexplained CT-related mortality)`
  `- ERCC1 continues to be predictive for CT benefits`
> Preoperative CDDP+gemci in early stage NSCLC : promising
> Maintenance Pemetrexed prolong PFS and OS. Superior activity in non-squamous histology
> Flex trial : - CDDP + NVB + Cetuximab > CDDP + NVB (EGFR +)
  `- Role of EGFR FISH & K-ras mutation in efficacy ?`
> IGFR is a potential new target and CP-751.871 seems to be exquisitely active in squamous histology
> SCLC : CDDP + topotecan or irinotecan are not superior but could be alternative to CDDP + etoposide
> Gene signature may refine prognosis but need further validation

**Supportive Care**

**Oral Mucositis**

> Recombinant human intestinal trefoil factor (rhITF) in mucositis
> Trefoil factor: peptide produced by GI tract.
> Formulation: oral spray
> Patients, n = 99, with symptomatic mucositis, grade >= 2, at first cycle, were given rhITF in 2nd cycle of same treatment.
> Mucositis rhITF vs placebo: 9% vs 48,5% , p< 0.001

<table>
<thead>
<tr>
<th>BV +/- irinotecan in recurrent GBM</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=82)</td>
</tr>
<tr>
<td>Median OS</td>
</tr>
<tr>
<td>PFS 6 mos (%)</td>
</tr>
<tr>
<td>O R R (%)</td>
</tr>
</tbody>
</table>

**Melanoma**

> Stage II melanoma : adj. ganglioside GM2-KLH-QS21 vaccination is inferior to observation !
> Sentinel lymph node biopsy improves survival among SEER patients in particular in thin and intermediate thickness lesions
> Promising agents :
  `*Axitinib an inhibitor of VEGFR (ORR 19%)`
  `*Second generation, GM-CSF encoding oncolytic viruses (ORR: 26%)`
  `*IFNα2b + anti-CTLA4 : ORR 19%`
> Imatinib may be an useful agent in mutated kit mucosal and acral melanomas

**Lung cancer**

> IALT : - Efficacy of adj. CT for the first 5 years
  `- Diminished benefit > 5 years (unexplained CT-related mortality)`
  `- ERCC1 continues to be predictive for CT benefits`
> Preoperative CDDP+gemci in early stage NSCLC : promising
> Maintenance Pemetrexed prolong PFS and OS. Superior activity in non-squamous histology
> Flex trial : - CDDP + NVB + Cetuximab > CDDP + NVB (EGFR +)
  `- Role of EGFR FISH & K-ras mutation in efficacy ?`
> IGFR is a potential new target and CP-751.871 seems to be exquisitely active in squamous histology
> SCLC : CDDP + topotecan or irinotecan are not superior but could be alternative to CDDP + etoposide
> Gene signature may refine prognosis but need further validation

**Supportive Care**

**Oral Mucositis**

> Recombinant human intestinal trefoil factor (rhITF) in mucositis
> Trefoil factor: peptide produced by GI tract.
> Formulation: oral spray
> Patients, n = 99, with symptomatic mucositis, grade >= 2, at first cycle, were given rhITF in 2nd cycle of same treatment.
> Mucositis rhITF vs placebo: 9% vs 48,5% , p< 0.001

<table>
<thead>
<tr>
<th>BV +/- irinotecan in recurrent GBM</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=82)</td>
</tr>
<tr>
<td>Median OS</td>
</tr>
<tr>
<td>PFS 6 mos (%)</td>
</tr>
<tr>
<td>O R R (%)</td>
</tr>
</tbody>
</table>
Best of ASCO 2008 in Beirut, Lebanon

Nagi S. El Saghir, MD, FACP, Ali I. Shamseddine, MD, Joseph Kattan, MD, Khaled M Ibrahim, MD

(1) Clinical Professor of Medicine, American University of Beirut, Beirut, Lebanon
(2) Professor of Clinical Medicine, American University of Beirut, Beirut, Lebanon
(3) Associate Professor of Medicine, Saint Joseph University, Beirut, Lebanon
(4) Attending Oncologist, Hammoud Hospital, Saida, Lebanon

ISSN: 2070-254X

The Lebanese Society of Medical Oncology (LSMO) welcomed over 200 Arab cancer specialists to its 3rd Annual Best of ASCO meeting in Lebanon. Best of ASCO (BOA) is a program licensed by the American Society of Clinical Oncology (ASCO) and held in conjunction with LSMO. BOA 2008 was a two-day conference where a selection of the most highly rated abstracts of the 44th ASCO Annual Meeting held in Chicago May 30-June 3, 2008, were presented and discussed. In addition to people who attended ASCO, many people who did not travel to Chicago found BOA a great opportunity for them to hear the most important advances in cancer research.

