CLINICAL INVESTIGATION

EDITORIAL

Clin. Invest. (2013) 3(2), 101–103

Challenges in incentivizing the pharmaceutical industry to supporting pediatric oncology clinical trials

Paola Angelini[1], Kathryn Pritchard-Jones[2] & Darren R Hargrave*[1]

"The system of mandatory requirements for pediatric trials and financial rewards to pharmaceutical companies has not translated into an increase in the number of clinical trials, or of drugs with pediatric indications, so far."

In high-income countries cancer is the leading cause of disease-related death in children older than 1 year of age and therefore represents a significant public health burden. However, pediatric cancer represents only approximately 1% of all cancer cases in the Western world and all childhood cancers are individually rare (incidence <6/100,000 per year) [101]. Pediatric oncology is therefore of negligible significance to pharmaceutical companies, compared with the adult market. Historically, several additional noncommercial barriers have also been highlighted as possible blocks to drug development in childhood cancer: rare populations leading to slow accrual and small samples sizes for conventional trial designs, the need for suitable pediatric formulations (tablets and capsules are less appropriate than intravenous or liquid formulations), concerns for both acute and long-term safety in the developing child and anxiety over real and perceived ethical difficulties in studying new agents in this vulnerable population [1]. This has meant that pediatric oncologists have been obliged to prescribe drugs off-label as there is no suitable alternative and the dose and schedule are often empirical, based on extrapolation from adult data and historical experience of relatively safe usage, without appropriate pharmacokinetic information.

To try and tackle this gridlock, the regulators on both sides of the Atlantic have tried to incentivize and mandate pediatric investigations in order to license a drug for an adult indication. The USA led the way with the Best Pharmaceutical for Children Act (initiated in 2002) [101], which issues written requests to a company with regard to pediatric development, the incentive being additional exclusivity. This voluntary process is augmented by the Pediatric Research Equity Act (initiated 2003) [102], which can mandate studies in children when the same indication exists in adults. Europe has followed with the regulation of the European Parliament on medicinal products for pediatric use (EC) 1901/2006 [103,104]. The aim of the regulation was to increase the availability of safety information on drugs in children, without undue delay in licensing of drugs for adult indications. The regulation made a Pediatric Investigation Plan (PIP) mandatory for any new drug, at the end of the Phase I trials in adults and there was an incentive of an extension of 6 months to the patent for the relevant adult indication. However, both the US and European programs have allowed waivers based on adult disease indications and have failed to recognize the potential for the effectiveness of therapy when based on biology rather than tumor classification.

Keywords: cancer • children • clinical trials • drug development • incentives • investigation plans • pediatric oncology • pharmaceutical • regulators

[1]Pediatric Oncology Unit, Great Ormond Street Hospital for Children NHS Foundation Trust, Great Ormond Street, London, WC1N 3JH, UK
[2]Institute of Child Health, University College London, 30 Guilford Street, London, WC1N 1EH, UK
*Author for correspondence:
Tel.: +44 207 829 8832
Fax: +44 207 813 8588
E-mail: darren.hargrave@nhs.net

ISSN 2041-6792
10.4155/CLI.12.150

As of October 2012, the US regulations had led to just 15 cases of new pediatric labeling information for oncology drugs on the US FDA website (Pediatric Labeling Information Database) [101]. In Europe, pediatric development was waived in 63% of adult oncology conditions (197/313 reviewed from April 2008 to April 2012) despite the pediatric committee identifying possible potential for pediatric use for many of the medicines [2,105].

In the 5 years since the implementation of the European and a decade after the initial US regulations, it is time to review their efficacy in promoting pediatric oncology clinical trials, and rethink approximately how to incentivize companies to support pediatric oncology clinical trials.

Working together focusing on the child

To date, companies have been focused on adult patients. Drugs to be developed are selected based on their preclinical activity on adult cancers and prepared in formulations with the best acceptance in adults (e.g., oral tablets). Pediatric trials are performed because of the mandatory requirement in order to obtain the license for the adult indications, and in view of the financial reward. Prolonged delays have been observed in the presentation of PIPs (median 35 months) and not all PIPs presented have been completed [2,3]. Actually, it is normal practice for the companies to stop the development of a drug if the interest for the adult population of patients vanishes. In some cases, an intravenous formulation has been developed and subsequently the production was discontinued due to a preference for oral tablets, thus making the drug inaccessible to a considerable number of children because of their size or age. As previously stated, waivers have been widely requested, based on diseases, rather than mechanisms of action resulting in delayed pediatric investigations; for example, ALK inhibitors being granted a waiver because their adult indication (lung cancer), does not affect children, although there is strong evidence suggesting that ALK plays a role in two pediatric malignancies – neuroblastoma and anaplastic large-cell lymphoma [105].

In this system drugs that are potentially of great interest in pediatrics, but without an adult indication are not likely to be tested in clinical trials. This is of particular concern, since the pathogenesis of pediatric cancer is largely different from adult cancer.

