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5: Cancer Therapy

5(i(a)): Radiotherapy & Chemotherapy

5(i(b)): Radiotherapy & Chemotherapy

Session Chair
Dr. Sherif G. Nour
Emory University School of Medicine, USA

Session Co-Chair
Dr. Liang Xu
University of Kansas Cancer Center, USA

Session Introduction

Title: **Magnetic resonance imaging guided thermal ablation for cancer**
Dr. Sherif G. Nour, Emory University School of Medicine, USA

Title: **Molecular cancer therapy via modulating autophagy**
Dr. Liang Xu, University of Kansas Cancer Center, USA

Title: **Pathobiology and prevention of bone Loss caused by cancer chemotherapy**
Dr. Cory J Xian, University of South Australia, Australia

Title: **What is the optimal treatment for metastatic colorectal cancer?**
Dr. Esther Una Cidon, Clinical University Hospital, Spain

Title: **Biomarkers in relation to response of preoperative radiotherapy in rectal cancer patients- A Swedish rectal cancer clinical trial of preoperative radiotherapy**
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Title: **The effect of preoperative chemoradiotherapy on lymph nodes harvested in laparoscopic TME for rectal cancer**
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Title: **Intensity modulated radiotherapy in chemoreduced retinoblastoma**
Dr. Aman Sharma, All India Institute of Medical Sciences, India

Title: **Retrospective analysis of total skin electron beam radiation therapy in cutaneous t-cell lymphoma- a developing nation experience**
Dr. Manoj Kumar B, All India Institute of Medical Sciences, India

Title: Acute or subacute cor pulmonale: When should we look for malignancies?

Dr. Raniero Di Giovambattista, Hospital of Avezzano, Italy

Title: Different expression of ERK1/2 and pERK proteins in MDA-231 and MCF7 cells after chemotherapy with doxorubicin or docetaxel

Dr. Aliakbar Taherian, Kashan University of Medical Science, Iran

Title: Treatment with AS101 sensitizes acute myeloid leukemia cells (AML) to chemotherapy by disrupting the interaction between the integrin VLA-4 and Fibronectin: Mechanisms of action and clinical applications

Dr. Benjamin Sredni, Bar-Ilan University, Israel

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Magnetic Resonance Imaging Guided Thermal Ablation for Cancer

Sherif G. Nour

Emory University Hospitals and School of Medicine, USA

Although thermal treatment of localized malignancies has been practiced under direct surgical and laparoscopic visualization, much of the excitement over expanding the therapeutic uses of radiofrequency and other forms of thermal energy has been provoked by the advancements in imaging technology. The ability to perform thermal treatment of cancer percutaneously under image guidance has changed thermal ablation from an adjuvant surgical technique to a minimally invasive alternative that is more suited to poor surgical candidates. Unlike radiation therapy, thermal ablation can be repeated multiple times without concern for cumulative dose effects.

The primary contribution of image guidance to needle-based thermal treatment is securing safe, precise electrode delivery into the targeted pathology. The ideal electrode trajectory during actual procedure execution is sometimes significantly different from that suggested on the pre-procedure imaging data owing to shift of anatomical structures when using modified patient positions during treatment. Once the electrode is successfully delivered into the targeted tumor, image guidance adds to treatment efficacy by optimizing electrode position within the pathological tissue and by enabling confident inclusion of an adequate 'safety margin' to the ablated volume.

Compared to ultrasound and CT, the major contribution of MR imaging is its ability to monitor the zone of tissue destruction during the procedure therefore providing real-time guidance for energy deposition and permitting accurate tumor destruction. Other than its ability to define the treatment endpoint, MRI guidance is also advantageous in certain situations such as when a tumor is not adequately visualized on ultrasound or CT or when the complex anatomical location of a tumor renders multiplanar image guidance a safer approach, such as in liver dome lesions.