ASCO has become a very large meeting and ASCO attendees can no longer possibly attend all ASCO sessions. Therefore oncologists and related cancer specialists find ASCO highlights and summaries very useful. LSMO has been organizing annual ASCO Highlights meetings since it was founded in 1997. LSMO was privileged to host BOA meetings on a yearly basis for the last 3 years. LSMO organized BOA as Regional meetings and oncologists from Lebanon and Arab and neighboring countries attended them.

Like in previous years, a superb International Faculty including Ahmad Awada, MD (Brussels, Belgium), Ghassan Abou-Alfa, MD (New York, NY), Toni Choueiri, MD (Boston, MA), Ghandi Damaj, MD (Amiens, France), Fadlo Khuri, MD (Atlanta, GA), Adnan Munkara, MD (Riyadh, Saudi Arabia and Detroit, MI), as well a select group of Local and Regional Experts, presented original ASCO presentations and discussed them. The meeting was very successful with over 200 attendees from Egypt, Iran, Iraq, Jordan, Kuwait, Lebanon, Libya, Oman, Saudi Arabia, Syria, United Arab Emirates, and the United States of America. LSMO was very pleased that many young oncologists and fellows in training attended BOA. We had very positive feedbacks from attendees and speakers and is encouraged to continue this yearly tradition of Best of ASCO meetings. Even during hard times in 2007, LSMO relocated BOA Lebanon from Beirut to Cairo. This year, Lebanon has regained a very much deserved peace and speakers and attendees enjoyed a great meeting and a wonderful social program.

To quote from ASCO News and Forum: “Many of the BOA selections of this year were very relevant for cancer research and treatment in Lebanon and the region. Hormonal therapy of breast cancer, adjuvant zoledronic acid, and vitamin D research were particularly discussed as very relevant because 50% of breast cancer in our patient population is seen in women below the age of 50 years. Also, although we have beautiful sunny weather in this part of the world, serum vitamin D levels are rather insufficient or deficient in many studies. Speakers and discussants stressed the needs to study vitamin D levels and possible effects on prognosis of breast cancer, and make sure patients, and women in general, get enough vitamin D supplementation. Attendees also focused on the new studies for anti-EGFR therapy and KRAS mutations in colon cancer and concluded that strict guidelines to forbid usage of cetuximab in patients whose tumors have mutant KRAS gene. Research to better identify patients who would benefit from expensive monoclonal antibody was felt to be of high priority. Increased participation from Arab countries in International research and clinical phase III trials was recommended as a top priority. Many of the attendees practice in countries with limited resources where patients cannot have access to new expensive targeted therapies. There was a great interest from participants in research leading to identify factors that would help select patients for various therapies to avoid costs and improve access to new medications” (ASCO News and Forum, October 2008: www.asco.org).
The World Cancer Declaration adopted by the UICC World Cancer Congress 2008 in Geneva

Michel Daher, MD, FACS

Corresponding Author: Michel Daher, MD, FACS, President Lebanese Cancer Society, Department of Surgery, Saint George Hospital, POBox: 166378, Beirut, Lebanon; Email: mndaher@inco.com.lb

Key words: UICC, World Cancer Declaration 2008.

Submitted: 28 September 2008; Accepted: 28 September 2008.

ISSN: 2070-254X

The World Cancer Declaration 2008 was developed by the International Union Against Cancer (UICC), adopted by the World Cancer Summit 2008, and endorsed by the World Cancer Congress 2008.

The World Cancer Summit was hosted by the International Union Against Cancer (UICC), the leading international non-governmental organization dedicated to the global control of cancer. The World Cancer Congress took place in Geneva, Switzerland, from 27 to 31 August 2008. The congress brought together about 2,500 cancer specialists and advocates from around the world. The scientific programme covered:

Cancer prevention and control, Tobacco control, Knowledge transfer (research, detection, treatment), Supportive care, and Capacity building.

A call to action from the global cancer community

“We the global cancer community call on governments, international governmental organizations, the international donor community, development agencies, professional organizations, the private sector and all civil society to take immediate steps to slow and ultimately reverse the growth in deaths from cancer, by committing to the targets set out below and providing resources and political backing for the priority actions needed to achieve them.”

