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

B. Geoerger. *Institut Gustave Roussy, Department of Pediatrics and "Pharmacology and new treatments in cancer", Villejuif, France*

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

P. Kearns. *The institute of Child Health, Birmingham, United Kingdom*

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?

3. Is it useful to identify more advanced disease in order to be able to restrict invasive / toxic treatments to those patients who can benefit?

We can use stage in clinical practice as a guide to planning the multidisciplinary approach to therapy. The concept of systemic treatment intensification for poorer prognosis patients is unproven, at least in solid tumours, has been discredited in breast cancer and is still under investigation for Ewing's family tumours. This is most likely due to the very narrow therapeutic index of cytotoxic chemotherapy relative to many-fold levels of resistance of cancer cells. However, defining the presence and sites of metastatic disease can be vital to the choice of treatment, e.g. by indicating a need for systemic therapy, lymph node dissection, radiotherapy, etc.

19-FDG-PET and PET-CT are being used increasingly in routine clinical practice. PET can be used to define the treatment volume for radiotherapy and identify which patients are responding or not. PET-CT is becoming an integral part of staging prior to surgery for NSCLC. Although false positives may occur, it is possible to identify occult mediastinal nodal involvement and prevent pneumonectomy from being performed inappropriately. PET is also used to identify residual active disease after systemic treatment of Hodgkin's lymphoma and testicular tumours, requiring local therapy. MRI, including whole body STIR, can be used to identify metastatic bone disease not visible on isotope bone scan, e.g. in Ewing's. MRI may be the only means of detecting bone disease in metastatic myxoid liposarcoma. Cancer may often be a systemic disease, but local therapy is often the only curative modality. To apply it appropriately requires an accurate knowledge of the disease.

Finally, modern imaging tools are capable of telling us about the biology of a cancer and its response to molecularly targeted therapy. This is put to good use in the management of GIST with imatinib and sunitinib, where FDG-PET can be used to define response or progression within a matter of days and is used to plan local therapies such as radiofrequency ablation of liver metastases. In conclusion, improved whole body imaging techniques are capable of helping deliver genuine improvements in cancer control and should be welcomed.

13 INVITED

Whole-body MRI

H. Schlemmer. *University of Tübingen, Radiologische Diagnostik, Tübingen, Germany*

A malignant tumor is in per se a potential systemic disease. Imaging is of fundamental importance for initial and follow-up staging as serum tumor markers cannot provide information about the localization of tumor tissue and secondary complications related to possibly harmed surrounding anatomic structures. Precise staging and accurate therapy monitoring in individual patients are essential for assessing prognosis and achieving best patient outcome in terms of survival and quality of life.

High-resolution whole-body MRI is a novel and promising technique and its medical and economic is of considerable importance. Due to the provided high soft tissue contrast it is the modality of choice for local staging in a variety of tumors. The method plays particularly an important part for evaluating metastatic disease and for estimating the individual total tumor burden. Compared to CT and PET/CT it has been proven as the most accurate method for detecting metastases in the brain, abdominal organs and bone marrow. Regarding bone metastases, it is particularly more sensitive than conventional bone scintigraphy, X-ray, CT and PET/CT for different tumor types. One major drawback of MRI remains the limited accuracy for an early detection of lymph node metastases. Novel contrast media containing lymphotropic paramagnetic nanoparticles (USPIO) may help to increase the specificity. There is a need of more representative studies evaluating teh benefits of whole-body MRI versus whole-body CT end PET/CT with respect to specific tumor types and stages.

Whole-body imaging significantly increases the number of acquired images per patient. One examination comprises up to 1000 images, which all have carefully to be reviewed for the presence or absence of suspicious mass lesions consuming a notable amount of time and concentration. The time required for reading, documentation and discussion of the high number of images vary substantially, and 15−60 minutes are needed, particularly if additional images, e.g. from follow-up and/or multimodal diagnostic approaches with CT, PET or PET/CT have to be evaluated. Finally, a small number of essential images showing all relevant findings have to be sorted out and demonstrated in a fast and comprehensive manner as therapeutic decisions are increasingly based on recommendations by multidisciplinary conferences. The involved Radiologists will accordingly be faced with heavier workload, in particular as referring clinicians are getting more and more aware of a comprehensive whole-body approach probably cutting down the total time demand for imaging. Logistical implications for work flow optimization have therefore increasingly to be considered to minimize the time demand not only of the patient examination but also of the reading and reporting process. Novel ideas for redesigning the department's workflow concepts are challenging but a reasonable prerequisite for utilizing the potential of whole-body imaging technology.

