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

S. Aamdal. *The Norwegian Radium Hospital, Dept of Clinical Research, Oslo, Norway*

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

in the development of pancreatic ductal adenocarcinoma (Guerra et al., Cancer Cell, 2007).
We have used the same targeting strategy to generate mice carrying an endogenous H-ras oncogene. As recently reported in humans suffering from Costello syndrome, germ line expression of H-RasV12, unlike that of K-RasV12, is tolerated during embryonic development. Moreover, these mice do not develop overt tumor formation at least for nine months. These observations indicate that H-Ras and K-Ras oncoproteins have significantly different properties in vivo.

107 INVITED

Biological roles of PI 3-kinase isoforms

B. Vanhaesebroeck. *Ludwig Institute for Cancer Research, Cell Signalling Group, London, United Kingdom*

The PI 3-kinase pathway has been implicated in a wide variety of physiological responses, and is considered as a therapeutic target amongst other in cancer and inflammation. Mammals have 8 distinct isoforms of PI3K, and global inhibition of all isoforms of PI3K is toxic in vivo. Therapeutic intervention with the PI3K pathway will therefore most likely have to be centered on specific (subsets of) PI3K isoforms. However, identifying the indications that will provide the best opportunity for isoform-selective PI3K inhibitors is the subject of intense debate. Indeed, it has turned to be particularly difficult to gain insight into the physiological roles of PI3K isoforms by classical mouse gene targeting/knock-out approaches. We have pioneered the use of so-called 'kinase knockin' mice in which we have created germline inactivating mutations in the ATP-binding site of PI 3-kinase isoforms. This strategy more faithfully mimics pharmacological inhibitors than the classical knock-out approaches, and has allowed us to uncover isoform-selective roles of several isoforms of PI3K and begin validation of these PI3Ks as therapeutic targets. An overview of these efforts will be presented.

108 INVITED

Preclinical and clinical studies

G.B. Mills. *USA*

Abstract not received.

Symposium (Tue, 25 Sep, 14:45−16:50)
Issues in geriatric oncology

109 INVITED

The right treatment for elderly with cancer is not easy to determine: a research strategy

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Background: Never ending discussions on the right oncological treatment of, especially frail, elderly with cancer; obvious reasons being a limited but often varying, life expectancy, vulnerability, complicating presence of co-morbidity, increasign with age flattening above 80 years and social reasons like being cared for at home, transportation. Quality of life matters a lot when your time is relatively short. Communication problems are large. One could argue that the right treatment hardly exists: there is either over- or undertreatment.
Materials: Data from the population-based Eindhoven Cancer Registry that comprise co-morbidity and SES and various studies on prevalence, effects on stage and treatment policy and outcome; literature on research strategy and a forthcoming special issue on Cancer management in the Elderly of the European Journal of Cancer based on an ESO course in april 2007.
Results: Prevalence of serious co-morbidity is substantial in elderly (less than one third being without overt serious co-morbidity, with sometimes small, sometimes large effects on life expectancy, but necessitating medical and organizational adaptations in care supply. Medical care in the (very) elderly is in fact individualized, as patients become more unique medically and socially, thus hampering traditional clinical research e.g. by means of RCT's. The annual number of specific (with respect to pattern of co-morbidity) older patients per hospital is usually rather small, which points to regional collaboration. Geriatricians with extensive knowledge of oncological treatments are usually scarce.
Conclusions: Prospective (and also retrospective, if suitable) research should be population-based, thus exhibiting the broad spectre of disease and health status. Collaborations of large numbers of hospitals is necessary in order to have adequate numbers in subgroups. When the standard oncological treatment risks to be overtreatment, the study should rather focus on complications, side effects that determine QL. When, more or less deliberately, undertreatment is administered (less lymphnode sampling and/or adjuvant treatment) studies are necessary of recurrence rates and metastasis, and of QL at short and longer term. One could argue to learn more from at short term less risky undertreatment than from (the oncologically right?) overtreatment. Results should be more expressed in numbers needed to treat, stage, etc to avoid one (extra) recurrence, or side effect or complication.
With respect to care development, practical steps should be taken to develop or cut care paths (in the jungle of) the hospital that take account with co-morbidity management and address communication problems.

110 INVITED

Comorbidity assessment and the influence of comorbidity on toxicity and choice of treatment

C. Terret, J.P. Droz. *Centre Léon Berard, Medical oncology, Lyon, France*

One characteristic of ageing is an increased prevalence of comorbidity. In western coutries, 35% of people aged 65−79 reports at least two diseases, this ratio increases up 70% at age 80 and older.
Comorbidity may affect the accuracy of cancer screening or diagnosis. It can also influence both treatment and prognosis of cancer itself. Then, comorbidity requires careful assessment before planning cancer treatment. Various scales are available to measure it, with the capacity for predicting, for instance, the risk for hospitalization or death. Concomitant morbid conditions may be more difficult to treat, adding complexity in terms of competing risks; potentially incompatible therapies; burden or costs of therapies that patient can not tolerate, and synergistic likelihood of adverse outcomes, including disability and death. In many cases, geriatricians should help oncologists to define the hierarchy of patient diseases, including cancer and prioritize those requiring immediate treatments.
On the other hand, a common comorbidity in elderly patients such as diabetes mellitus has been suspected to worsen cancer outcomes. Obesity appears also to affect the prognosis of prostate cancer or breast cancer. Conversely hypothyroidism seems to be associated with a lesser incidence of breast cancer.
Furthermore, multiple concomitant diseases frequently lead to polypharmacy, increasing the likelihood of drug interaction with chemotherapy agents or supportive treatment. In fact, inappropriate medication use is frequent in older people taking at least 5 medications.
The management of elderly cancer patients should take into account not only the impact of cancer treatment on comorbidity and the effect of comorbidity in delivering cancer treatment, but also the impact of comorbidity on the behavior of the cancer in the elderly patients.

111 INVITED

The essentials of geriatric oncology studies: do's and don'ts

M. Aapro. *Imo – Clinique de Genolier, Institut Multidisciplinaire d'Oncologie, Genolier, Switzerland*

What is a geriatric oncology study? This is not a study of elderly patients defined as aged above 65, but it should be a study that takes into account principles of geriatric assessment. It should ideally include patients representative of all "elderly categories". This means including frail patients, because of age alone or because of biological limitations. Study endpoints may vary, from relapse-free survival to overall survival, as in many settings deth from other causes may become a predominant issue, while patients value relapse-free time. Geriatric oncology studies need also to overcome the perceived "impossibility" that prevails in many settings. Well informed elderly patients and their caregivers will never refuse a well conceived study. There is a need to define standardized geriatric assessment tools to collect information in cancer patients. Once ongoing studies will have provided further information, an effort to coordinate cooperative groups should be done, so that all use a common tool, which will be a means to compare studies. This is similar to the easier but long process which lead to the adoption of performance status as a key element of all studies in oncology. The SIOG (International Society for Geriatric Oncology) Task Force on Geriatric assessment suggested that some of the data analyzed should be: checking whether screening tools correctly identify patients (i.e., too well, too ill); validating inclusion/exclusion categories; developing a scoring algorithm to identify target groups, identifying the best candidates for a specific intervention. b) defining the patient's status: prospective data about the importance of hemoglobin levels, albumin levels, creatinine clearance and drug interactions are needed. Studies should evaluate these determinants prospectively in order to define for which drugs such data are important in the choice of the treatment. c) definition of the disease: