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Commentary

Commentary on "European collaboration in trials of new agents for children with cancer" by Ablett et al.

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Abstract

Recent progress in establishing a European network to conduct paediatric oncology phase I/II clinical trials calls attention to the challenges facing researchers developing new agents for children with cancer. These challenges include: ensuring that effective infrastructures are in place to safely and efficiently conduct early phase clinical trials in children while meeting all ethical and regulatory requirements associated with such trials; obtaining timely access to new agents from pharmaceutical sponsors for both preclinical testing and for phase I and phase II testing; and effectively prioritizing new agents for evaluation in children so that those agents most likely to benefit children with specific cancers are brought forward for clinical testing. The use of public funds to develop and maintain clinical trials infrastructures devoted to paediatric oncology drug development can help in addressing these challenges and can facilitate the timely paediatric evaluation of new agents, thereby contributing to the goal of identifying more effective treatments for children with cancer.

The report from Dr. Ablett and colleagues is a welcome addition to the oncology literature and addresses important strategic issues in European paediatric oncology drug development. The challenges faced by European researchers as they bring new agents into the treatment armamentarium of paediatric oncologists are much the same as those faced by researchers in North America. The potential solutions are also similar on both continents. We see three key challenges. The first is to ensure that effective infrastructures are in place to conduct early phase clinical trials safely and efficiently whilst meeting all applicable ethical and regulatory requirements. Second, paediatric researchers need to have timely access to new agents for preclinical testing and for phase I and II studies. Third, researchers need to prioritise these new agents for evaluation so that those most likely to benefit children with specific cancers are expeditiously brought forward for clinical testing. We now address each of these challenges.

Dr. Ablett and colleagues are to be commended for the steps they have taken in addressing the first challenge, the establishment of an infrastructure for the timely and safe conduct of early phase clinical trials in children with cancer. This clinical trials infrastructure must perform well across each stage of protocol development and clinical study conduct, ranging from preparation of the initial protocol document by a study committee working with its operations centre, to timely reporting of patient toxicity data and submission of relevant blood and tissue samples by participating institutions, to data analysis and reporting of results by the study team. Staff at both ends of this process must have experience and expertise in the distinctive ethical and regulatory requirements that govern research in children and should be appropriately trained to follow good clinical practice in clinical trials. Establishment of a common, stable clinical trials infrastructure helps researchers to apply the experience gained during the conduct of each trial to the development and conduct of future studies, and it reduces the costs and delays that often occur when researchers have to start each new protocol *de novo* (i.e., "reinventing the wheel"). The relatively small number of children diagnosed annually with cancer means that the childhood cancer market is of limited interest to pharmaceutical companies. Hence,

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public resources are needed to support paediatric clinical trials infrastructures by providing the stable funding required to recruit and maintain research teams both at the Operations/Statistical Centre and at participating institutions.

The second challenge – to gain timely access to new agents from pharmaceutical sponsors for preclinical evaluations and for phase I and II testing – has been addressed by the Paediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee of the United States (US) Food and Drug Administration (FDA). The subcommittee recommended that, in general, paediatric oncology clinical studies should be initiated as soon as phase I studies in adults have been completed (http://www.fda.gov/cder/cancer/Presentations/phaseone.htm). Decisions as to when to initiate individual paediatric oncology studies should consider the type of agent, its putative mechanism of action, its known safety profile, and its potential clinical indications.

Dr. Ablett appropriately draws attention to US legislation that provides financial incentives to industry in exchange for performing paediatric studies [1]. These inducements have begun to increase the interest of pharmaceutical sponsors in studying their anticancer agents in children in the US. Providing pharmaceutical companies in Europe with similar incentives will presumably have much the same influence, although the global nature of the pharmaceutical industry may blunt the additive effect. Incentives aimed at encouraging pharmaceutical sponsors to study their new agents in children must build in concomitant safeguards to assure that financial interests do not assume undue influence over scientific merit and clinical need in prioritising new agents for study.

Other steps to enhance the flow of new anticancer agents from industry into paediatric evaluations are the development and promulgation of standard procedures and the establishment of a track-record for the conduct of early phase clinical trials. Pharmaceutical sponsors need to be assured that the new agents they provide will be properly and expeditiously evaluated using accepted norms for clinical trials conduct in children. Establishment of the Joint French/United Kingdom (UK) collaboration described by Dr. Ablett and the 17 studies of 10 different drugs conducted through this collaboration are important steps in establishing the necessary track-record that can provide industry with greater comfort for testing their new agents in this age group. Similarly, in North America, the National Cancer Institute (NCI) has established cooperative agreement funding mechanisms with the Children's Oncology Group (COG) Phase I/Pilot Consortium and with the Paediatric Brain Tumour Consortium to conduct early phase paediatric clinical trials. By providing a consistent source of funds to a limited set of experienced clinical institutions and their associated Operations/Statistical centre, the NCI has established clinical trials infrastructures that are attractive to industry because of their experience and expertise in developing, implementing and reporting early phase paediatric clinical trials.

