Friday, 19 November 2010 11:00–13:05

PLENARY SESSION 8

Angiogenesis and tumour microenvironment

460 INVITED

Antiangiogenic drug alterations of the tumor microenvironment which can impact chemotherapy efficacy

R. Kerbel[1], J. Ebos[1], Y. Shaked[2]. [1]*Sunnybrook Health Sciences Centre, Molecular and Cell Biology Research, Toronto, Canada;* [2]*Technion, Molecular Pharmacology, Haifa, Israel*

Among the most interesting findings of antiangiogenic drugs assessed in phase III trials is the necessity for bevacizumab (the anti-VEGF antibody) to be combined with chemotherapy in order for it to achieve a clinical benefit in most approved indications, and in contrast, the failure of VEGF receptor tyrosine kinase inhibitors (TKIs) such as sunitinib or sorafenib to improve chemotherapy efficacy. As a result, there is much interest in uncovering the mechanisms by which an antibody drug such as bevacizumab can enhance chemotherapy efficacy and why TKIs fail to do so. Results will be summarized implicating one potential mechanism for antibodies: inhibiting the mobilization and tumor colonization of a variety of circulating bone marrow-derived cell (BMDC) populations, including endothelial progenitor cells (CEPs) induced by chemotherapy. Thus certain chemotherapy drugs or other agents such as vascular disrupting agents (VDAs) using maximum tolerated doses can induce a rapid host response comprised of multiple elevated cytokines and chemokines, including G-CSF and SDF-1. This in turn promotes the mobilization of CEPs. However, other types of BMDCs appear to be involved as well, the nature of which is under study. They may include various monocytic/macrophage populations in addition to Gr1+CD11d+ myeloid derived suppressor cells. The BMDC VDA or chemotherapy-induced mobilization and tumor colonization response can be blocked by co-treatment with an antiangiogenic antibody targeting the VEGF pathway, and thus increase the VDA/chemotherapy efficacy. However, some limited data we have obtained indicate that antiangiogenic TKIs may not possess this inhibitory effect.
The nature of the growth factors contributing to the BMDC response are being evaluated. In the case of VDAs, the major growth factor implicated is G-CSF, whereas in the case of paclitaxel, it is SDF-1. Thus the results suggest a way in which targeting SDF-1 may improve chemotherapy efficacy while the G-CSF results may have implications for the use and effects of recombinant G-CSF growth factor support to accelerate recovery from myelosuppression.
Finally, we have also found that antiangiogenic TKIs such as sunitinib and sorafenib can also induce a host multi-cytokine response and as such, this may blunt their ability to enhance the efficacy of chemotherapy. This host response may also contribute to other important outcomes including drug resistance and alterations in tumor aggressiveness over time.

461 INVITED

Third generation anti-angiogenic strategies: novel players, novel principles

P. Carmeliet. *Belgium*

Abstract not received

462 INVITED

Micro-environmental influences on cancer stem cells

L. Ellis[1], J. Lu[1], S. Samuel[1], F. Fan[1], L. Xia[1], X. Ye[1], E. Sceusi[1], F. Tozzi[1], Y. Zhou[1]. [1]*University of Texas MD Anderson Cancer Center, Unit 173, Houston Texas, USA*