Biography

Dr. Nour is one of the world's leaders in the field of interventional MRI. For more than a decade, he dedicated his pre-clinical and clinical research to optimizing MRI guided interventions and to developing new minimally invasive tretmant approaches under MRI guidance. He is currently the Director of interventional MRI program at Emory University. He has 25 peer-reviewd original manuscripts published in leading medical journals. He also has 60 peer-reviewed proceedings manuscripts and research abstracts, 8 textbook chapters, and 7 filed patent applications in the field of interventional MRI.

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Molecular cancer therapy via modulating autophagy

Liang Xu

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Radioresistance markedly impair the efficacy of cancer therapy. Anti-apoptotic Bcl-2 family proteins such as Bcl-xL, Bcl-2 and Mcl-1 are overexpressed in prostate cancer and contribute to prostate tumor initiation, progression and resistance to radiotherapy. A natural BH3-mimetic, small molecule inhibitor of Bcl-2, (-)-gossypol, shows promise in ongoing Phase II clinical trials for human prostate cancer. We have recently shown that (-)-gossypol preferentially induces autophagy in androgen-independent (AI) prostate cancer cells that have high levels of Bcl-2 and are resistant to apoptosis, both in vitro and in vivo, but not in androgen-dependent cells with low Bcl-2 and sensitive to apoptosis. Our results demonstrate for the first time that (-)-gossypol can also interrupt the interactions between Beclin1 and Bcl-2/Bcl-xL at the endoplasmic reticulum, thus releasing the BH3-only pro-autophagic protein Beclin1, which in turn triggers the autophagic cascade. (-)-Gossypol-induced autophagy is Beclin1- and Atg5-dependent, together with Bcl-2 downregulation and Beclin1 upregulation. (-)-Gossypol increased autophagy induced by X-ray radiation in the AI prostate cancer cells. Orally administered (-)-gossypol achieved a much greater efficacy with long-term tumor regression when used in combination with ionizing radiation. (-)-Gossypol significantly enhances the anti-tumor activity of radiotherapy in vitro and in vivo, and represents a promising new regime for treatment of hormone-refractory human prostate cancer with overexpression of Bcl-2. Our data provide new insights into the mode of cell death induced by Bcl-2 inhibitors, which would facilitate the rational design of clinical trials by selecting patients who are most likely to benefit from the Bcl-2-targeted molecular therapy.

Biography

Dr. Liang Xu obtained his M.D. and Ph.D in China and did postdoctoral studies in Louvain University in Belgium, Stanford University and Georgetown University in USA. He has been an Assistant Professor at University of Michigan and now an Associate Professor with Tenure at University of Kansas. He has published more than 75 papers and serving as an editorial board member of multiple journals. He holds many USA and international patents including two agents in Phase I and II clinical trials. His major research interest is molecular cancer therapy targeting cancer and cancer stem cells.

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Pathobiology and prevention of bone Loss caused by cancer chemotherapy

Cory J Xian
University of South Australia, Australia

Cancer chemotherapy often induces bone loss or osteoporosis in cancer patients and survivors; yet the underlying mechanisms remain unclear and currently no specific adjuvant treatments are available to reduce these side effects. This study characterized damaging effects and action mechanisms of commonly used anti-metabolites methotrexate (MTX) and 5-fluoruracil (5-FU) on bone formation and osteoporosis in rats, and investigating effects of supplementary treatments with clinically used antidote folinic acid and some nutraceuticals which are known to possess anti-inflammatory, anti-oxidant, and/or anti-resorptive properties. We found that MTX or 5-FU chemotherapy increases expression of proinflammatory cytokines (TNF-α, IL-1β, IL-6, RANKL) and attenuates Wnt/β-catenin signaling in bone and bone marrow stromal cells. MTX or 5-FU chemotherapy causes osteoporosis by reducing bone formation, decreasing pool of bone marrow osteoprogenitor cells and differentiation of bone forming cells osteoblasts, enhancing adipocyte differentiation, increasing formation of bone-resorptive cells osteoclasts, resulting in bone loss and marrow adiposity. Supplementation with folinic acid attenuated MTX damaging effects on growth plate and production of primary bone. Oral doses of some nutraceuticals preserved osteoprogenitor cell content and bone formation, suppressed expression of osteoclastogenic factors in bone, osteoclast number on bone surface and bone resorption, and/or minimized accumulation of marrow fat. Sustaining/activating Wnt signaling by blocking its antagonist(s) also abrogated the bone defects. These observations suggest that cancer chemotherapy causes bone defects by damaging multiple compartments in the bone, and that some supplementary treatments may be beneficial in preserving bone integrity during chemotherapy.