The third challenge – prioritising agents for evaluation in children – may seem paradoxical following a discussion about the difficulty in obtaining new agents from industry. Delayed access to new agents has severely limited paediatric drug developers. However, the number of potential paediatric phase II and pilot studies that can be conducted, based on reasonable scientific rationale, will usually exceed the number that can actually be performed. Taking neuroblastoma as an example, a number of single agent phase II studies and/or studies of combination regimens including new agents are either ongoing or under consideration, including evaluations of the following: the demethylating agent decitabine [2,3], fenretinide [4,5], interleukin-12 [6], Trk tyrosine kinase inhibitors [7–9], the platinum analogue oxaliplatin [10], and histone deacetylase inhibitors such as SAHA and depsipeptide [11,12]. Paediatric researchers do not yet have a rational means for determining the priority that should be assigned to each of these agents.

Developing a systematic approach to the preclinical testing of new agents in relevant Paediatric Cancer models should make a positive contribution to prioritising new agents for evaluation in children. The US NCI is establishing a Paediatric Preclinical Testing Programme (PPTP) that will study 10–15 new agents (or combinations of agents) annually against a panel of paediatric *in vitro* and *in vivo* models for the most common childhood cancers (e.g., acute lymphoblastic leukaemia, neuroblastoma, rhabdomyosarcoma, osteosarcoma, Ewing's sarcoma, and medulloblastoma). Testing is scheduled to begin in the second half of 2004. Data developed by the PPTP should be increasingly useful for prioritisation as the predictive value of the programme's tumour panels is better understood.

We commend Dr. Ablett and colleagues for promoting a network for phase I and II clinical trials in paediatric oncology between several European countries. The goals of their proposed Innovative Therapies for Children with Cancer (ITCC) project are laudable. When implemented, the project should make important contributions to the effective development of new agents for children with cancer. The use of public funds to develop and maintain such clinical trials infrastructures will surely encourage and facilitate the timely evaluation of new agents, thereby contributing to the identification of more effective treatments for children with cancer.

References

1. Hirschfeld S, Ho PT, Smith M, Pazdur R. Regulatory approvals of pediatric oncology drugs: previous experience and new initiatives. *J Clin Oncol* 2003, **21**(6), 1066–1073.

2. Yang QW, Liu S, Tian Y, Salwen HR, Chlenski A, Weinstein J, *et al*. Methylation-associated silencing of the thrombospondin-1 gene in human neuroblastoma. *Cancer Res* 2003, **63**(19), 6299–6310.
3. Teitz T, Wei T, Valentine MB, Vanin EF, Grenet J, Valentine VA, *et al*. Caspase 8 is deleted or silenced preferentially in childhood neuroblastomas with amplification of MYCN. *Nat Med* 2000, **6**(5), 529–535 [see comments].
4. Maurer BJ, Melton L, Billups C, Cabot MC, Reynolds CP. Synergistic cytotoxicity in solid tumor cell lines between N-(4-hydroxyphenyl)retinamide and modulators of ceramide metabolism. *J Natl Cancer Inst* 2000, **92**(23), 1897–1909.
5. Lovat PE, Ranalli M, Bernassola F, Tilby M, Malcolm AJ, Pearson AD, *et al*. Synergistic induction of apoptosis of neuroblastoma by fenretinide or CD437 in combination with chemotherapeutic drugs. *Int J Cancer* 2000, **88**(6), 977–985.
6. Wigginton JM, Wiltrout RH. IL-12/IL-2 combination cytokine therapy for solid tumours: translation from bench to bedside. *Expert Opin Biol Ther* 2002, **2**(5), 513–524.
7. Jaboin J, Hong A, Kim CJ, Thiele CJ. Cisplatin-induced cytotoxicity is blocked by brain-derived neurotrophic factor activation of TrkB signal transduction path in neuroblastoma. *Cancer Lett* 2003, **193**(1), 109–114.
8. Ho R, Eggert A, Hishiki T, Minturn JE, Ikegaki N, Foster P, *et al*. Resistance to chemotherapy mediated by TrkB in neuroblastomas. *Cancer Res* 2002, **62**(22), 6462–6466.
9. Evans AE, Kisselbach KD, Liu X, Eggert A, Ikegaki N, Camoratto AM, *et al*. Effect of CEP-751 (KT-6587) on neuroblastoma xenografts expressing TrkB. *Med Pediatr Oncol* 2001, **36**(1), 181–184.
10. Riccardi A, Ferlini C, Meco D, Mastrangelo R, Scambia G, Riccardi R. Antitumour activity of oxaliplatin in neuroblastoma cell lines. *Eur J Cancer* 1999, **35**(1), 86–90.
11. Coffey DC, Kutko MC, Glick RD, Butler LM, Heller G, Rifkind RA, *et al*. The histone deacetylase inhibitor, CBHA, inhibits growth of human neuroblastoma xenografts *in vivo*, alone and synergistically with all-trans retinoic acid. *Cancer Res* 2001, **61**(9), 3591–3594.
12. Glick RD, Swendeman SL, Coffey DC, Rifkind RA, Marks PA, Richon VM, *et al*. Hybrid polar histone deacetylase inhibitor induces apoptosis and CD95/CD95 ligand expression in human neuroblastoma. *Cancer Res* 1999, **59**(17), 4392–4399.