Symposium (Tue, 25 Sep, 14:45−16:45)
Vaccines and cellular treatments

101 INVITED

Targeting CD137 pathway to enhance cancer immunotherapy

L. Chen. *Johns Hopkins University School of Medicine, Dermatology, Baltimore MD, USA*

CD137 (4−1BB) is a tumor necrosis factor receptor superfamily molecule and could be detected on the surface of activated T, B and NK cells. In addition to providing a costimulatory signal to primed CD8+ T cells in the presence of antigenic signal, CD137 triggering could also inhibit CD4+ T cell response and antibody response to antigens. This unique feature makes targeting CD137 a promising approach to stimulate antitumor immunity whereas inhibiting autoimmune diseases. I will focus my discussion on mechanistic aspects of CD137-induced antitumor immunity and inhibition of autoimmunity, as well as its therapeutic application.

102 INVITED

Current clinical experience with melanoma vaccines: peptides, proteins and dendritic cells

D. Schadendorf. *Germany*

Abstract not received.

103 INVITED

WT1 peptide vaccines in leukaemias and WT-1 expressing carcinomas

U. Keilholz. *Charité-Universitätsmedizin, Department of Medicine III, Berlin, Germany*

Several clinical trials of vaccination with the HLA-A2-restricted WT1.126–134 peptide and the A24 restricted peptide have been performed in patients (pts) with AML, MDS and WT1-overexpressing carcinomas mainly in Berlin, Germany and Osaka, Japan. The general trial endpoints were to determine toxicity, immunogenicity, and molecular and clinical activity.
Methods: Patients received vaccinations of WT1 peptide with various adjuvants. Vaccination was biweekly x 4 followed by 4-weekly. Early disease progression until vaccine #6 was allowed, if not requiring alternative treatments. WT1-specific T cell responses were measured by tetramer and cytokine flow cytometry. WT1 levels were assessed by qRT-PCR. Clinical response assessment in leukemias followed IWG-MDS criteria, capturing stable disease and hematologic improvement, and RECIST criteria in solid tumors. S
Results: Of special relevance and most mature were the results of the AML trials. In the berlin trial the following observations were made: Of 29 pts enrolled 25 were evaluable, 23 with AML and 2 with RAEB. 15 AML pts had >5% marrow blasts and 8 had high-risk CR with detectable WT1 mRNA. A median of 11 (range 3−25) vaccinations was administered, 3 pts are ongoing. No relevant toxicity occurred. There were no obvious differences in outcome parameters between the 2 vaccination schedules. The percentage of patients with WT1 tetramer response increased from 28% prior to vaccination to 80% at week 10 ($p = 0.003$), while the WT1 peptide specific cytokine response increased from 20% to 57% ($p = 0.012$) of patients. WT1 mRNA-levels increased in 22% of patients, were stabel in 26%, and decreased in 52% (2- to >50-fold). One CR (514 days) and 13 SD (99 to 339 days) were observed, 5 SD with >50% blast reduction and 3 with hematologic improvement. The CR and 3 SD occurred after initial PD. The median time to treatment failure (TTF) was 143 days. There was a significant association between decrease in WT1 mRNA levels and TTF ($p = 0.026$). The clinical trials in patients with WT1-expressing carcinomas are maturing and the current status will be presented at the meeting.
Conclusions: Current study results prove immunological, molecular and clinical efficacy of WT1 peptide vaccination in AML and also in patients with carcinomas with very limited toxicities.

