IgH rearrangements and the main recurrent cytogenetic abnormality is 6q deletion. Gene-expression studies showed that WM has a gene expression profile similar to CLL and normal B cells; IL6 and MAPK signaling pathway associated genes are the most significantly up-regulated genes.
Clinical manifestations and laboratory abnormalities in WM are related to direct tumor infiltration and the amount and specific properties of the monoclonal IgM. Weakness and fatigue are usually related to anemia secondary to marrow infiltration; B symptoms are common. Hepatomegaly, splenomegaly and lymphadenopathy occur in 15−30% of patients. Peripheral neuropathy, symptoms and signs of cryoglobulinemia, cold agglutinin disease or amyloidosis may predominate. Hyperviscosity syndrome occurs in 10−30% of patients at diagnosis.
Diagnosis of WM should be confined to patients with a lymphoplasmatcytoid lymphoma with compatible immunophenotype involving the bone marrow with demonstrable IgM monoclonal protein. Differential diagnosis of WM includes other B-cell lymphoproliferative disorders including splenic marginal zone lymphoma, CLL and IgM-Multiple myeloma. Immunophenotyping and clinical criteria are helpful for an accurate diagnosis. IgM-MGUS is far more common than WM and is characterized by the absence of morphologic evidence of marrow infiltration. Patients with monoclonal IgM and overt manifestations such as peripheral neuropathy, cryoglobulins, cold agglutinin disease, AL amyloidosis or other rare manifestations, without evidence of marrow infiltration, should be regarded as IgM-related disorders.
Median survival of patients with WM ranges between 5 and 10 years. Therapy is indicated for patients presenting with symptoms and signs due to malignant infiltration of organs or tissues or due to circulating or deposited IgM. Age, hemoglobin concentration, serum albumin and ?2-microglobulin have all been identified as significant prognostic factors while IgM levels have no prognostic value. Consensus criteria have been proposed for the evaluation of response to treatment and have been updated recently. Oral alkylating agents such as chlorambucil, had been the standard of care for many years. Nucleoside analogues (fludarabine, cladribine) have been effective in patients who failed primary treatment as well as in newly diagnosed patients. Combination chemotherapy has also been used. Rituximab induced responses in both previously treated and untreated patients and has been used in combination with dexamethasone, cyclophosphamide or nucleoside analogues resulting in high response rates and long remissions. Bortezomib is also active in both pretreated and untreated patients. High dose therapy with autologous stem cell transplantation and reduced-intensity allogeneic transplantation may have a role in the management of selected patients.

Symposium (Wed, 26 Sep, 14:45−16:45)
Molecular biology in paediatric tumours

180 INVITED

Paediatric brain tumours: exploiting genomics to improve therapies

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Background: Brain tumours represent the most common cause of cancer-related death in childhood. Current therapies fail to cure a significant proportion of cases, and are associated with long-term sequelae. Moreover, disease-risk is difficult to predict based on current clinical and histopathological criteria. Major challenges therefore exist in the individualisation and optimisation of current therapies, alongside a clear need for the development of novel therapeutic approaches. Focussing on medulloblastoma, the most common malignant brain tumour of childhood, this lecture will review our current understanding of the molecular events that underlie medulloblastoma pathogenesis, and how this knowledge is being exploited for potential therapeutic benefit.
Results: Major insights to the genetic basis of medulloblastoma have emerged from rare familial cancer syndromes. The observation of medulloblastoma as a feature of Gorlin, Turcot and Li-Fraumeni syndromes has led to the demonstration of somatic mutations of the genes responsible for these syndromes (ie. the PTCH, APC and P53 tumour suppressor genes) in significant subsets of sporadic cases. Studies in the human disease and transgenic mouse models have since established critical roles in normal cerebellar development for the sonic hedgehog (SHH) and wnt/wingless (Wnt) cell signalling pathways, in which these genes reside, and for their aberrant activation in medulloblastoma. Using contemporary genomics approaches, we have recently identified SHH and Wnt pathway mRNA expression signatures which characterise distinct sub-groups of medulloblastomas, into which genetic mutations affecting the respective pathways cluster. Moreover, genetic mapping analysis revealed tumours within these sub-groups are further defined by unique patterns of chromosomal aberrations. Together, these data are enabling the development of a robust classification of medulloblastoma molecular sub-groups, and the identification of markers which are independently predictive of poor (eg. 17p loss, MYC amplification) and favourable (eg. Wnt pathway activation) prognosis. These markers offer utility for improved disease-risk stratification, and are currently under assessment for this purpose in Europe-wide clinical trials. Finally, our developing understanding of medulloblastoma biological pathways is facilitating the selection, pre-clinical and early clinical assessment of new generations of molecularly targeted agents (eg. SHH antagonists) in this disease.
Conclusions: Recent advances highlight the potential translational impact of a detailed characterisation of the biological basis of medulloblastoma. Advances in medulloblastoma provide a 'roadmap' for translational research strategies in other paediatric brain tumour types, with the overall goal of delivering an improved outlook for children with these diseases.

