

## Making paediatric precision oncology a reality

Despite accounting for only 1% of all cancers, childhood cancer is the leading disease-related cause of death in children in both the USA and the UK. In a report released in September, 2016, to coincide with Childhood Cancer Awareness Month, the American Cancer Society and the Alliance for Childhood Cancer summarise progress in paediatric cancers, and highlight research gaps and ongoing challenges in these rare but devastating diseases.

Substantial progress in childhood cancer treatment has been achieved in recent decades. 5-year survival has improved greatly, increasing from 63% in children diagnosed between 1975–79 to 84% in those diagnosed in 2005–11. However, some childhood cancers remain difficult to treat. For example, 5-year survival is now 78% for neuroblastoma overall, but only 40–50% for some high-risk subtypes, and some tumours, such as diffuse intrinsic pontine glioma, are almost always fatal. Additionally, many childhood cancer survivors suffer late effects as a consequence of treatments administered during vulnerable phases of development: more than 40% of childhood cancer survivors aged 35 years or older have experienced severe or life-threatening treatment-related health problems and much still remains to be done to meet the health and psychosocial needs of long-term survivors.

Drug development for childhood cancers is a particularly difficult area. Paediatric cancers are rare, many tumours are unique to children, and drugs developed for adults do not have the same effect or activity in children. Consequently, specific paediatric oncology trials are needed. However, the high cost, complexity, and likelihood of a low return make pharmaceutical companies reluctant to invest in research and drug development for childhood cancers. Children with cancer are often only granted access to experimental drugs in exceptional situations through compassionate use or early access schemes. Moreover, children's participation in trials is not always feasible. Special ethical protection afforded to children states that there must be a potential benefit to every child enrolled in a clinical trial, and the process of obtaining informed consent is complicated. The small numbers of children affected by specific cancer types also creates competition between different research projects to enrol potential participants.

So, what can be done to accelerate research and drug development in childhood cancers? Incentives are needed

to encourage investment in paediatric cancer-specific research or in the further development of drugs already approved for adult indications. Some progress has been made here: the USA's 2003 Pediatric Research Equity Act (PREA) requires sponsors who are developing a drug for adult indications to also test the drug in children with the same condition. However, since rare orphan diseases affecting fewer than 200 000 people nationwide are exempt, PREA has had little effect on drugs for rare childhood cancers. In July, 2016, the Research to Accelerate Cures and Equity (RACE) for Children Act was introduced to the US Congress. RACE would require companies to apply PREA to any treatment with a molecular target that is relevant to both an adult and a childhood disease. Meanwhile, the European Society of Paediatric Oncology is calling for revisions to the EU Paediatric Medicine Regulation to expedite the paediatric development of oncology drugs to increase young patients' access to innovative therapies. Trial design also needs to be flexible to solve the problem of a limited pool of children with cancer who can participate. Adaptive designs that allow modification of the trial as it proceeds help to address uncertainty during study planning. Master or umbrella protocols, which consolidate several different studies of various targeted drugs into one large trial, increase the size of the patient pool. Networks and consortia that facilitate sharing of research data between trial groups can also ensure that trial sizes are sufficiently large to achieve reliable results.

In an era of rapid progress in targeted therapies against cancer, we must ensure that children do not miss out. Precision oncology increasingly offers new treatment solutions in adult cancers; this approach must be redeployed to the paediatric setting. The US National Cancer Institute's Moonshot Blue Ribbon Panel has identified the targeting of fusion oncoproteins in childhood cancer—a major driver of many childhood tumours—as a key priority to accelerate progress in cancer research. Such goals, in combination with increasing children's access to existing appropriate therapies, encouraging investment in new drug research and development, and re-evaluating trial designs for children, are all essential to help overcome the difficult, but surmountable, challenges unique to this small yet important patient population. ■ *The Lancet Oncology*



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For the report see <http://www.cancer.org/acs/groups/content/@editorial/documents/document/acspc-048347.pdf>