104 INVITED

Vaccine approaches to kidney cancer in the era of tyrosine kinase inhibitors

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Renal cell cancer (RCC) accounts for 3% of all tumours and is the 10th most common cancer in adults. Up to 30% of the patients present with metastatic disease and recurrence develops in 40−50% of the patients treated for localized disease. The survival rate at 5-year for patients with metastases is less than 10% and has remained unchanged for a number of years. RCC is highly resistant to chemotherapy and IL-2 and interferon alpha is widely used as first line treatment of metastatic disease. Although response rates to IL-2 are low (5−20%), 5−7% of patients deemed small suitable for high-dose IL-2 have durable and complete responses and long term survival (10−15%). A predictive model currently tested in a clinical trial, selecting patients most likely to respond, has the potential of increasing IL-2 response rates. Recent molecular targeted therapies with tyrosine kinase inhibitors including sorafenib, sunitinib and the rapamycin derivative temsirolimus has led to high number of objective responses and prolonged progression-free survival in large trials. Durable remissions and prolonged survival have however not yet been reported. Hence there is still room for significant improvements.
Therapeutic cancer vaccines including, Heat Shock Protein peptide complex vaccine (HSSPC-96), tumour RNA transfected dendritic cells (DC) and DC fused with tumour cells have shown objective responses and long term stable disease. Injections of cryo-preserved tumour cells have demonstrated prolonged disease-free survival in radically resected patients (adjuvant). However the number of patients benefiting from vaccine therapy has until now been low. Possible explanations may be down-regulation caused by a new class of T-cells, CD4+CD25¬+ (T-reg) and the fact that most vaccine trials are in patients with advanced cancer disease. To harness the immune response future vaccine trial should include patients with limited disease, preferably in adjuvant setting, and include procedures to reduce down regulation by T-regs.

Symposium (Tue, 25 Sep, 14:45−16:45)
PI3 kinase pathway inhibition

105 INVITED

The role of PI3K in cancer

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Mutations in genes that control the phosphoinositide 3-kinase (PI3K) pathway are some of the most common events in human cancers. PI3K generates the lipid, phosphatidylinositol-3,4,5-trisphosphate (PIP3), that acts as a membrane bound second messenger to activate AKT/PKB family protein Ser/Thr kinases as well Tec family protein-Tyr kinases. PIP3 also regulates proteins that control Arf, Rac and Ras family GTP-binding proteins. This lipid is elevated in cancers, either due to loss of PTEN, the phosphatases that degrades it, or due to constitutive PI3K activity because of activating mutations in PIK3CA or an upstream activator of PI3K. The ultimate consequence of activating PI3K is to generate changes in signaling networks and gene expression patterns that promote cell growth, cell survival and cell movement. In order to elucidate the role of the PI3K pathway in cancer, we have generated mice in which genes for PI3K are deleted or activated in specific tissues. In addition, we have investigated the biochemical mechanisms by which PI3K becomes activated in human cancers. Our progress in these areas will be summarized.

106 INVITED

What can be revealed using mouse models?

M. Barbacid. *Centro National de Investigaciones, Department of oncology, Madrid, Spain*

Ras oncogenes were identified in human tumors more than twenty years ago. Since then, much work had been done towards understanding their role in signal transduction and in tumor development (Malumbres and Barbacid, Nature Rev. Cancer, 2003). Yet, there are still a number of highly relevant questions that need to be addressed. For instance, why are ras oncogenes frequently mutated only in certain types of human neoplasia? is oncogenic ras expression sufficient to initiate a tumoral response? what other factors contribute to the phenotypic expression of Ras oncogenes?, etc.
To address some of these issues, we have generated animal models in which an endogenous K-ras (Guerra et al., Cancer Cell, 2003) can be activated in a spatially and temporally controlled manner. Previous studies have shown that expression of endogenous K-ras oncogenes during embryonic development lead to tumor formation in most tissues (Johnson et al., Nature 2001; Jackson et al., Genes & Dev. 2001; Brown et al, PNAS 2003; Hingorani et al., Cancer Cell 2003). However, widespread expression in postnatal mice, only elicits efficient tumor development in lungs. Since K-ras oncogenes are commonly activated in adult (non-pediatric) human tumors, we are currently investigating under what conditions adult cells become susceptible to transformation by K-ras oncogenes. I will summarized our recent results demonstrating a critical cooperation between K-Ras oncogene expression and chronic pancreatitis