71 INVITED

Defining Response − Oncological Imaging's New Challenge

L.S. Fournier[1], R. Thiam[2], D. Balvay[2], S. Oudard[3], C.A. Cuenod[1].
[1]*Hopital Europeen Georges Pompidou, Radiology Department, Paris,* [2]*INSERM U970, Paris Cardiovascular Research Center, Paris,* [3]*Hopital Europeen Georges Pompidou, Oncology Department, Paris, France*

Research in imaging has long focused on detecting cancer. However, oncologists also need fast and reliable tools for evaluating efficacy when treating a patient. New challenges for imaging treatment response are emerging as patients benefit from targeted therapies stabilizing rather than curing them, or repeated focal therapies inducing changes in lesion morphology but not size.
Morphological criteria based on size (RECIST) are commonly used but seem inadequate in patients with metastatic renal cell carcinoma (mRCC) under anti-angiogenic (AA) therapy, which present clear benefit in terms of survival, but low rates of response. It is therefore important to define new criteria of response to guide the clinician in his decisions to continue or interrupt treatment.
The first possible strategy is to use size, but define a new threshold for detection of response. In a study performed in our institution, we showed that a variation of −10% of the sum of longest diameters was the optimal threshold for detection of response to AA therapy, with a significantly longer PFS for patients who reached this threshold compared to those who did not (11.1 vs. 5.6 months).
A second possible strategy is based on the evaluation of tumour necrosis. CHOI criteria were developed for evaluation of GIST under imatinib therapy, with response defined as a decrease superior to −10% in size of target lesions or −15% in attenuation of target lesions. We performed a study to test these criteria in patients with mRCC, showing that Choi separated two groups of patients with distinct outcomes (PFS = 10.7 vs. 6.8 months). However, it appeared that the most important criteria was size decrease rather than necrosis, concurring with the previous study.
The last strategy is to use perfusion imaging for the evaluation of response. Indeed, tumour vessels display structural and functional changes compared to normal vessels. It seems very logical therefore to quantify tumour vessels since these are targeted by AA drugs. Dynamic contrast-enhanced imaging follows the biodistribution of a contrast agent, allowing quantification of parameters such as blood volume, blood flow and permeability. In a study, we showed that perfusion CT predicts and detects early response to AA therapy (median decrease of −50% of blood volume and blood flow in the AA group vs. −6% and +2% respectively for the interferon group), and can be integrated in a regular clinical work-up. However, these novel techniques of functional imaging require validation by large-scale studies before being used in daily practice.

72 INVITED

New Agents in Renal Cancer

B. Escudier[1]. [1]*Institut Gustave Roussy, Department of Medicine, Villejuif, France*

Treatment of metastatic renal cell carcinoma (mRCC) has dramatically changed in the past 6 years, with the approval of 6 new agents: sorafenib, sunitinib, temsirolimus, bevacizumab plus interferon, everolimus and pazopanib. The development of these agents has been encouraged by the demonstration that the VHL-HIF-VEGF pathway was stimulated in RCC, more than in any other cancer. Despite this enrichment of therapies, mRCC remains a lethal disease in the vast majority of patients.
Development of new agents continues in many directions:

- More active and less toxic drugs, active on the VHL-HIF-VEGF pathway, such as axitinib and tivozanib. Axitinib for example, which is a more potent and more selective VEGF inhibitor, has been shown to be more active that sorafenib in a large randomized phase 3
- New targets are also under investigation, such as cMET, angiopoietin etc. . . inhibition. Preliminary data are encouraging
- Immunotherapy finally has got a new development with promising data with new "targeted immunotherapy", ipilimumab, anti PD1 antobody and vaccines.

All these new agents will be presented during the meeting, and future perspectives will be addressed.

