the distinct tumor entity ALK-positive ALCL. The fusion gene represents a tumor marker that can be exploited for diagnostic purposes and a tool to study bone marrow (BM) and peripheral blood (PB) minimal residual disease (MRD). Gene expression profile and proteomic analysis have recently been used to study ALCL.
We analyzed NPM-ALK transcript expression in tumor biopsies from children enrolled in the AIEOP LNH97 trial for ALCL and found that more than 90% of the cases were positive. BM aspirate was also studied for tumor dissemination by RT-PCR. The prevalence of minimal BM disease at diagnosis was 60%. When analyzed by real-time PCR, NPM-ALK expression levels showed a wide variability, but NPM-ALK copy number was generally higher in PB compared to BM.
In our study, minimal BM infiltration by tumor cells at diagnosis was a negative prognostic factor as children with positive BM fared significantly worse that the negative counterpart. In addition, we found that the majority of the patients had serum anti-ALK antibodies at diagnosis and that initial levels, as well as titer decrements, varied significantly among patients.
Recently, the differential gene expression profile of a series of ALCL was published. The results of such a study confirmed that differences exist at the transcriptome level between ALK-positive and ALK-negative ALCL and that distinct signatures may be associated with different histological subtypes. Gene expression profiles and proteomic analysis of ALCL cells have identified several tumor associated markers that could possibly be exploited both for diagnosis and for therapeutic intervention.
We have also studied the fate of the fusion protein NPM-ALK and its interactions with the heat shock proteins. Our data support a role of hsp70 and hsp90 in folding, activity and degradation of NPM-ALK.
Recent advances in the biology of ALCL will improve our understanding of ALCL tumorigenesis, will allow us to determine the role of MRD and will be of great relevance to define new therapeutic targets in this disease.

183 INVITED

Molecular diagnosis and prognosis in rhabdomyosarcoma

S. Gallego. *Spain*

Abstract not received.

Thursday, 27 September 2007

Symposium (Thu, 27 Sep, 09:00−11:00)
Advances in new drugs for breast cancer

184 INVITED

The pros and cons of signal transduction inhibitors in breast cancer

J. Baselga. *Spain*

Abstract not received.

185 INVITED

Inhibiting angiogenesis – a new weapon in the therapeutic armamentarium

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Over the last three decades substantial laboratory and clinical evidence has accumulated to support the central role of angiogenesis in breast cancer progression. Multiple angiogenic factors are commonly expressed by invasive human breast cancers with the 121-amino acid isoform of vascular endothelial growth factor (VEGF) predominating. Bevacizumab (Avastin™, Genentech, South San Francisco) is a humanized monoclonal antibody directed against all isoforms of VEGF-A. A phase I/II study testing three different doses of bevacizumab monotherapy (3, 10, or 20 mg/kg every two weeks) in 75 patients with previously treated MBC reported a 9.3% objective response rate with 17% of patients responding or stable at 22 weeks. In a phase III trial the addition of bevacizumab to capecitabine in patients previously treated with anthracyclines and taxanes significantly increased response rate (9.1% vs. 19.8%; $p = 0.001$) but not progression free (4.17 vs. 4.86 mo; HR = 0.98) or overall survival (15.1 vs. 14.5 mo). As VEGF inhibitors such as bevacizumab are likely to be more effective in patients with less heavily pretreated disease, E2100 compared paclitaxel monotherapy to paclitaxel plus bevacizumab as initial chemotherapy for patients with MBC. Combination therapy significantly increased response rates in all patients (35.8% vs. 20.9%; $p < 0.0001$) and in the subset of patients with measurable disease (47.2% vs. 25.2%; $p < 0.0001$). Paclitaxel + bevacizumab significantly prolongs PFS (11.3 vs. 6.0 mo; HR = 0.60, $p < 0.0001$). Grade 3/4 hypertension (15% vs. 0%; $p < 0.0001$), proteinuria (3.5% vs. 0%; $p = 0.0002$), headache (2% vs. 0%; $p = 0.009$) and cerebrovascular ischemia (2% vs. 0%; $p = 0.009$) were more frequent in patients receiving paclitaxel + bevacizumab. Additional studies will determine the impact of adding bevacizumab to other treatment regimens. Angiogenesis inhibitors significantly curtail primary tumor growth and establishment of metastases in several pre-clinical minimal disease models; overt shrinkage of large, well established tumors is less common. As tumors progress, increasing numbers of pro-angiogenic peptides are produced making resistance to any single anti-angiogenic agent more likely. As such, the most successful clinical application of angiogenesis inhibitors is likely to be in patients with micrometastatic disease that is in the adjuvant setting. Clinical trials evaluating bevacizumab in the adjuvant setting have begun.

186 INVITED

Synthetic lethal approaches as potential therapies for tumours deficient in DNA repair pathways

A. Ashworth. *The Institute of Cancer Research, Breakthrough Breast Cancer Research Centre, London, United Kingdom*

About one in nine women in the Western world develop cancer of the breast and at least 5% of these cases are thought to result from a hereditary predisposition to the disease. Two breast cancer susceptibility (BRCA) genes have been identified and mutations in these genes account for most families with four or more cases of breast cancer diagnosed before the age of 60. Women who inherit loss-of-function mutations in either of these genes have an up to 85% risk of breast cancer by age 70. As well as breast cancer, carriers of mutations in BRCA1 and BRCA2 are at elevated risk of cancer of the ovary, prostate and pancreas. The genes are thought to be tumour suppressor genes as the wild-type allele of the gene is observed to be lost in tumours of heterozygous carriers. Both BRCA1 and BRCA2 have significant roles in the maintenance of genome integrity via roles in the repair of DNA damage via homologous recombination. The specific DNA repair defect in BRCA-mutant cells provides opportunities for novel therapeutic approaches based on selective inhibition of functionally interacting repair pathways. These approaches may also be applicable to a wider range of sporadic cancers.

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187 INVITED

Challenges and opportunities in the intergration of new and old treatments

K.S. Albain. *USA*

Abstract not received.

Symposium (Thu, 27 Sep, 09:00−11:00)
Controversies in the local management of breast cancer

188 INVITED

Lessons and questions from the overview

T. Whelan. *Hamilton Regional Cancer Center, Dep. of Radiation Oncology, Hamilton Ontario, Canada*

Randomized trials of adjuvant treatment for early breast cancer may be too small to reliably detect important differences in long-term survival and recurrence. The 2000 Early Breast Cancer Trialists' Collaborative Group (EBCTCG) overview (Lancet 2005; 36:2087) considered randomized