Biography

Prof Xian obtained his PhD in 1993 from Murdoch University (Australia). He has been interested in fundamental and strategic research into tissue growth, injury repair and roles of growth factors/cytokines and progenitor cells. His earlier research positions include those at Child Health Research Institute (Australia), University of North Carolina at Chapel Hill (USA), Flinders University, University of Adelaide and Women's and Children's Hospital (Australia). Since 2001, he has been leading his research group (currently at University of South Australia) conducting bone growth and repair research. He serves as Associate Editors for 4 journals and editorial board members for 8 international scientific journals.

Esther Uña Cidón, J Cancer Sci Ther, 3:7
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What is the optimal treatment for metastatic colorectal cancer?

Esther Uña Cidón

Department of Oncology, Clinical University Hospital, SPAIN

Colorectal cancer is the second leading cause of death from cancer in the developed countries. Although great efforts have been made to early diagnosis a relevant number of cases will present metastases. The natural history of metastatic Colorectal Cancer (mCRC) has dramatically evolved in the recent years thanks to the introduction of modern chemotherapy.

Nowadays with the new drugs, such as oxaliplatin and irinotecan or modern drugs based on molecular targets (bevacizumab or cetuximab) the response rate has increased to 50% and the survival has been improved not only progression free survival, which has reached 12 months, but also overall survival which is longer than 2 years.

Despite this progress many questions remain to be answered, mainly those related to the sequential regimens, drug rotation, alternant or intermitent schedules, optimal duration of chemotherapy, the role of maintenance chemotherapy and the role of doublets or triplets.

The optimal duration of chemotherapy is very important because it has a direct influence on the patient quality of life, survival and costs.

There are several studies addressing this topic and the alternatives we have, such as "stop and go", intermittent strategies or maintenance of only several agents and these studies reinforce the frequent behaviour of the oncologists to stop the treatment when the patient has obtained the maximum response. But there are some methodological problems in the analyzed trials which have determined that not all the professionals agree with this proposal.

With this context it is essential to perform well designed clinical trials incorporating new drugs and addressing these questions. This presentation tries to review all these controversial points.

Biography

Medical training in Medical Oncology at University Hospital of Oviedo where she collaborated in a Pharmacokinetic Laboratory combining traslational research (cancer drug sensitivity) in cancer. Doctorate courses and Advanced Studies Certificate in Research in Cancer with the best qualification (BQ). PhD with a project "Colon Cancer Follow-up Strategies and their Cost-effectiveness" with BQ. She works in Medical Oncology Department at Clinical University Hospital of Valladolid where she´s been carried out several clinical projects mainly in Digestive Tumors (Gastric and CRC) related to new prognostic/predicitive factors, tumour markers and its clinical utility, biomarkers...In this moment she is carrying out several clinical and pathological projects in CRC and Gastric Cancer. She has completed a Master in Palliative Medicine and other in Molecular Oncology. She´s awarded in two times with National Awards "Profesor Barea" to the best projects related to health management and cost in 2009 and in 2010.

She also works as an Oncology Associated Professor and she´s more than 70 communications to International/National Congress in Oncology and Health Care Quality and Management (HCQM), more than 40 articles published in relevant International and National Scientific Journals (SJ), including HCQM and she´s a reviewer of SJ such as: "European Journal of Surgical Oncology", "Journal of Oncology Pharmacy Practice", "Clinical Medicine: Oncology", "World Journal of Gastroenterology"... She is member of the Editorial Board of "Global Journal of Surgery" and Editor in chief of a Review Book of Colorectal Cancer which is in development. She is member of Spanish Society of Medical Oncology, American Society of Clinical Oncology, European Association of Cancer Research, International Society of Gastrointestinal Oncology and Society for Translational Oncology among others. She has been invited several times to be a speaker in International Congress.

