types. Pharmacokinetic studies of these drugs will finally prepare them for evaluation in future clinical studies in childhood cancer patients.

9 INVITED

Targeted therapies for paediatric brain tumours

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Tumors of the central nervous system (CNS) as an entity represent the most common solid tumors in childhood. Despite an intensive multi-disciplinary treatment approach combining surgery, radiation therapy and chemotherapy (including high-dose regimens), 45% of children with CNS tumors still die of their disease. Moreover, current treatment protocols are at their limit of cumulative toxicities and induce significant sequelae. The recent development of targeting agents, particularly tyrosine kinase inhibitors and monoclonal antibodies, opens a new horizon for the treatment of children. Cell survival pathways through epithelial growth factor receptor (EGFR), platelet-derived growth factor (PDGFR) and insulin-like growth factor receptor 1 (IGF1-R) and downstream mediators are activated in childhood CNS tumors, although the molecular mechanism may be distinct to those found in adults. EGFR inhibition, by the small molecule tyrosine kinase inhibitors, gefitinib and erlotinib, as well as the anti-EGFR antibody nimotuzumab are currently being evaluated in children with malignant brain tumors, particularly malignant gliomas, alone or in combination with radiation therapy. Furthermore, the dual inhibition of EGFR and ErbB2 may be of advantage to reduce cell activation through their hetero-dimerization and a clinical phase II study of lapatinib is ongoing in children with relapsing brain tumors. The role of PDGFR tyrosine kinase inhibitors, such as imatinib mesylate, is not yet determined although it may be useful in PDGFR-driven tumors such as medulloblastoma and oligodendroglioma. Combination studies with irradiation or other chemotherapeutic agents will be more favored than single agent treatment. Pediatric malignancies are excellent targets for anti-angiogenic treatment and preliminary results of the first approved monoclonal anti-VEGF antibody bevacizumab and irinotecan in recurrent adult GBM are promising. Other targeted agents such as mTOR, hsp90 and PI3 kinase inhibitors as well as DNA repair modulators e.g. Poly(ADP-Ribose) polymerase (PARP)-1 inhibitors are currently under evaluation in preclinical or adult trials and may be interesting for combination treatments in children. Whether the inhibition of the Notch or SonicHedgehog signaling pathways through gamma-secretase and smoothened inhibitors, respectively, may lead to enhanced response and survival in children with primitive neuroectodermal tumors/medulloblastoma needs further evaluation, as the inhibition of cyclin D1 or multiple growth factor receptors present in the hSNF5/INI-1 deficient atypical teratoid/rhabdoid tumors, and therapies to disrupt CNS cancer stem cells. Advances in genetics and molecular biology led to the development of these targeted agents and will determine future new targets with a potential to change significantly the treatment of cancer. With a close dialog between basic researchers and clinicians, these new therapies promise the ability to improve treatment and survival in children with malignant brain tumors.

10 INVITED

Targeted therapies for acute leukaemias in children

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Stepwise optimisation of treatment protocols over the last 2 decades has led to major improvements in the survival in children with acute leukaemias, however, high risk sub-groups remain refractory to currently available therapies. Future progress may be achieved by focussing more targeted therapies at refractory high risk sub-groups and reducing the burden of therapy for those children cured with current intensive multi-agent treatment protocols. Recent developments in the understanding of the molecular basis of leukaemogenesis and the cellular processes maintaining the malignant phenotype has increased interest in the possibility of exquisitely targeted therapies. Several genetic aberrations have been identified which define poor risk sub-groups of ALL and AML which may be exploited as therapeutic targets, the most advanced examples being the BCR-ABL fusion protein and activating mutations of FLT3. Nevertheless, defining potential targets for therapeutic exploitation remains a considerable challenge with the additional complexity in leukaemia of the inherent heterogeneity of the disease. Both AML and ALL comprise a wide range of phenotypic and genotypic sub-types. Moreover, there is increasing evidence of sub-populations of leukaemic cells with properties of self-renewal, multi-potentiality and proliferative capacity, thought to constitute 'leukaemia stem cells'. To date, this has been best characterised for AML and chronic myeloid leukaemia. Unique molecular features are being defined in putative leukaemia stem cells, which may provide important novel approaches to treatment in the future. New targeted agents are being considered for potential application in the paediatric setting including several tyrosine kinase inhibitors; for example dasatinib and nilotinib in philadephia positive disease, CEP 701 and PKC 412 in FLT3 mutated disease and the antigen-directed immuno-conjugate gentuzumab ozogamicin in AML. In addition, an exciting range of new cellular targets is emerging, including within aberrantly activated signal transduction pathways implicated in the pathogenesis of acute leukaemias, for example the RAS mediated and PI3K-Akt / mTOR pathways. The successful translation of targets within these pathways into effective new treatment modalities is awaited. An overview of the potential application of novel therapeutic approaches in the management of paediatric acute leukaemias will be presented.