Targets: by 2020

> Effective pain control measures will be available universally to all cancer patients in pain
> The number of training opportunities available for health professionals in different aspects of cancer control will have improved significantly
> Emigration of health workers with specialist training in cancer control will have reduced dramatically
> There will be major improvements in cancer survival rates in all countries

Priority actions

These targets are ambitious. During the past few years, however, there is growing evidence that concerted action can make a difference in a short time. We believe, therefore, that the targets can be achieved provided a number of priority actions are implemented:

Health policy

> Place cancer on the development agenda. Increase the political priority given to cancer by demonstrating that a country’s investment in dealing with its growing cancer problem is an investment in the economic and social well-being of the country. Organizations concerned with cancer control should work with the global donor community, development agencies, the private sector and all civil society to invest in cancer control
> Mobilize stakeholders to ensure that strategies to control cancer globally are targeted at those who are most in need. Involve all major stakeholder groups in the development, or updating, of national cancer control policies
> Implement strategies that have been proven to bridge existing cancer surveillance gaps
> Increase efforts to involve cancer patients in cancer control planning at a local and national level

Cancer prevention and early detection

> Increase efforts to reduce tobacco consumption by encouraging governments to fully implement and enforce the FCTC
> Raise awareness about the need for culturally sensitive cancer risk reduction campaigns, along with public and professional education about cancer warning signs. Push governments to implement policies that will support risk-reducing strategies at a community level and enable individuals to make more informed consumption choices and adopt healthier behaviour.
implement measures to reduce people’s exposure to environmental and occupational carcinogens

> Undertake actions to ensure that vaccines and other strategies that are shown to prevent cancer-causing infections are made more widely available.
> Advocate for the provision of affordable screening programmes for which there is evidence of efficacy in the population in question. Undertake pilot projects that are designed to evaluate the feasibility and efficacy in populations in which the screening technology has not yet been tested.

Cancer treatment

> Promote the development and use of cancer treatment guidelines that are relevant to local needs and resources. Ensure that sufficient treatment, rehabilitation and palliative care facilities and well-trained staff are available to meet the physical, social and emotional needs of patients with cancer.
> Take steps to tackle the many barriers to optimal pain control. Work with governments to address the over-regulation of pain medicines. Cooperate with international organizations, including the International Narcotics Control Board and the World Health Organization, to ensure that global implementation of the UN’s international drug control conventions do not unduly interfere with legitimate efforts to advance access to pain medicines for cancer patients in pain.
> Work with the pharmaceutical industry to increase access to cancer medicines that are affordable and of assured quality.
> Increase the number of health professionals with expertise in all aspects of cancer control by providing specialist training opportunities and fellowships to enable professionals to study in specialist settings.
> Raise awareness about the impact of health worker emigration on the ability of countries to provide adequate levels of cancer care and work collectively to address global and national health workforce shortages and the resultant deepening of inequity.
> Increase investment in independent basic and applied cancer research and accelerate the translation of research findings into clinical and public health practice.
> Encourage cancer research organizations in different countries to collaborate, share data and define complementary research objectives to optimize the use of the limited funds available for cancer research and reduce duplication of effort.

> Last year, cancer killed about 7.9 million people, about 72% of whom were in developing countries. The World Health Organization (WHO) forecasts that by 2030, the annual global death toll will rise to about 11.5 million. Cancer kills more than malaria, AIDS and tuberculosis combined.
> Cases are on the rise across the world, but survival rates are improving in affluent countries because more cancers are detected early and treated appropriately. In contrast, both the incidence and death rates are worsening in the developing world.
> The gap is expected to widen substantially and health economists predict that cancer could become an impediment to socioeconomic development in low-income and economically emerging nations. However, much can be done to help developing countries cope with the impending crisis and lessen the toll of disease, suffering and death from cancer.

Progressing towards the 2020 targets

> Through its member organizations, now more than 300 in over 100 countries, the International Union against Cancer (UICC) will promote partnerships and international collaboration aimed at accelerating progress towards achieving the 2020 targets.
> Given the huge variability in cancer burden and service provision throughout the world, the UICC will encourage members to use the World Cancer Declaration as a template to develop regional or national cancer declarations that can better reflect local needs and priorities and allow for more accurate quantification of targets where data exists.
> The UICC will take responsibility for preparing a report every two years on the progress made towards achieving the 2020 targets. These reports will be presented at the biennial World Cancer Congress.