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Biomarkers in relation to response of preoperative radiotherapy in rectal cancer patients- A Swedish rectal cancer clinical trial of preoperative radiotherapy

Xiao-Feng Sun

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The introduction of preoperative radiotherapy (RT) in the treatment of rectal cancer has reduced the frequency of local recurrence and improved patient survival, and RT is now a part of the standard treatment regime in Sweden. However, it is still a major problem that there are unknown factors contributing to variations in recurrence and survival after RT and surgery among rectal cancer patients with the same tumour stage, therefore it is important to search for biological markers that might influence recurrence and survival, and to identify the patients who benefit from RT.

The study included primary tumours from 163 rectal cancer patients who participated in a clinical trial of preoperative RT (87 patients without and 76 with RT before surgery), alone with the corresponding distant and adjuvant normal rectal mucosa, as well as lymph node metastasis.

We have examined p53, WRAP53, p73, survivin, apoptosis, Cox-2, legumain, FXYD-3, MAC30, PRL, ATM, Ki-67, CD163, PPARδ and PINCH, by PCR using confronting two-pair primers and electrophoresis, immunohistochemistry, Western blot and TUNEL.

Expression of WRAP53, p73, Cox-2, legumain, FXYD-3, MAC30, PRL, ATM, PPARδ increased from either distant or adjacent normal mucosa to primary tumour. In the RT group, overexpression of p53, WRAP53, p73, Cox-2, legumain, FXYD-3 and PRL was related to less tumour necrosis or apoptosis, increased incidence of local or distant metastasis, and an unfavourable prognosis independent of both the tumour stage and differentiation. However, none of these effects was seen in the non-RT group. In further interaction analyses, the correlations with prognostic significance of these factors were different between the patients with RT and the patients without RT.

In conclusion, certain biomarkers were independent prognostic factors in patients receiving preoperative RT for rectal cancer, which might provide additional information for selecting patients for preoperative RT.

Biography

Xiao-Feng Sun is professor at Department of Oncology, Institute of Clinical and Experimental Medicine, University of Linköping, Sweden.

Xiao-Feng Sun started medical education in 1977 and obtained MD in 1982 and Msc in 1988 in China. She moved to Sweden in 1989 and obtained PhD in 1993 at Linköping University, Sweden, and did her postdoctor training at Lund University, Sweden, and became professor at Onoclogy in 2005 at Linköping University, Sweden.

Her work focuses on study of genetic alterations in colorectal cancer patients and cell lines, in order to find biomarkers for identifying high-risk individuals, selecting patients who will benefit from chemo/radiotherapy, and evaluate patient prognosis, as well as the mechanisms of biomarker effects.

She has published 132 original full-length publications and three review papers in various international journals, such as Lancet, JNCI, J Clin Oncol, Clin Cancer Res, and Oncogene, and two book chapters.

Dr. Sun has received numerous international, national and local grants/award:

Dr. Sun serve as editorial board member in six international journals, and as reviewers for more than 30 international journals.

Dr. Sun is a member of numerous professional organizations, including Association of International Union Against Cancer Fellows (UICC), American Association for Cancer Research (AACR), European Association for Cancer Research (EACR), Gastrointestinal Society of Oncology, Swedish Society of Medicine, Swedish Society of Oncology, Swedish Cancer Society, and Swedish Proteomics Society.

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The effect of preoperative chemoradiotherapy on lymph nodes harvested in laparoscopic TME for rectal cancer

Stefano Scabini, Edoardo Rimini, Andrea Massobrio, Emanuele Romairone, Renato Scordamaglia and Valter Ferrando

Department of Emato-Oncology, San Martino Hospital, Italy

Background: Adequate lymph node resection in rectal cancer is important for staging and local control.This study aims to verify the effect of neoadjuvant chemoradiation, as well as some clinicopathological features, on the yield of lymph nodes in rectal carcinoma.