11 INVITED

Challenges in recruiting patients for early clinical trials

B. Morland. *Birmingham Children's Hospital, Department of oncology, Birmingham, United Kingdom*

There are many challenges facing clinicians recruiting patients into clinical trials. These challenges are compounded further when the patients being recruited are children. There are a number of separate issues to be considered. Firstly the regulatory environment in which patients are being treated. Many regulatory authorities permit the undertaking of Phase I clinical trials in children, but not all. European advice, until relatively recently did not specifically identify the importance of early clinical trlals in children for example. In many situations clinicians need to be able to demonstrate clear "benefit" to the patient being treated. With early clinical trials however this is a real challenge. The endpoint of a Phase I study, by definition is normally to reach an dose determined by toxicity, not efficacy. Indeed the concept of effectiveness as measured by conventional oncology endpoints, response etc are normally not seen in such studies.
The ethical question of conduct of Phase I trials in children often blurs into the regulatory requirements. The ethical challenges are in some senses common to all trials involving minors. The term "informed consent" is used by most clinicians involved in the process, but how many of us have stepped back from the process and asked how vaild the consent porcess is. Things are compounded further when parents act as a proxy for their child's consent, particulary in the challenging area of multiply relapsed patients where every "last ditch" effort needs to be explored by the parent. But is this in the best interest of the child? Here the clinician may have a personal dilemma acting as the advocate for the child, whilst wishing to increase recrutment into specific trials.
One area which is perhaps less understood is the whole area of cultural differences in acceptance of experimental therapies in childen. We are working in an increasingly international environment and it is invitable that some cultural differences in general approach to clinical trials are allowed for and accepted as part of the study design. Within the European consortium running early clinical trials, Innovative Therapies for Children with Cancer (ITCC) we are successfully conducting Phase I and early Phase II studies across 5 EU Member States. In so doing we have to deal with a variety of regulatory, ethical and cultural differences. We believe that well established networks such as ITCC can assist individual families and clinicians in participation in these challenging studies. In adition we believe we can be a source of shared experience and good practice for regulatory and ehtical committees.

Special session (Mon, 24 Sep, 13:30−14:30)
Increasing sensitivity of whole body imaging in oncology – a blessing or a curse?

12 INVITED

Increasing sensitivity of body imaging in oncology – a blessing or a curse? Expectations of the oncologist

I. Judson. *The Institute of Cancer Research, CR UK Centre for Cancer Therapeutics, Sutton, United Kingdom*

The so-called "Will Rogers phenomenon" is based on his quote "When the Okies left Oklahoma and moved to California, they raised the average intelligence level in both states". Stage migration occurs when more sensitive imaging techniques identify hitherto unsuspected disease, placing better prognosis patients in a worse stage category and improving the outcome in both stage groups without any change in treatment. We have to ask what such imaging improvements actually achieve in clinical management.

1. Is "stage" a useful concept outside clinical trials?
2. Is it valuable to identify more advanced stage disease in order to treat it more intensively?