244 INVITED

ITTC: a European biology and clinical research network for new drug development for children with cancer within the new European Pediatric Medicine Regulation

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Cancer is a rare disease in children. Each year, 12000 children are diagnosed with more than 60 different malignancies in Europe. Pediatric cancers represent 1% of all cancers in humans. 75% of those children will be cured with multimodality treatments that may often induce sequellae in long-term survivors. However, cancer is still the first cause of death by disease in children over one year of age. Innovative and safe therapies are urgently needed to improve further survival and quality of cure.

Many new anticancer compounds with new mechanisms of action are being developed in adults. A global pediatric development strategy needs to be set up considering the limited number of pediatric patients who may participate to early drug trials. The 4 major aims are: (1) *to improve access to new drugs for children:* the new European Regulation (to be launched in 2007) will facilitate the evaluation of anticancer medicines through the obligation to submit a Pediatric Investigation Plan and incitives for Industry which will study their compounds in children. Such a regulation proved to be effective in the USA. (2) *to choose the best candidate drugs:* biological evaluation of the role of therapeutic targets in pediatric tumors along with *in vitro* and *in vivo* evaluation of anticancer compounds in relevant pediatric tumor models will help to identify compounds being developed in adults that deserve evaluation in children. (3) *to speed up the early clinical development* with new trial designs and new pharmacodynamic endpoints through networks of well-qualified clinical centers able to meet the high quality criteria and timely–fashion recruitment. (4) *to consider the unique ethical dimension of testing new drugs in children* by improving information and participation of patients and parents.

The European Consortium for Innovative Therapies for Children with Cancer (ITCC, www.ITCCconsortium.org) is a Biology and Clinical Network that runs a clinical and translation research programm connecting new drugs, biology and the unmet needs of children with cancer. The 5 ITCC goals are: (1) *to select and prioritize adult compounds* through biology and preclinical evaluation. (2) *to identify new pediatric targets* through a fundamental and translational research project untitled KidsCancerKinome in the European Framework Program. (3) *to conduct early drug clinical evaluation* with improved methodology, and to validate the use of new pharmacodynamic endpoints and imaging. (4) to improve parents and patients information, participation and related issues. (5) *to educate and train professionals* who will develop innovative therapies, and to disseminate knowledge and results.

ITTC is composed a consortium of *9 European research laboratories* with expertise in pediatric tumor biology, pharmacology, experimental therapeutics, high-throughput technologies, and with a large mutualized biobank, and a clinical network of *32 centers* in 5 countries (France, United Kingdom, Netherlands, Italy, Germany). In addition, the Internationl Confederation of Children Cancer Parents Organisation (ICCPO) is a full member of ITCC.

Several new anticancer compounds such as imatinib, erlotinib, dasatinib, plitidepsin are currently being evaluated in children in partnership with Pharmaceutical Companies. In addition, ITCC did participate to the definition of the EMEA guidelines for the evaluation of anticancer medicinal products in children, and several ITCC members are EMEA experts.

In conclusion, ITCC is a well-structured clinical and translational research European network for new drug development for children with cancer in partnership with Pharmaceutical Companies and Regulatory Bodies.

245 INVITED

Approaches to shortening the timeline of paediatric phase I trials

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The advances in the care of children with cancer have primarily been made through the systematic investigation of a relatively small library of cytotoxic chemotherapeutic drugs and an increased understanding of the heterogeneity of childhood cancers. The past 10 to 15 years, however, have witnessed a relative plateau in outcome for most childhood cancers, and is primarily a reflection of our inability to identify and develop new therapeutic agents. The global landscape of cancer drug development has also changed, with a near logarithmic increase in the number of new agents in the clinical development pipeline. The approach to pediatric phase 1 trials however, has not changed in more than 40 years. Pediatric phase 1 studies follow adult phase 1 studies, accruing patients according to the standard 3 + 3 design. Better utilization of early phase adult trial data can improve the efficiency of pediatric phase 1 trials. The 3 patient cohort approach is inherently inefficient, with the greatest contributor to the prolonged timeline being the multiple periods of time a study remains suspended to accrual awaiting tolerability results form a cohort. Results of analyses exploring alternatives to the 3 + 3 design will be presented, including COG plans that streamline the development of targeted agents from focused phase 1 trials into randomized phase 2 studies.