Matierial and methods: Data on consecutive patients who had laparoscopic total mesorectal excision for rectal adenocarcinoma at a single cancer center between July 2005 and July 2010 were reviewed. No patient had any prior pelvic surgery or radiotherapy. Patients had neoadjuvant chemoradiotherapy if they were stage II or III.

Results: A total of 79 patients were included. The mean age was 67.1 years (range 36-84). Twenty-six patients (33%) received neoadjuvant therapy before resection. The mean number of lymph nodes removed was 14.4 (range 3-39) per specimen. There was less lymph node yield in patients who received neoadjuvant therapy (11.6 vs. 15.6, p 0.05). Only 46% of patients who had preoperative therapy had 12 lymph nodes or more in the specimen as opposed to 64% of those who had surgery upfront (p: 0.03). Other factors associated with lower lymph node yield included stage (p 0.03) and grade (p 0.007) of the tumour. Age, sex, site, type of operation, surgeons and pathologists did not affect the number of lymph nodes removed.

Conclusion: in laparoscopic surgery preoperative chemoradiotherapy for rectal cancer results in reduction in lymph node yield. Early cancer and low-gradind also associated with retrieval of fewer lymph nodes.

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Intensity modulated radiotherapy in chemoreduced retinoblastoma

Aman Sharma

Dr. B. R. A. Institute Rotary Cancer Hospital (IRCH), All India Institute of Medical Sciences (AIIMS), India

Background: Intensity modulated radiotherapy (IMRT) has the potential of reducing dose to adjacent critical structures, achieves better target coverage, dose uniformity and sharp dose fall-off. Therefore, aim of our present study is to assess the feasibility of IMRT as a focal therapy for chemo-reduced group II retinoblastoma with regard to target coverage and sparing adjoining critical normal structures.

Material and methods: Six patients of chemo reduced group II retinoblastoma were undertaken for the study. Radiation therapy planning was done with all immobilized in supine position by a thermoplastic cast under general anesthesia. Planning CT was done with 3mm slice thickness and Gross Tumor Volume (GTV) was delineated in CT images as per the post chemotherapy clinical, radiological and opthalamoscopic examination under anesthesia findings. A margin of 2mm was given to generate Clinical Target Volume (CTV), a further expansion of 4mm was given for Planning Target Volume (PTV). The delineated organs at risk (OAR) include optic nerve, temporal lobe, hypo-thalamo pituitary axis (HPA), lacrimal gland, orbit, cornea and the retina. Nine field non-coplanar beam arrangement was used for IMRT planning in the Pinnacle TPS for Elekta synergy linear accelerator. The planning objectives were: prescribed dose of 45Gy/25f for PTV and HPA<37.5Gy temporal lobes<37.5Gy, lacrimal gland <34Gy, orbit<20Gy, lens<10Gy, cornea <23Gy and retina<40 Gy.

Results: IMRT achieved adequate coverage to the PTV. For all patients, 95% of the PTV was covered by 98% of the isodose line. The calculated Conformity Indices (TVRI/VRI) were 0.9391±0.96. Homogeneity Indices (I_{max}/RI) were 1.1475±0.55. Quality of coverage indices (I_{min}/RI) were 0.80±0.40. For ipsilateral OAR doses, the maximum dose to the brain stem was 5.155±1.45Gy and temporal lobe was 40.65±0.53Gy. Maximum dose to the optic chiasm was 8.94±2.51Gy. Optic nerve maximum dose was 45.81±1.74Gy and cornea max dose was 24.98±12.32Gy. Similarly, max dose for the lens and HPA were 15.51±4.50Gy and 8.505±2.86Gy, respectively. Maximum dose to the lacrimal was 34.41±10.32Gy and mean was 20.62±3.37Gy. Orbital mean doses were 16.04±4.34Gy. The maximum doses to the retina were 45.50±1.72Gy and mean doses were 30.75±1.67Gy.

Conclusions: Delivery of IMRT as a focal therapy in chemo-reduced group II retinoblastoma is feasible and provides adequate dose coverage to the target volume. The IMRT spares the adjoining critical normal structures with the given priority apart from the lens.