Cancer stem cells (CSC), can arise either from normal stem cells or due to the influence of the tumor micro-environment. Although the vasculature of tumors delivers oxygen and nutrients to the growing tumor, it has also been hypothesized that endothelial cells contribute to the growth of tumor cells in a paracrine fashion. Gilbertson and colleagues have shown that glioma cancer stem cells reside in the perivascular niche (Caner Cell 2007). We studied the potential role of endothelial cell (EC) derived paracrine factors on promoting the CSC phenotype in human colorectal cancer (CRC) cells. Co-culturing of CRC cells with ECs markedly increased the ALDH-positive population and the sphere forming ability in CRC cells. In addition, CRC cells also displayed increased CD133 and CD44 protein levels. Furthermore, this effect could be mimicked simply by co-culturing CRC cells with conditioned media obtained from ECs. Similarly, treatment of CRC cells with conditioned medium from ECs significantly increased the ALDH-positive population, sphere forming ability, and the expression of CD133 and CD44. Conditioned medium from ECs, concomitantly decreased spontaneous apoptosis in CRC cells as demonstrated by a decrease in Annexin V-positive population, down-regulation of cleaved PARP and Caspase 3, and up-regulation of Bcl2. CRC cells exposed to EC conditioned medium also displayed decreased sensitivity to 5-FU, oxaliplatin and irinotecan. Subsequent studies have been repeated in pancreatic cancer. The search for soluble factors that mediate this observation are ongoing.

463 INVITED

Immunotherapy in 2010 – still alive?

C. Punt[1]. [1]*University Hospital Nijmegen, Oncology, Nijmegen, The Netherlands*

For too long, the immunotherapy of solid tumours has been considered as a promising treatment modality without being firmly established as a standard treatment option. Objective remissions were consistently reported, however with a great variety of approaches and only in a minority of patients in whom this could not be predicted. On the other hand, in some (randomized) trials with vaccine therapy the results suggested a detrimental effect. However, data on the efficacy of T-cell directed therapy are accumulating, and these are being supported by a positive correlation with specific immune parameters. Robust phase III data on T-cell directed immunotherapy are scarce, which is largely due to the lack of financial support by pharmaceutical industries. Immunotherapy directed to the regulatory T cell response is another area that showed great promise in small (pre) clinical studies, and this line of reserach was strongly boosted by the positive results of a phase III trial in melanoma with ipilimumab, an anti-CTLA4 antibody. Further benefit may be expected to combine this with tumor antigen-specific immunotherapy. Lastly, data are accumulating that certain cytotoxic drugs may have immunostimulatory effects, which provides a rationale to combine chemotherapy and immunotherapy. Taken together, immunotherapy is more alive than ever, but will only outgrow its status of promising treatment when convincing results from well-designed trials are available.

464 INVITED

Molecular imaging of therapy response

W. Weber. *Germany*

Abstract not received

Friday, 19 November 2010

Poster Sessions

Angiogenesis, metastasis and inhibitors

465 POSTER DISCUSSION

A Phase 1 dose escalating study of ACE-041, a novel inhibitor of ALK-1 mediated angiogenesis, in patients with advanced solid tumors

S. Sharma[1], J.C. Bendell[2], H. Hurwitz[3], C.H. Condon[4], B.J. Thornell[4], P.L. Slatcher[4], N.G. Borgstein[4], M.L. Sherman[4], M.S. Gordon[5]. [1]*Huntsman Cancer Institute – University of Utah, Center for Investigational Therapeutics, Salt Lake City, USA;* [2]*Sarah Cannon, Research Institute, Nashville TN, USA;* [3]*Duke University, Medical Center, Durham NC, USA;* [4]*Acceleron Pharma, Inc., Cambridge MA, USA;* [5]*Pinnacle Oncology, Hematology, Scottsdale AZ, USA*

Background: Activin receptor-like kinase-1 (ALK-1) is a type I receptor predominantly expressed on activated vascular endothelial cells that mediates signaling by members of the TGF-β superfamily of proteins. ACE-041, a soluble receptor fusion protein consisting of the ligand-binding extracellular domain of ALK-1 linked to a IgG1-Fc region, binds with high affinity to BMP9 and BMP10 but not TGFβ1, 2 or 3, VEGF or bFGF. ACE-041 is able to inhibit both VEGF and bFGF stimulated angiogenesis indicating that ALK-1 is downstream of VEGF and bFGF signaling. In a variety of murine tumors, ACE-041 has demonstrated the ability to decrease both tumor vascularity and growth.