

Let kids be kids

New treatments have greatly improved the survival rates of children. However, evidence is now starting to emerge that the level of treatment given to children is unnecessarily high. At this year's annual meeting of the American Society for Therapeutic Radiology and Oncology (Atlanta, GA, USA; Oct 5–7, 2004), researchers showed that children with Hodgkin's disease do not always need adjuvant radiotherapy to reduce their chance of recurrence. Furthermore, a recent study in *The Lancet* (2004; **364**: 1229–35) showed that the duration of postoperative chemotherapy for patients with stage I intermediate risk and anaplastic Wilm's tumour could be shortened to less than a quarter of the standard 18 weeks while maintaining the same event-free survival. So why is the quality of life for children being jeopardised by such unnecessary levels of treatment?

Because of the nature of cancer, initial treatment tends to be aggressive to lower the risk of recurrence. But we are now starting to see the first generation of children who were treated for cancer emerge into adulthood, and the late effects of such aggressive treatments are only now becoming evident. For example, survivors of cancer have an increased risk of heart disease, and radiation can impair the development of children's bones and muscles. It is therefore imperative that treatment for children maximises the chance of event-free survival, but minimises the possibility of late effects, especially in children with early-stage cancer or who go into remission immediately after the first course of treatment.

Because more than 50% of drugs in Europe have not been tested, or approved, for use in children and adolescents, they often need to be used in the off-label setting. Traditionally, the optimum regimen for children was calculated by adjustment of data obtained from adults according to the child's weight or height, and this approach is still used in many circumstances today. However, children are not just small adults; growth and development greatly affects the side-effects of drugs, and the dose and duration of treatment needed depends on a range of physiological variables. But age is also an important factor. It affects the severity of disease, pathological agents, and natural history, and these factors change not just between childhood and adulthood, but all along the continuum

of childhood. Extrapolation of data from adults is now widely accepted not to be the best approach; however, this recognition has not been followed through in all circumstances. The testing of drugs in children has been limited because pharmaceutical companies often do not receive much revenue from children's drugs, recruitment of children to clinical trials is difficult, and because investigators are unwilling to risk side-effects in children. Consequently, the drugs that have been adequately tested in the paediatric setting have tended to be those used for common childhood illnesses, which have a good market potential.

However, these issues are now starting to be addressed. In December, 2003, the USA adopted the Pediatric Research Equity Act, which mandates that all licensing applications of new drugs in the USA must contain information about the drug's effect on children or include a waiver request if the drug is not likely to be used in a substantial number of children. A similar proposal was adopted by the European Commission on Sept 29, 2004. These regulations have been coupled with financial incentives to pharmaceutical companies in the form of 6-month patent extensions for drugs that have also been tested in children. As a result of these incentives, investment in paediatric and adolescent research is likely to increase. It is important that this research is of the highest quality, that children are not put at unnecessary risk, and that the same stringent rules applied to adult research are carried through to studies involving children.

The over-treatment of children is ironic when you consider that the first anticancer chemotherapy resulted from research done in children with leukaemia in 1947, and that the current stringent regulations for testing drugs in adults were developed mainly in response to the effects of drugs on children seen in the 1950s and 1960s. Research into cancer treatment for children needs to take into account the biological factors that change with age, and, in particular, the increased vulnerability to late effects in younger people. Children should no longer just receive a scaled-down version of adult treatment—they should receive the same level of clinical excellence afforded to adult medicine.

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