

Discussion: A large number of "de novo" HCC cases and fairly high response rate to preop.CHT constitute a significant difference in comparison with adult HCC series. Angiostatic treatment combined with standard CHT might find a role in HCC. It has potential advantages: broad spectrum of activity, decreased resistance, improved drug access to targets, more tolerable side effects. Thus in the next SIOPEL-5 trial PLADO will be combined with thalidomide. To prevent recurrence post resection prolonged metronomic chemotherapy with oral cyclophosphamide and thalidomide will be applied.

Conclusions: 1. Survival for pediatric/adolescent HCC patients remains unsatisfactory because of low rate of complete tumor excision due to advanced/multifocal disease and high rate of local recurrence. 2. Intensification of standard systemic chemotherapy has not improved prognosis. 3. New treatment approaches and novel concepts are needed. Efforts of pediatric and adult oncologists should be combined within the frames of the new SIOPEL-5 HCC Family of Tumors Trial.

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INVITED

SIOPEL 5, a new protocol for the management of the HCC family of tumours in children/adolescents and young adults

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The International Society of Paediatric Oncology Childhood Liver Tumours Strategy Group (SIOPEL) has conducted a number of successful multinational clinical trials since 1990. The group has focused on chemotherapy strategies for the commonest childhood liver tumour, hepatoblastoma. However in the three successive clinical trials conducted to date significant numbers of children with hepatocellular carcinoma (HCC) have been treated with combination chemotherapy based on cisplatin/doxorubicin +/- carboplatin. Results have been disappointing with 5yr OS figures in the order of 30% in common with the majority of reported series. This is despite the fact that chemotherapy "responses" can be observed in up to 50% of patients. Complete surgical excision remains the key to the successful management of HCC and the conversion of "unresectable" to "resectable" tumours confined to the liver will be the major goal to improvement in survival.

In an attempt to improve the proportion of resectable localised tumours, the SIOPEL group has devised a specific protocol (SIOPEL-5) for the management of children and young adults (up to 30yrs of age) with HCC not associated with underlying cirrhosis. A new chemotherapy strategy combining conventional cisplatin/doxorubicin with thalidomide in an attempt to target tumour vasculature is proposed. This in combination with guidance on the use of chemo-embolisation of localised tumours we hope will result in surgical options being explored in more patients. Alongside the chemotherapy strategy has been discussion concerning the applicability of patients for liver transplantation. A post operative anti-angiogenic "metronomic" maintenance chemotherapy schedule is also being piloted in those patients achieving disease clearance with surgery. The concept protocol will be discussed along with the scientific rationale proposed.

Scientific Symposium

The modern management of early stage NSCLC

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INVITED

Proteomics of lung cancer

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Until recently, the only clinically useful classification of lung tumors was based on light microscopy and treatment was determined by this and the distribution of the tumor in the patient. It is clear that these features do not adequately describe the patient-to-patient variability observed in the clinic. Recent data are likely to change this situation in the near future. Mutations in the EGFR and gene amplification are associated with response to gefitinib/erlotinib. However, there are clearly those who respond to gefitinib or have stabilization of disease or symptom improvement in the absence of these features. Therefore, even for this targeted drug, the situation is more complex. It is as yet impossible to predict chemotherapy response, nodal involvement or patient survival. To better understand these more complex features of cancer cells, we have used a proteomics-based approach to

classification and prediction of lung cancer biology. We have used matrix-assisted laser desorption/ionization mass spectrometry directly from 1 ng of a single frozen tissue section for profiling of protein expression from surgically resected tissues to classify human lung tumors. Class-prediction models based on differentially expressed peaks were found to classify lung cancer histologies, distinguish primary tumors from metastases to the lung from other sites as well as classify nodal involvement in both training and testing cohorts. We also obtained a proteomic pattern comprised of 15 distinct mass spectrometry peaks that distinguished resected non-small cell lung cancer patients with a poor prognosis. Many of the important discriminatory proteins have been identified and have already led to interesting potential mechanistic insights. We have also identified protein fingerprints associated with response to chemotherapy and targeted therapies. We have applied this technology to the analysis of serum samples to develop serum markers for early detection, and have a profile capable of detecting lung cancer with high specificity in a blinded test cohort.

New technologies are being developed that will allow the use of material from fine needle aspirates and greatly increase the amount of proteomic information obtained from biological samples, as well as generate protein and/or drug distribution images in tissue sections.

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INVITED

Targeted therapies in non small cell lung cancer

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The last 20 years have witnessed an explosion of knowledge in the biology of cancer. This new knowledge has permitted the development of new medicines targeted at specific molecular alterations present in cancer cells. Several of these new agents are being developed for lung cancer where multiple cellular and molecular defects have been described. Among the most common genetic alterations are p53 mutations and mutations of K-ras. However, so far no medicine has been developed that successfully targets these common genetic alterations. The ErbB family of tyrosine kinase receptors has been successfully targeted by several monoclonal antibodies and small molecules, and some of them are now available for the treatment refractory NSCLC. Two tyrosine kinase inhibitors that target EGFR (erlotinib and gefitinib) have demonstrated a response rate in about 10% of these patients and erlotinib has also demonstrated greater survival in these patients compared to best supportive care. The activity of these two drugs has been reproducibly shown to be related to the presence of EGFR mutations in the ATP binding site; other genetic abnormalities, such as amplification might also help in identifying the patients who benefit from the treatment. Prospective studies testing these drugs in selected patients will be required in order to adequately validate these markers of sensitivity. Cetuximab, a monoclonal antibody to the extracellular domain of EGFR, also has similar activity, but the presence of EGFR mutations would not seem to be important and some degree of non-overlapping activity may be expected between monoclonals and small molecules.

Angiogenesis inhibitors have also been investigated in lung cancer. Bevacizumab in combination with chemotherapy has demonstrated increased survival compared to combination chemotherapy alone in patients with non-squamous histology, without brain metastases and serious hemoptysis. Development of other angiogenesis inhibitors or multiple targeted agents is underway.

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INVITED

Image guided radiotherapy for early stage non small-cell lung cancer

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Some patients present with surgically resectable disease and have medical contraindications or refuse surgery [1]. For such patients, primary radiation therapy offers an alternative and potentially curative approach. The very good results reported with surgery for early stage disease may in part be due to the more favorable performance status of surgical patients and the fact that surgically treated patients are more rigorously staged and the results are reported by pathological stage rather than clinical stage. Most patients who receive primary radiation therapy are not surgically staged and may have occult N2 (mediastinal) disease, whereas such patients may be excluded or reported separately in surgical series.

Results of radiation alone for medically inoperable early stage lung cancer: There are many series which document reasonable survival following radical radiation alone for stage I and II cancers [2-6]. While 5-year survival from all causes may be low, the cause specific survival is often substantially higher due to high rates of intercurrent illnesses. Cause specific survival ranges from 20-50% at 5 years [7,8]. Locoregional failure (using traditional radiologic and clinical criteria) is the dominant cause of failure ranging from approximately 40-50% [8,9]. This may underestimate local failure as traditional clinical/radiologic assessment of local failure