181 INVITED

International consensus for neuroblastoma molecular diagnostics: report from the international neuroblastoma risk grouping (INRG) biology committee

P.F. Ambros[1], I.M. Ambros[1], G.M. Brodeur[2], M. Haber[3], J. Khan[4], A. Nakagawara[5], G. Schleiermacher[6], F. Speleman[7], R. Spitz[8], J.M. Maris[9]. *[1]C.C.R.I., St Anna Kinderkrebsforschung/Tumorcytogenetics, Vienna, Austria; [2]Children's Hospital of Philadelphia, Dept of Oncol., Philadelphia, USA; [3]Children's Cancer Institute Australia, Children's Cancer Institute Australia, Randwick, Australia; [4]National Cancer Institute, Oncogenomics Section, Bethesda, USA; [5]Chiba Cancer Center Research Institute, Division of Biochemistry, Chiba, Japan; [6]Institut Curie, Département d'Oncologie Pédiatrique, Paris, France; [7]Ghent University Hospital, Centre for Medical Genetics, Ghent, Belgium; [8]University of Cologne, Department of Pediatric Oncology and Hematology, Cologne, Germany; [9]University of Pennsylvania School of Medicine, Children's Hospital of Philadelphia, Philadelphia, USA*

Background: Neuroblastoma serves as the paradigm for utilizing tumour genomic data for patient prognosis and treatment allocation. However, there is no worldwide consensus on markers, methodology or data interpretation, inhibiting translational research efforts.
Methods: The Biology subcommittee of the INRG working group (International Neuroblastoam Risk Grouping) was charged with developing an international consensus on all aspects of neuroblastoma molecular genomic diagnostics, including future directions. Consensus was achieved at the September 2005 conference in Whistler, Canada.
Results: A common protocol for specimen acquisition, preparation and banking was approved that focuses on tight quality control, since samples will be used for patient care as well as preservation of high quality research reagents. The working group defined MYCN amplification as >4-fold MYCN signals compared to chromosome 2q reference-probe (FISH method preferred). Whereas MYCN remains the main genomic factor currently used for treatment stratification, the INRG working group has also identified 11q23 allelic status and ploidy as independent markers of survival in certain patient subgroups. Common data elements to be obtained by all groups include these markers as well as allelic status of chromosome band 1p36 and 17q23−25, which are also related to a high-risk phenotype. Pan/multi-genomic methodologies are preferable for collecting DNA copy number data. Thus, genetic characterization of neuroblastomas according to INRG guidelines will require at least 10^7 tumour cells, information regarding the tumour cell content, and certified reference laboratories with expertise in the genetic assays described.
Conclusions: Neuroblastoma treatment planning is closely related to tumour cell genomic features, and it is likely that a panel of DNA-based biomarkers will be used in future risk assignment algorithms. Consensus on methodology and interpretation of these increasingly complex assays is essential and depends on continuous cooperation amongst international cooperative groups as proposed in the INRG.

182 INVITED

Molecular biology of anaplastic large-cell lymphoma

A. Rosolen[1], P. Bonvini[1], M. Pillon[1], K. Ait-Tahar[2], L. Mussolin[1]. *[1]University of Padua, Department of Paediatric Hematology Oncology, Padova, Italy; [2]University of Oxford, Department of Clinical Laboratory Sciences, Oxford, United Kingdom*

Anaplastic large-cell lymphoma (ALCL) accounts for approximately 10−15% of all non Hodgkin lymphomas of childhood. It is characterized by a typical morphological appearance and by a peculiar immunophenotype. The great majority of the cases express the chimeric NPM-ALK protein, originating from the t(2;5)(p23;q35).
The availability of monoclonal antibodies reacting against the ALK moiety of NPM-ALK (and other fusion proteins) has permitted the identification of

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

K. Miller, G.W. Sledge. *Indiana University Medical Center, Department of Medicine Division of Hematology/Oncology, Indianapolis IN, USA*

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