Facts about cancer

> About 25 million people worldwide are living with cancer. It is the second leading cause of death worldwide, accounting for about 13% of all deaths.
Cancer Prevention & Early Detection

Date:
October 22 - 23, 2008
Shawal 22 - 23, 1429

Venue:
Riyadh Marriott Hotel

Topics:
Role of Family Physicians
Lifestyles and Cancer
Women's Oncology
Breast Cancer in Arab Countries
Role of Imaging in Early Detection
Gynecological / GI Malignancies
Lung / Prostate Cancer

Target Audience:
Family Physicians
Internal Medicine
Oncologists
General Surgeons
Radiologists
Dietician
Nurses
Other Health Care Professionals
2nd LSH Regional Meeting

The Second Regional Meeting of the Lebanese Society of Hematology and Blood Transfusion

23 - 25 October 2008
Movenpick Hôtel
Beirut - Lebanon

Main Topics
Coagulation and Thrombosis
Laboratory Medicine
clinical Implications of New Data on Iron Chelation Therapy
Unmet Needs in Hemostasis Management

Pediatrics Leukemia
Targeted Therapy in adult Leukemia
Multiple Myeloma and Myelodysplasia
Towards Improved Survival with New Promising Data in Multiple Myeloma and Myelodysplasia
Revolutionizing Patients Survival: Rituximab Based Therapy in NHL
A Fresh Look at Venous Thromboembolism in Medically Ill Patients
Integrated Management of CML in the Era of Second Generation TKIs

Lymphoma
Congenital Neutropenia
Transfusion Medicine
Erythropoiesis a matter of life and death
Clinical Trials in MENA

Under the Patronage of His Majesty King Abdullah II

Facilitating Clinical Trials in MENA Region

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

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

Organized by

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

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

King Hussein Institute For Biotechnology and Cancer (KHIBC), Jordan
Dr. Samir Khleif
LSMO 7

The Lebanese Society of Medical Oncology

LSMO 7 National Forum

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

Dear colleagues,

On behalf of the Lebanese Society of Medical Oncology, it is my pleasure to invite you to participate in the LSMO 7 National Forum to be held in Lebanon Beirut, November 13-15, 2008, entitled “Commitment to Cure Cancer.”

Controversial and established indications for adjuvant therapy will represent the main topics of the program, as well as unusual subjects such as sarcomas, endocrine tumors, and unknown primaries. Eminent international speakers who are experts in the field, are invited to share with us their knowledge and their latest achievements.

LSMO 7 will also follow the tradition by holding a session for clinical trials in Lebanon and the Arab world. So, we are calling for local and regional clinicians and researchers to submit abstracts for selection presentation and awards.

Our radiotherapy colleagues, members of the Lebanese Society of Radiation Oncology, will be holding their second LSRO symposium during LSMO 7. A pathology workshop will also take place under the Lebanese Society of Pathology. Special nursing session will be also organized.

Distinguished colleagues and friends from Lebanon, the Middle East, and the Arab world are cordially invited to attend our outstanding meeting and to express their solidarity towards our fight against cancer.

LSMO President
Joseph Kattan, MD
EASO Lymphoma day

EASO DAY ON LYMPHOMA
13 JANUARY 2009
Alexandria, Egypt

Chair: N. Pavlidis, GR - M. Gadallah, EG
Host Chair: N. Lotfy, EG

In collaboration with
Best of CTRC-AACR

SAN ANTONIO

BREAST CANCER SYMPOSIUM
RIYadh, SAUDI ARABIA

Date:
January 17-18, 2009

Venue:
Four Seasons Hotel

For inquiries, please call:
Dr. Omalkhai Abulkhair, Chairman, Scientific Committee
Phone Nos: +966 1 2520088 Ex 14077 / 14183
Fax: +966 1 2520088 Ex 14601
E-mail: abulkhair@trigha.med.sa / rosalesc@trigha.med.sa
NEWS FROM THE ARAB WORLD

The Arab Medical Association Against Cancer (AMAAC)

Annual Conference 2009

Twenty Years of Fighting Cancer

7 - 9 May 2009 - Grand Hyatt Hotel
Cairo - Egypt

www.amaac.info
Invites you To Join US

Annual Conference 2009
Twenty Years of Fighting Cancer

Main Topics
- Head & Neck
- Lung
- Breast
- GIT
- Hematological Malignancies
- Pediatric Oncology

Visit our website
www.amaac.info
The Gulf Journal of Oncology

Dr. Khaled Al-Saleh, Editor in Chief

The Gulf Journal of Oncology was started as an official journal for the Gulf Federation for Cancer Control. The first issue was published in January 2007 & since then it is being published biannually. So far we have published 3 issues and the 4th one will come in July 2008. Eminent doctors from the Gulf Arab world, Europe & USA are on the editorial board of the journal. The journal publishes original research articles, review articles, controversies, reports from conferences and commentaries.

