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.

sorafenib, (pancreatic or hepatocellular carcinoma), reported by others, have indicated suppression of disease progression and increased survival times. Reasons for the different results are unknown but highlight the need for more studies.
Conclusions: A convincing biologic rationale for using antiangiogenic drugs to treat *early* stage microscopic metastatic disease has yet to be established. More intensive preclinical efforts to model adjuvant therapy (and compare the results to those obtained in metastatic models) in different disease indications are urgently needed, not just for antiangiogenic drugs but other therapeutic modalities as well.

References

Ebos & Kerbel "Antiangiogenic therapy: impact on invasion, disease progression, and metastasis." *Nat Rev Clin Oncol*. 8: 210–221, 2011.

76 INVITED
Biomarkers & Angiogenesis

Abstract not received

Scientific Symposium (Sat, 24 Sep, 16:00−18:00)
Probiotics, Calories and Cancer Care

77 INVITED
Probiotics and Colon Cancer Prevention

J. Rafter[1]. [1]*Karolinska Institutet, Department of Biosciences and Nutrition, Huddinge, Sweden*

While a myriad of healthful effects have been attributed to probiotic bacteria, a controversial one is that of anticancer activity. Reports in the literature, regarding the anti-coloncancer effects of lactic acid bacteria, fall into the following categories: *in vitro* studies and *in vivo* studies in laboratory animals; dietary intervention studies in human volunteers and epidemiological studies correlating colon cancer and certain dietary regimes. It must be emphasised that, to date, there is no direct experimental evidence for colon cancer suppression in humans as a result of consumption of lactic cultures in fermented or unfermented dairy products. However, there is a wealth of indirect evidence, based largely on laboratory studies, in the literature and this will be summarized in my presentation. At present, the results from the epidemiological studies do not appear to support the results from experimental studies. The reason for this is unclear but might be explained by differences in bacterial strains, with the strains being used in the experimental studies surviving better in the gastrointestinal tract than the strains present in fermented dairy products. It should also be emphasized that great care must be exercised in extrapolating the results of *in vitro* and animal studies to the human system. It must also be pointed out that the precise mechanisms by which probiotic bacteria may inhibit colon cancer are presently unknown and these will be discussed. However, even with these reservations in mind, the use of lactic cultures for human colon cancer suppression holds promise and deserves more scrutiny. The latter should involve carefully designed human dietary intervention studies to corroborate the wealth of experimental studies. I will report on such an intervention study that was recently completed as part of an EU funded project "Synbiotics and Cancer Prevention in Humans".

78 INVITED
Assessment and Management of Gastrointestinal Symptoms After Cancer Treatments

J. Andreyev[1]. [1]*Royal Marsden Hospital, Department of Oncology, London, United Kingdom*

Background: Chronic GI symptoms significantly impacting on quality of life after cancer therapy, affect more people annually than are diagnosed with Ulcerative Colitis **and** Crohn's disease together. Yet, whilst almost every hospital has one or more specialists in Inflammatory Bowel Disease, few patients with treatment related GI symptoms are referred to a gastroenterologist. When they do, most meet a professional who is not trained to manage their symptoms. As a result ineffective or dangerous treatments are frequently prescribed.
Results: The current priority of follow up after cancer is to detect disease recurrence. Patients will therefore often not tell their oncologists about symptoms if they do not feel they are due to cancer. Patients frequently believe that symptoms after treatment are inevitable, that little can be done and are embarrassed to seek help. Robust strategies to detect patients who need help are urgently required and every unit must develop reliable referral pathways to gastroenterologists who in turn need training to manage post treatment symptoms optimally.
The gastrointestinal tract is only able to respond to physical insults in a limited number of ways. Identical symptoms can arise from many different causes. The majority of patients with new onset gastrointestinal symptoms will have more than one cause for symptoms, surprisingly often not even related to their previous cancer therapy. Empirical treatment often fails to anticipate the true cause of symptoms and for this reason may be ineffective. A systematic, logical, physiological investigative approach will frequently allow straightforward, helpful and sometimes curative treatments to be prescribed.
Conclusions: It is no longer acceptable to ignore the GI morbidity of cancer therapies, which is the current norm for the vast majority of patients. A completely new approach to the management of chronic GI side effects of cancer treatment is required. Large numbers of patients are affected. Most patients can be helped or cured. Some problems are preventable.

79 INVITED
Continence Interventions − Bowel Problems

C. Taylor[1]. [1]*Kings College, Macmillan Education Unit, London, United Kingdom*

There is increasing evidence to indicate that cancer survivors have concerns and physical problems which are not being adequately addressed. One of the main difficultes which individuals diagnosed with colorectal cancer treatment can experience is an alteration in their bowel function. In particular, it is known that the majority of those recovering from rectal cancer surgery will have to cope with undesirable bowel symptoms; urgency, frequency, stool fragmentation and/or incomplete bowel emptying plus changes in levels of continence. Bowel continence embraces the ability to control flatus, liquid and stool.
This presentation will consider the particular effects for individuals suffering from anterior resection syndrome who following a low rectal resection may for example manage to remain continent to stool but when unable to control the release of flatus in public, feel acutely embarrassed. Another patient with this condition may manage to control their stool by day but then experience an urgent need to defecate at night which if not responded to in time may 'cause an accident to happen'. These bowel symptoms can be particularly problematic post stoma reversal and also for those post multimodal treatment i.e. after receving a combination of chemotherapy, radiotherapy and surgery. These symptoms have to date not been well articulated.
These symptoms may persist for a few weeks to months and although for many there will be improvement over time, there is unlikely to be a return to the same function relied upon pre-treatment. It seems that despite the potential for such symptoms to adversely affect quality of life, many individuals do not receive the help they need to manage them. It is suggested that without appropriate intervention these symptoms can become a late treatment effect which then impact on other health domains and disrupt normal daily functioning.
At present in the UK the nature of bowel assessment and frequency of monitoring during the follow-up period is subject to local service delivery models and variation exists. A more systematic approach to bowel assessment and management following such treatment is advocated. These is clear benefit in early intervention (Camelleri-Brennan 2002) but it is often not sought or offered. Work is underway within the National Cancer Survivorship Initiative within the UK to improve the after-care these patients receive, testing new models of assessment, integrating improved care planning and information exchange between care providers and the patient at the end of treatment. In line with these developments, this presentation will indicate ways we can ameliorate bowel continence problems, in order to enhance their cancer survivorship experience.

80 INVITED
The Experience of Living With a PEG

L. Martin[1]. [1]*Karolinska Institutet, Upper Gastrointestinal Research Department of Molecular Medicine and Surgery, Stockholm, Sweden*

Previous research has shown that appropriate nutritional interventions reduce the risk of surgical complications *(Bozzetti, 2001)* shorten the recovery time and the length of hospital stay *(Pirlich, 2006),* improves tolerance to treatment *(Braga, 2002)* and increase the chance of survival *(Stratton, 2007).* This improved awareness of the relevance of nutrition support in the treatment of diseases has contributed to a rapid increase in the use of percutaneous endoscopic gastrostomies (PEG) worldwide *(NCEPOD, 2004, Gauderer, 2002).*
For patients with preserved intestinal function but with inadequate or no independent oral food intake, enteral nutrition therapy with PEG is one of the preferred alternatives *(Kurien, 2010, ESPEN guidelines, NICE guidelines)* to nutrition support. The PEG is discrete and does not interfere with speech or swallowing *(Gomes, 2010)* but the social role with a meal