Biography

Dr Aman Sharma MBBS IGMC Shimla (1997-2003), Medical officer incharge Ex-HPHS(2003-2006), MD Radiation oncology (2006-2009) Regional Cancer Centre IGMC Shimla, Ex-Fellowship Neuroradio-oncology TATA Memorial Hospital Mumbai(sept2009-dec2010), presently work as Senior Resident in All India Institute of Medical Sciences New Delhi. He has conducted a prospective randomized phase III trial in locally advanced HNSCC, scientific paper presented at 13 chapter AROI, review article accepted in NNP, abstract accepted for poster ASCO, three abstracts submitted in ESTRO & head and neck conference.

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Retrospective analysis of total skin electron beam radiation therapy in cutaneous t-cell lymphoma- A developing nation experience

Manoj Kumar B
All India Institute of Medical Sciences, India

Introduction: Total Skin Electron beam Therapy (TSET) is an effective therapeutic strategy in the management of advanced Cutaneous T-cell lymphoma. The presents study reports the retrospective analysis of patients treated with TSET at our center.

Material & Methods: A total of 12 patients of Cutaneous T-cell lymphoma were analyzed from January 2004 to March 2011. Patients were treated with Elekta Precise Linear accelerator with HDR mode of 3000cGy/min at isocenter. All the patients were treated as per the Stanford technique, delivering a total dose of 36Gy with a dose of 1.2Gy/f/day using 4MeV electron beam. Out of 6 fields planned, 3 fields per day were delivered alternatively. In all the sessions nails and eyes were shielded with 3mm lead shield. Boost dose of 10 Gy was delivered to the self-shielded regions.

Results: Out of 12 patients studied, nine had stage IIB disease. Seven patients achieved complete remission following TSET while 5 patients died of progressive disease during treatment. After completion of radiation, seven patients continued on PUVA therapy. The main complication observed were non hematological toxicities: four patients had grade III skin reaction and rest patients had grade II dermatitis. At median follow up time of 3.5 years, four patients were alive without any disease. Three patients died due to relapse in non cutaneous sites within 2 years.

Conclusion: Total Skin Electron Beam Therapy was well tolerated and found to be effective treatment of advanced Cutaneous T-cell lymphoma.

Biography

Dr. Manoj Kumar Behera has completed MD in Radiation Oncology from Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh, one of the premiere institutes in Radiation oncology in India in 2009. Now he is in 2nd year of Senior Residency (SR) in All India Institute of Medical Sciences (AIIMS). He is specifically interested in SBRT/SRT, brachytherapy and Clinical oncology research as well as patients care.

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Acute or subacute cor pulmonale: When should we look for malignancies?

Raniero Di Giovambattista
Hospital of Avezzano, Italy

Recently we observed a case of a 51-year-old women who died in our hospital for respiratory distress related to a widespread invasion of the pulmonary vessel by metastatic cells of a gastric cancer. Autopsy showed an indifferentiated carcinoma of the gastric fundus with diffuse permeation of the pulmonary vascular and lymphatic channels. Acute respiratory failure and severe pulmonary hypertension was the first clinical presentation of the malignancy. Echo 2D examination showed marked dilatation and D-shape right ventricular (RV) deformation. PAP max was 80 mmHg. D-Dimer 1230 mg/dl. Angio-CT scan of the chest permitted us to rule out our first clinical diagnosis of acute pulmonary thromboembolism (PE).

4 months ago a new, similar case came to our attention. A 62 year-old-man who suffered in the past of COPD, was admitted to our hospital after a brief clinical observation in another facilities, complaining of progressive, severe dyspnea and weakness. He dated the onset of progressive deterioration of his symptoms about 1 month earlier, in absence of fever, chest pain, palpitations or significant changes of the BP. Heart rate at entry was 110/min, BP 105/60 mmHg, D-Dimer value was 3650 mg/dl. Echo 2D showed dilatation and RV D-shape deformation. PAP max measured by echo was about 100 mmHg. Even in this case the chest CT-scan failed to demonstrate pulmonary thromboembolism. On the fifth day of the hospital stay he died of respiratory failure. Autopsy showed a signet ring carcinoma of the stomach with diffuse permeation of the pulmonary vascular and lymphatic channels.