The main interests of the journal are Cancer Research, Cancer Care & Medical Education. We are publishing around 3000 copies which are circulated free of cost to the doctors & hospitals in the Gulf and Arab world. There has been a tremendous response from the readers and we are receiving lot of the scientific papers for the publication in the journal.

E-mail: gffccku@yahoo.com
# THE GULF FEDERATION FOR CANCER CONTROL

## Scientific & Social Events

*Activities within GCC between October 2008 & January 2009*

<table>
<thead>
<tr>
<th>Date</th>
<th>Event Description</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 October 2008</td>
<td>Breast Cancer Conference</td>
<td>Jeddah, KSA</td>
</tr>
<tr>
<td>10-12 November 2008</td>
<td>The 1st International Gulf Conference on Head &amp; Neck Cancer</td>
<td>Yemen</td>
</tr>
<tr>
<td>December 2008</td>
<td>Layla Al-Othman - Short Story Festival, Cancer &amp; Sport</td>
<td>Kuwait</td>
</tr>
</tbody>
</table>
COMO 8

8th Middle East Oncology Congress

8ème Congrès d’Oncologie du Moyen-Orient

5-7 November, 2009

Mark your Calendar!

Organized by

For more information contact the Lebanese Cancer Society
Tel/Fax: 961-1-217 342 | POBOX: 165883-Beirut | E-mail: lcs@cancer.org.lb
<table>
<thead>
<tr>
<th>JANUARY</th>
<th>Cervical Cancer Awareness Month</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEBRUARY</td>
<td>Screening and Early Detection Awareness Month</td>
</tr>
<tr>
<td>MARCH</td>
<td>Colorectal Cancer Awareness Month</td>
</tr>
<tr>
<td>APRIL</td>
<td>Cancer Fatigue Awareness Month</td>
</tr>
<tr>
<td>MAY</td>
<td>Melanoma and Skin Cancer Awareness Month</td>
</tr>
<tr>
<td>JUNE</td>
<td>National Cancer Survivors Day</td>
</tr>
<tr>
<td>JULY</td>
<td>Sarcoma Awareness Month</td>
</tr>
<tr>
<td>AUGUST</td>
<td>Pain Medicine and Palliative Care</td>
</tr>
</tbody>
</table>
| SEPTEMBER              | Gynecologic Cancer Awareness Month  
Prostate Cancer Awareness Month  
Leukemia and Lymphoma Awareness Month |
| OCTOBER                | Breast Cancer Awareness Month |
| NOVEMBER               | Lung Cancer Awareness Month  
Smoking Cessation |
| DECEMBER               | 5 A Day Awareness Month |
## INTERNATIONAL EVENTS