14 INVITED

PET/CT: improved sensitivity and specificity in staging and therapy monitoring

G. von Schulthess. *University Hospital Zürich, Department medical radiology Clinic for nuclear medicine, Zurich, Switzerland*

Since its first worldwide introduction into clinical practice at our institution in March 2001, PET-CT has been the most rapidly growing imaging modality worldwide, developping into an annual market of over 1 billion US$. There are very good reasons for this, which have been amply documented in the last 6 years:

1. PET is well known to be highly sensitive in detecting tumor manifestations.
2. PET as most Nuclear Medicine procedures, lacks sensitivity in many settings.
3. Adding CT to PET improves – above all – examination specificity.
4. PET-CT is a more accurate examination than either PET, CT or PET and CT read side-by-side.

The purpose of this presentation is to familiarize the participant with the key indications for PET-CT in tumor staging (e.g. NSCLC) and therapy monitoring (e.g. lymphoma). As the CT portion of PET-CT can be run mainly for anatomic localization as a low dose CT, but also as full scale, contrast enhanced multi-phase CT, it is critical for the referring physician to understand, that frequently when the diagnosis is clear and staging with a cross-sectional imaging exam is to follow, referral directly to PET-CT can be made with the advantage that the resulting data are comprehensive, integrated and the patient only needs a single appointment. If CT or MR data exist from a very recent examination, a repetition of a full scale CT within PET-CT frequently is unnecessary.

While deeper insights into reading PET scans is beyond the scope of this presentation, it is a second aim to familiarize the referring physician with some important pitfalls in PET imaging. It is well known that inexperienced PET readers and particularly radiologists who have little formal PET training, are too sensitive in PET image interpretation which in turn leads to too many false positive diagnoses.

In summary, PET-CT has proven to be the staging modality of choice in many important tumors and due to its unique feature of depicting molecular processes rather than just anatomy, is rapidly gaining acceptance as excellent imaging procedure to monitor therapy

Special session (Mon, 24 Sep, 13:30−14:30)
Biosimilars in oncology and hematology – what should a physician know

15 INVITED

Open questions about biosimilars – pharmacovigilance, substitution, labelling, naming and economy

H. Mellstedt[1], H. Ludwig[2], D. Niederwieser[3]. *[1]Karolinska Institute, Dept of Oncology, Stockholm, Sweden; [2]Wilhelminenspital, Dept of Medicine, Vienna, Austria; [3]University of Leipzig, Dept of Hematology and Oncology, Leipzig, Germany*

Biosimilars are new, non-innovative biopharmaceutical agents that are "similar", but not identical to reference biopharmaceutical products. Biosimilars should provide cost savings and greater access to biopharmaceuticals; however, they are unique molecules and should not be considered generic versions of reference products. Characteristics of any biopharmaceutical are closely related to its manufacturing processes (eg, cellular expression system, extraction/purification process), many of which are proprietary information. Thus, biosimilar manufacturers cannot duplicate a reference product. Moreover, small differences between biopharmaceutical products may produce clinical differences with respect to efficacy, safety, and immunogenicity. Because of these issues, the approval process required for biosimilars is not as straightforward as that for small molecule generics. The EMEA has developed a general regulatory pathway for the approval of biosimilars. The approval process will vary according to the product category. For example, specific guidelines have been developed for biosimilar epoetins and biosimilar granulocyte colony-stimulating factors (G-CSFs). In general, the approval of biosimilars will be based on the demonstration of comparable efficacy and safety to an innovator reference product in a relevant patient population. Because clinical data for biosimilars will be limited at the time of approval, regulatory guidelines also require post-approval monitoring (ie, pharmacovigilance) to establish