In the last 12 months we observed 2 cases of subacute cor pulmonale as the first clinical presentations of massive, microscopic pulmonary tumor embolism (PTE) arising from gastric cancer. The clinical presentation as acute or subacute RV pressure overload and respiratory distress is a very rare but a fatal complication of cancer, and often a post-mortem diagnosis. When present, adenocarcinoma - more frequently arising from stomach, breast, lung, gallbladder, colon or prostate - is the most common histological tumor type. The tumor involvement of the pulmonary vessels develops from either lymphangitic and/or hematogenous spread. In both cases we observed, as well has been reported in literature, the first clinical diagnosis was pulmonary embolism. D-dimer values were very high. Echocardiographic examination showed signs of acute, severe right ventricular pressure overload and positivity of the Mc Connell sign. This instrumental findings together with the severity of respiratory distress and a shock index > 1 (defined as heart rate divided by systolic blood pressure) observed in both our cases , reinforced in our mind the first clinical suspect of massive P.E. Microscopic PTE and pulmonary thomboembolism are clinically almost indistinguishable, and PTE is often mistaken for thromboembolism. Oxygen desaturation is generally more severe in PTE's patients. D-Dimer values might be as high as they are actually seen in the course of PE. Chest angio CT-scan plays a pivotal role for ruling out the diagnosis of acute pulmonary thromboembolism. Large pulmonary arteries indeed are generally involved in the course of thromboembolic disease: filling defects in the large pulmonary vessels and/or pulmonary infarction are quite always demonstrated by CT-scan. By contrast, with the exception of choriocarcinoma or hepatoma which may provoke acute cor pulmonale by large vein invasion, the tumor emboli usually occlude small vessels and produce subacute cor pulmonale. The parenchyma can be normal or near to normal in these patients. The cases we described remind physicians to consider unknown malignancies as a direct (not thrombus-mediated) causes of acute or subacute cor pulmonale. Chest CT-scan is usually negative in this clinical scenario, so in this case we should look for malignancies. The 2 cases we observed represent in our view also a reminder for physicians and sonographers that echocardiographic examination is a very useful tool to demonstrate pulmonary hypertension and acute right ventricular pressure overload, but not always is able to put light on the etiology of pulmonary hypertension. Take home messages from our experience:

- Unknown adenocarcinoma may have its first clinical presentation as acute or (more frequently) subacute cor pulmonale. It is a very rare but a fatal complication of cancer, and often a post-mortem diagnosis.
- Microscopic PTE and pulmonary thomboembolism are clinically almost indistinguishable, and PTE is often mistaken for thromboembolism. AngioCT-scan is the tool of choice for ruling out the diagnosis of pulmonary thromboembolism as a cause of acute or subacute cor pulmonale
- Echocardiography is quite always useful to evaluate the severity of pulmonary hypertension (PH) and right ventricular overload. Is not the right tool to establish the etiology of PH.

If chest CT-scan fails to demonstrate either the presence of emboli in the large pulmonary vessels as well parenchymal abnormalities which well fit the severity of PH and respiratory failure, we should always look for malignancies.

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Different expression of ERK1/2 and pERK proteins in MDA-231 and MCF7 cells after chemotherapy with doxorubicin or docetaxel

Aliakbar Taherian and Tahereh Mazoochi

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Objective(s): Curative treatment of breast cancer patients using chemotherapy often fails as a result of intrinsic or acquired resistance of the tumor to the drug. In this study, cytotoxicity and the expression of Erk1/2 and phospho-Erk was compared in MDA-231 (ER-) and MCF7 (ER+) cell lines after treatment with doxorubicin (DOX) or docetaxel (DOCT).

Materials and Methods: Cell cytotoxicity of DOX or DOCT was calculated using MTT assay. Immonofluorescent technique was used to show Mdr-1 protein in MDA-231 and MCF7 cells after treatment with DOX or DOCT. The expression of ERK1/2 and phpspho-ERK was assayed with immunobloting.