One could foresee how a model based on pediatric cancer priorities and strong collaboration between academia, pharmaceutical companies and regulators could be more effective in delivering successful pediatric oncology clinical trials. Pediatric oncologists have a long-standing history of strong, worldwide collaboration. Most Phase III trials are multinational and consortia have been created both in Europe and in the USA to test potential new drugs *in vitro* and *in vivo*, and to perform early clinical trials [4,5]. The European regulation itself has fostered the creation of a network of excellence on pediatric oncology and a pediatric committee within the European Medicine Agency, to provide scientific advice to the companies. Most biological and genetic research happens in the universities. We could envision the pediatric oncology academic community performing preclinical testing and selecting the strongest candidates with pharmaceutical companies and regulators to prioritize for clinical trials. If a noncompetitive model could be developed and agreed with industry and regulators, it would be possible for academic collaborative groups to have a portfolio of high-priority new agents based on mechanism of action for childhood cancer. This would allow promising novel therapies to be studied in parallel and sequentially using innovative biomarker-led trial designs, (e.g., multi-arm Bayesian adaptive designs) to allow for more feasible, efficient and expedited clinical trials.

Promoting joint working

To facilitate this new model of noncompetitive collaborative working between academia, pharmaceutical firms, regulators and, ideally, patient and family representatives, will require a change in the current regulations, funding models and industry culture.

Existing regulations should be amended to consider mandatory pediatric investigations based on biology and mechanism of action rather than tumor indication. Pharmaceutical companies would obtain a waiver for drugs that have mechanisms of action that are not relevant or deemed low priority in pediatric oncology. We would suggest that more flexible incentives such as transferable rewards (patent extensions) or credit for alternative or future products might more successfully promote the development for drugs specifically for childhood cancer, even when there is no adult indication. The other area of regulation that may need to be amended is the European Clinical Trials Directive (Directive 2001/20/EC, Directive 2001/83/EC and Regulation [EC 776/2004]), issued in 2001 [106]. Despite the laudable goals to standardize regulations in Europe and ensure patients' safety, it has quickly proved to increase the bureaucratic and administrative burden on the sponsor, with soaring costs and delays in trial opening, particularly affecting academic-led trials. The Clinical Trials Directive will be reviewed at the end of 2012. In view of this revision, the International Society of Pediatric Oncology – Europe has been lobbying to obtain the implementation of significant changes to reduce the burden and costs associated with the current regulations.

Public funding has boosted clinical trials in the USA, but is not available in Europe. Pediatric oncology drug development should become a priority in the European agenda, given that cancer represents the leading cause of death in children older than 1 year of age, and public funds should be made available for not only investigating the biology of childhood cancer, but also to fund preclinical and clinical pediatric trials. As part of the joint working relationship, the pharmaceutical industry could commit to a joint public–private funding initiative to support this new model.

It would be hoped that industry would recognize that the new model and suggested changes to the regulations and incentives would have significant benefits for them and would result in a change in culture, promoting development of novel therapies specifically against childhood cancers.

Conclusion

The system of mandatory requirements for pediatric trials and financial rewards to pharmaceutical companies has so far not translated into an increase in the number of clinical trials, or of drugs with pediatric indications. New measures are therefore advocated.

Pediatric oncology clinical trials have been considered so far as ancillary to the adult trials. The biological evidence that pediatric cancer has a different pathogenesis than adult cancer is becoming ever stronger, and provides the rationale to plan pediatric trials separate from adults' trials, focusing on the most promising compounds/mechanisms of action. A new noncompetitive model should be developed involving scientists, pediatric oncologists, pharmaceutical companies, regulators and patient representatives. This will require amendments to reduce unnecessary regulatory burden and to mandate and promote pediatric investigations based on science and by using more flexible incentives. Public–private funding should be sought to adequately resource biological, preclinical models and innovative clinical trials in pediatric oncology. This would translate into more successful trials, to the benefit of the children and all stakeholders.

Financial & competing interests disclosure

DR Hargrave has worked as an advisor/consultant for AstraZeneca, Boehringer-Ingelheim, Glaxo-Smith-Kline, Merck-Sharp-Dhome, Merck-Serono, Pfizer and Roche. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

References

1 Boklan J. Little patients, losing patience: pediatric cancer drug development. *Mol. Cancer Ther.* 5(8), 1905–1908 (2006).

2 Saint-Raymond A, Herold R. Medicines for pediatric oncology: can we overcome the failure to deliver? *Expert Rev. Clin. Pharmacol.* 5(5), 493–495 (2012).

3 Olski TM, Lampus SF, Gherarducci G, Saint Raymond A. Three years of pediatric regulation in the European Union. *Eur. J. Clin. Pharmacol.* 67(3), 245–252 (2011).

4 Houghton PJ, Morton CL, Tucker C *et al.* The pediatric preclinical testing program: description of models and early testing results. *Pediatr. Blood Cancer* 49(7), 928–940 (2007).

5 Zwaan CM, Kearns P, Caron H *et al.* 'Innovative therapies for children with cancer' European consortium. The role of the 'innovative therapies for children with cancer' (ITCC) European consortium. *Cancer Treat. Rev.* 36, 328–334 (2010).

Websites

101 US Cancer Statistics: Childhood Cancer Data. http://apps.nccd.cdc.gov/uscs/ChildhoodCancerData.aspx

102 US FDA. Pediatric legislation. www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm

103 European Medicine Agency. Medicines for children. www.emea.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000023.jsp&mid=WC0b01ac05800240cd

104 Regulation of the European Parliament and of the Council on medicinal products for pediatric use. Regulation (EC) No 1901/2006. http://ec.europa.eu/enterprise/sectors/pharmaceuticals/files/eudralex/vol-1/reg_2006_1901/reg_2006_1901_en.pdf

105 Class waivers agreed by the Pediatric Committee. www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000036.jsp&mid=WC0b01ac05801177cd

106 Legal framework governing medicinal products for human use in the EU. http://ec.europa.eu/health/human-use/legal-framework/index_en.htm