**Book your calendar**  
**Selection of International Cancer Events**

<table>
<thead>
<tr>
<th>SUBJECT</th>
<th>DATE</th>
<th>CITY, COUNTRY</th>
<th>WEBSITE</th>
<th>EMAIL</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; October 2008</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2008 ASTRO Annual Meeting</td>
<td>October 5-9, 08</td>
<td>Baltimore, USA</td>
<td><a href="http://www.astro.org">www.astro.org</a></td>
<td><a href="mailto:meetings@astro.org">meetings@astro.org</a></td>
</tr>
<tr>
<td>Twelfth Conference on Cancer Therapy with Antibodies &amp; Immunoconjugates</td>
<td>October 16-18, 08</td>
<td>New Jersey, USA</td>
<td><a href="http://www.gscancer.org">www.gscancer.org</a></td>
<td><a href="mailto:rchurch@gscancer.org">rchurch@gscancer.org</a></td>
</tr>
<tr>
<td>9th meeting of the International Society of Geriatric Oncology</td>
<td>October 16-18, 08</td>
<td>Monteral, Canada</td>
<td><a href="http://www.cancerworld.org/siog">www.cancerworld.org/siog</a></td>
<td><a href="mailto:info@siogweb.org">info@siogweb.org</a></td>
</tr>
<tr>
<td>Primer on Tumor Immunology and Biological Therapy of Cancer</td>
<td>October 30, 08</td>
<td>California, USA</td>
<td><a href="http://www.isbtc.org">www.isbtc.org</a></td>
<td><a href="mailto:kpierce@isbtc.org">kpierce@isbtc.org</a></td>
</tr>
<tr>
<td>Workshop on Inflammation in Cancer Development</td>
<td>October 30, 08</td>
<td>California, USA</td>
<td><a href="http://www.isbtc.org/meetings/am08/workshop08">www.isbtc.org/meetings/am08/workshop08</a></td>
<td><a href="mailto:kpierce@isbtc.org">kpierce@isbtc.org</a></td>
</tr>
<tr>
<td>&gt; November 2008</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy Foundation Symposium, Innovative Cancer Therapy for Tomorrow</td>
<td>November 4-7, 08</td>
<td>New York, USA</td>
<td><a href="http://www.chemotherapyfoundationsymposium.org">www.chemotherapyfoundationsymposium.org</a></td>
<td><a href="mailto:jaclyn.silverman@mssm.edu">jaclyn.silverman@mssm.edu</a></td>
</tr>
<tr>
<td>&gt; December 2008</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50th ASH Annual Meeting and Exposition</td>
<td>December 6-9, 08</td>
<td>California, USA</td>
<td><a href="http://www.hematology.org/meetings/2008/index.cfm">www.hematology.org/meetings/2008/index.cfm</a></td>
<td><a href="mailto:sabcs@ctrc.net">sabcs@ctrc.net</a></td>
</tr>
<tr>
<td>31st San Antonio Breast Cancer Symposium</td>
<td>December 10-14, 08</td>
<td>Texas, USA</td>
<td><a href="http://www.sabcs.org">www.sabcs.org</a></td>
<td></td>
</tr>
</tbody>
</table>
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.

**OBJECTIVES & SCOPE OF THE PAJO**

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

1.3. Editorials / Comments / Controversies

The abstract, references, figures, and tables. The editors also suggest a limit of from Clinical Trials. Reviews are limited to 4,500 words of body text, excluding the abstract, references, figures, and tables. All abstracts are strictly limited to 250 words. Titles are to be descriptive, but succinct.

Results of clinical studies should be supported by a clear description of the study design, conduct, and analysis methods used to obtain the results.

Reports of phase II & III studies should include from the protocol a clear definition of the primary endpoint, the hypothesized value of the primary endpoint that justified the planned sample size, and a discussion of possible weaknesses, such as comparison to historical controls.

Phase I studies will be well received if they have interesting clinical responses, unusual toxicity that pointed to mechanism of action of the agents, and important or novel correlative laboratory studies associated with the trials.

1.2. Review Articles

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

1.3. Editorials / Comments / Controversies

The Editor-in-Chief may solicit an Editorial to accompany an accepted manuscript. Authors who wish to submit unsolicited Comments and Controversies should contact the Editor-in-Chief, before submission to determine the appropriateness of the topic for publication in the Journal. Editorials should be no more than four to five pages in length.

1.4. Articles on Health Economics

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

1.5. Case Reports / Correspondence / Special Articles

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

2. Manuscript submission procedure

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

3. Disclosures of Potential Conflicts of interest

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

4. Manuscript Preparation Guidelines

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

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

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

References
References must be listed and numbered after the body text in the order in which they are cited in the text. They should be double-spaced and should appear under the heading “REFERENCES.” Abbreviations of medical periodicals should conform to those used in the latest edition of Index Medicus and on MEDLINE. The «List of Journals Indexed in Index Medicus» includes the latest abbreviations. Inclusive page numbers must be cited in the reference. When a reference is for an abstract or supplement, it must be identified as such in parentheses at the end of the reference. Abstract and supplement numbers should be provided, if applicable. When a reference is a personal communication, unpublished data, a manuscript in 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.

Reference Style
* Journal article with one, two, or three authors

* Journal article with more than three authors

* Journal article in press (manuscript has been accepted for publication)
submitted with multiple parts will be renumbered. Tables should be submitted in a separate document. Legends must not exceed 55 words per table and should be written above the figure.

Appendices/Acknowledgments
Appendices and acknowledgments will appear in the print version of the article.
Language: Appropriate use of the English language is encouraged for publication in the Journal.

5. Post-acceptance Information

Copyright Form
Corresponding authors must provide unique e-mail address 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 author 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 1 week. 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.