Results: Comparing IC_{50} values showed that MDA-231 cells are more sensitive than MCF7 cells to DOX or DOCT. Immonofluorescent results confirmed the expression of Mdr-1 in these two cell lines after DOX or DOCT treatment. In MDA-231 cells the expression of ERK1/2 and pERK was decreased after DOX treatment in a dose-dependent manner. In contrast in MCF7 cells the expression of ERK1/2 and pERK was increased after DOX treatment. DOCT treatment resulted the same result with less significant differences than DOX.

Conclusion: The heterogeneity seen in cell lines actually reflects the heterogeneity of breast cancers that is why, patients categorized in one group respond differently to a similar treatment. These results emphasize the importance of a more accurate classification and a more specific treatment of breast cancer subtypes.

Keywords: Breast Cancer, pERK, MDA-231, MCF7, Doxorubicin, Docetaxel

Biography

Aliakbar Taherian completed his bachelor of science in Biology in Tarbiat Moallem University in Tehran. After a few years he was accepted in Medical School of Tehran University and received his Master of Science in Human Histology. After working in Kashan university of Medical Sciences for a few years teaching Human Histology to Medical students, he received a scholarship from the university to study his PhD. He was accepted in University of Saskatchewan to work with Dr. Patrick Krone and Nick Ovsenek in the Anatomy and Cell Biology Department. During his study he would publish two papers (1,2) and clone two genes (submitted to Genbank). After completing his PhD he worked as a postdoc in the same department with Dr Haas for a few years. In the postdoc period, He published one paper and has another submitted paper (3,4). Now he is working in Kashan University of Medical Sciences, teaching Human Histology to medical and paramedical students. Besides teaching he has a few research projects that occupies most of his time in university and home. The project that has been recently completed and submitted for publication (5) is about the different responses of breast cancer to chemotherapy.

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Treatment with AS101 sensitizes acute myeloid leukemia cells (AML) to chemotherapy by disrupting the interaction between the integrin VLA-4 and Fibronectin: Mechanisms of action and clinical applications

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Bone marrow minimal residual disease (MRD) causes relapse after chemotherapy in patients with acute myelogenous leukemia (AML) due to acquired drug resistance - this is induced by the attachment of the integrin receptor VLA-4 on leukemic cells to its ligand fibronectin (FN) on bone marrow stromal cells. We show that the non toxic compound AS101, previously shown to exert anti tumoral effects *in-vitro* and *in-vivo*, sensitizes AML cells to ARA-C only when leukemic cells are plated on FN but not on BSA-coated plates. This was associated with a significant decrease in pAkt and Bcl-2. The sensitizing effect of AS101 was also correlated with the ability of AS101 to deactivate VLA on AML cells. In a model of SCID mice implanted with leukemic cells either from established AML cell lines or with leukemic cells expressing high VLA-4, obtained from AML patients, co-treatment with AS101 and chemotherapy significantly increased mice survival while chemotherapy alone exerted only a modest effect. Furthermore, the combined treatment resulted in the elimination of leukemic cells from all organs tested. Moreover, mice transplanted with AML cells that express low VLA-4, considerably reacted to chemotherapy alone as expressed by increased survival, while co-treatment with AS101 resulted in similar effects. Importantly, AS101 increases migration of leukemic cells expressing high VLA-4 from the Bone-Marrow to the peripheral blood enabling their sensitization to chemotherapy.

We propose that treatment with AS101 currently used in treatment of cancer patients, combined with chemotherapy, has a potential to eradicate MRD and prolong survival of AML patients.

Biography

Prof. Benjamin Sredni, Head of The Cancer, AIDS and Immunology Research Institute at Bar-Ilan University in Israel - completed his Ph.D at Bar-Ilan and was a visiting scientist and associate many times at the Laboratories of Immunology, NIH, , US. Sredni served as Chief Scientist of the Ministry of Health in Israel and is Dean of the School of Graduate Studies at Bar-Ilan. He is a member of numerous reputed scientific organizations and was President of the Israel Association of Immunology. He has published over 175 papers in reputed journals and is guest editor in a special issue of Seminars of Cancer Biology.