246 INVITED

Imatinib mesylate in recurrent solid tumours expressing KIT or PDGFR (phase II)

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Background: Imatinib mesylate (Glivec®) selectively inhibits specific activations of the platelet-derived growth factor receptor (PDGFR), c-KIT and BCR/ABL tyrosine kinases and is approved for the treatment of chronic myeloid leukemia and gastro-intestinal stromal tumors (GIST). This study evaluated efficacy of imatinib in solid childhood tumors.

Methods: Phase II study of imatinib as single agent in children and adolescents with refractory or relapsing solid tumor expressing at least one of the receptors. Patients were to be treated at 340 mg/m^2, a dose escalation allowed to 440 mg/m^2 after 2 months in case of insignificant improvement. C-KIT, PDGFRa and b expression was determined on archive tissue sections by immunohistochemistry prior to study entry. Gene mutations, pharmacokinetics, pharmacogenetics, and positron emission tomography imaging were assessed.

Results: 36 patients, 21 boys, median age 13.7 years (2.2–22.5 y), 12 with brain tumors, 6 fibromatosis, 8 mesenchymal/bone tumors, and 10 other solid tumors, including 1 GIST and 3 chordoma, were treated at 340 mg/m^2 daily during a total of 168 months (median 1.9 months/patient, range 0.5–19). 18/36 expressed c-KIT, 10 PDGFRa, 21 PDGRb; 12 expressed more than 1 receptor. Ten patients were escalated to 440 mg/m^2 due to lack of efficacy. During the 1st month, 17 patients experienced mild toxicity (grade 1 and 2) related to study treatment: gastro-intestinal (n = 22), face edema (n = 7), asthenia (n = 5), tumor induration (n = 2), skin toxicity (n = 2), thrombocytopenia (n = 1). No partial or complete response was observed; 5 patients (2 fibromatosis, 1 GIST, 1 medulloblastoma, 1 pseudo-inflammatory tumor) experiencing durable stable disease have been under treatment for more than 12 months. Interesting tumor stabilization during 10 and 7 months, respectively, was achieved in a brain stem glioma and a renal carcinoma. Glucose uptake on 18FDG PET scan was reduced in a chordoma, although the child progressed and died due to disease. Pharmacokinetic and genetic data are currently evaluated.

Conclusions: Imatinib as single agent was well tolerated, but as used in our study failed to show measurable anti-tumor effects according to standard criteria in the pediatric malignancies studied.

247 INVITED

The development of VEGF blocking therapies for the treatment of pediatric tumours

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Blockade of vascular endothelial growth factor (VEGF) has been validated as a clinical therapy for adults with metastatic cancer. The prototypic agent is bevacizumab, a high affinity monoclonal VEGF neutralizing antibody, which received FDA approval for use in adult advanced stage colon cancer in early 2004. Despite robust preclinical data supporting the potential for tumor growth inhibition in xenograft models of solid embryonal tumors of childhood, pediatric development of this class of agents has been delayed due to concerns of adverse effects on growth and development: specifically, the preclinical finding of physeal dysplasia in juvenile monkeys. A phase I dose escalation study of bevacizumab administered by IV infusion every 2 weeks in children with clinically refractory solid tumors was conducted through the Children's Oncology Group (COG). Cohorts were enrolled at dose levels of 5, 10, and 15 mg/kg; the final dose level was expanded to include at least 3 children under 6 years of age. Minimal adverse effects were seen, with no dose-limiting toxicities observed and a maximum tolerated dose not reached. Non-dose limiting, grade 1–2 toxicities included infusional reaction (n = 3), rash (n = 3), mucositis (n = 2), and proteinuria (n = 3). There was no hemorrhage or thrombosis reported. Analysis of blood pressures revealed subtle but statistically significant increases in