Scientific Symposium (Sat, 24 Sep, 16:00−18:00)
Anti-Angiogenic Strategies for Cancer

73 INVITED

Vasculogenesis or Angiogenesis in Determining Tumour Regrowth After Cancer Therapy

M. Brown[1], G.O. Ahn[1], M. Kioi[1]. [1]*Stanford University Medical Center, Department of Radiation Oncology CCSR South Room 1255, Stanford, USA*

In addition to tumour cells cytotoxic cancer therapy kills the stromal cells including the endothelial cells of the tumour vasculature. Thus, for the tumour to recur from surviving cancer cells, the vasculature must be restored following therapy. Studies have shown that tumour blood vessels can derive from two sources: From angiogenesis, the sprouting of endothelial cells from nearby blood vessels, and from vasculogenesis, the formation of blood vessels by circulating cells. For most tumours following therapy angiogenesis is the most important process for the formation of these vessels. However, in the case of radiation, and with some anti-angiogenic therapies, angiogenesis can be abrogated thereby forcing the tumour to use vasculogenesis to restore the vasculature.
We have tested the hypothesis that the radiation response of tumours can be increased by blocking vasculogenesis using two human tumours (FaDu head and neck tumours and the U251 glioblastoma) transplanted into nude mice. We show that an essential contributor to vasculogenesis in irradiated tumours are CD11b+ myelomonocytic cells expressing MMP-9, and circulating endothelial cells or endothelial progenitor cells. These are recruited to the irradiated tumours by stromal derived factor 1 (SDF-1) induced by increased levels of HIF-1 in the irradiated tumours. Importantly, a variety of ways of blocking this process (neutralizing antibodies to CD11b, inhibition of the interaction of SDF-1 with CXCR4 and with CXCR7, antibodies against CXCR4, and inhibition of HIF-1) render tumours less able or unable to recur following irradiation. Though we also see tumour radiosensitization by inhibiting angiogenesis using the DC101 antibody against VEGFR2, this is not as great as with vasculogenesis inhibition after irradiation. We have alos tested the radiation + vasculogenesis inhibition strategy using a much more refractory model of "spontaneous" brain tumours in rats using an inhibitor of the interaction of SDF-1 with CXCR7. These tumours form in rats following administration of a single dose of the carcinogen ENU when in utero and reliably cause the rats to die from brain tumours from approximately 120 days after birth. We also show that blocking vasculogenesis does not increase the radiation damage to normal skin.
Thus blocking vasculogenesis can have a major positive impact on the response of solid tumours to irradiation and potentially represents a new paradigm for the treatment of such tumours.

74 INVITED

Hypoxia-Driven Angiogenesis

Abstract not received

75 INVITED

Differential and Unexpected Impact of Adjuvant Versus Metastatic Antiangiogenic Therapy

R. Kerbel[1]. [1]*Sunnybrook Health Sciences Centre, Molecular and Cell Biology Research, Toronto, Canada*

Background: The various successes of four different approved antiangiogenic drugs (bevacizumab; sunitinib; sorafenib; pazopanib) in the metastatic setting for a variety of indications (e.g. colorectal, non small cell lung, breast, renal cell and hepatocellular carcinomas) created a seemingly compelling rationale to evaluate such drugs in the early stage adjuvant disease setting. This was so despite the absence of any prior preclinical evidence indicating such drugs would be efficacious in treating supposedly non vascularized microscopic metastasis present after surgical resection of primary tumours. The results of the first phase III randomized adjuvant therapy trials of an antiangiogenic drug (bevacizumab, the anti-VEGF antibody) with chemotherapy in colorectal cancer (AVANT and CO8) failed to meet their primary endpoints of disease free survival at 3 years. In the case of AVANT, survival rates may be inferior in patients who received bevacizumab.
Material, Methods and Results: Preclinical models of postoperative adjuvant therapy have been reported recently by the Kerbel lab (Ebos et al. *Cancer Cell* 15: 232−9, 2009) and by other labs. Efficacy results are mixed. In one study (Ebos et al, above) brief treatment with single agent sunitinib, especially using higher doses, in a postoperative adjuvant therapy model of breast cancer resulted in accelerated disease progression and reduced survival times. Using other models and other drugs, e.g.