Challenges in Paediatric Oncology at the Onset of the 21st Century

a report by

Raphaël F Rousseau[1] *and* **Thierry Philip**[2]

1. Professor of Oncology, Institute for Paediatric Haemato-oncology, and Head, Paediatric Translational Research Programme, Léon Bérard Comprehensive Cancer Centre, Lyon; 2. Professor of Oncology, University Claude Bernard, and CEO, Léon Bérard Comprehensive Cancer Centre, Lyon

DOI: 10.17925/EOH.2007.0.2.19

Cancer is predominantly a disease of adults and the elderly. Fifty per cent of cancers occur after the age of 70 years, and 150,000 new cancers are diagnosed in France every year. Most adult cancers are slow-growing adenocarcinomas. In contrast, childhood cancers (occurring before the age of 16 years) represent around 1% of all cancers, with 2,000 new cases every year in France. Paediatric cancers are very different from adult cancers. Most paediatric tumours are made of immature and undifferentiated tissues with a high proliferation potential. Childhood cancers represent a multifaceted model. Seventy-five per cent of paediatric tumours can be cured upfront, multidisciplinary treatment shared between various physicians has been widely implemented for several decades and the patient–physician relationship is a '*dialogue à quatre*' between the physician, the patient and his/her two parents. Childhood cancers are also a model for research, as long-term quality of life and minimisation of sequels in a growing body must be taken into account from the onset. Forty-three per cent of paediatric cancers are haematopoietic malignancies (of which 30% are acute leukaemias and 13% non-Hodgkin's lymphomas). Solid tumours consist of central nervous system tumours (20%), neuroblastomas of the adrenal gland or the sympathetic nodes (10%), sarcomas of the muscle (7%), renal or Wilm's tumours (6%) and osseous sarcomas, including Ewing sarcomas, and osteosarcomas (5%). Tumours of the retina and liver and several adult-like tumours complete the global picture of childhood cancers.

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Management of childhood cancer is a multidisciplinary endeavour, including general paediatricians (who rarely see more than two cases of childhood cancer in their entire career) and general practitioners. The role of several specialists is fundamental in early treatment of the disease. Pathologists and diagnostic imagers with a solid background in paediatrics are particularly important. Bad news is broken in two steps. It is first discussed where the diagnosis is made, and then in the specialised paediatric unit in which specific treatment will take place. Whatever the age of the patient, one must first explain the disease to the parents and then to the child. Several interviews will be necessary to help parents manage the initial shock of a cancer diagnosis and proceed to a more constructive emotional phase, where they will be able to ask specific and practical questions. Siblings, family members and school friends will also require specific information and care.

Treatment almost always consists of a combination of chemotherapy and surgery, usually in that order. Radiation therapy is used as rarely as possible during the curative phase due to the likelihood of irreversible sequels in this age group. Brain tumours and retinoblastomas usually require this particular treatment modality, and sarcomas may require radiation for local control or in cases of relapse. Since the 1990s, chemotherapy has become the main tool for treatment of childhood cancer. Treatment design must take into account efficacy, quality of life and long-term sequels.

Childhood cancer therapy can be seen to encompass two lines of enquiry. The first applies to children with good prognosis, in whom the future is the priority. The important question in this patient group is 'what price should be paid for a cure?' Burkitt's lymphoma (90% cure rate), acute leukaemias and lymphomas (>80% cure rate), Wilm's tumours (80% cure rate), Hodgkin's lymphoma (80% cure rate), localised neuroblastomas (70–90% cure rate), osteosarcomas (75% cure rate) and retinoblastomas (85% cure rate) fall into this category. The second group of patients is made up of those for whom 'cure has a heavy price'. Ewing's sarcomas

Raphaël F Rousseau is a Professor of Oncology at the University Claude Bernard, Lyon and an Adjunct Assistant Professor of Paediatrics at Baylor College of Medicine in Houston, Texas. He is also Head of the Paediatric Translational Research Programme at the Institute for Paediatric Haemato-Oncology at Léon Bérard Comprehensive Cancer Centre in Lyon, France. His laboratory at INSERM U590 at Léon Bérard Cancer Centre focuses on immunotherapy of paediatric and adult malignancies using gene-modified tumour cells and/or immune effectors. He also works on new technologies using nanoparticles to improve detection and treatment of solid tumours. Dr Rousseau serves as an expert in medical biotechnologies for the treatment of cancer in several national and international regulatory agencies and scientific societies. He is the co-ordinator of a large EU-funded research consortium dedicated to the immunotherapy of children with cancer (CHILDHOPE). Dr Rousseau received his MD from the University René Descartes, Paris, and his PhD from University Denis Diderot, Paris. He is board-certified in paediatrics and paediatric oncology.

E: roussea@lyon.fnclcc.fr

Thierry Philip is a Professor of Oncology at Claude Bernard University and CEO of Léon Bérard Comprehensive Cancer Centre in Lyon. He is an elected member of the International Society of Pediatric Oncology (SIOP), the American Society of Clinical Oncology (ASCO) and the International Society of Experimental Hematology (ISEH). He has served on the Editorial Boards of a number of national and international journals, including *Bone Marrow Transplantation*, *Pediatric Hematology and Oncology* and the *Journal of Experimental & Clinical Cancer Research*. He graduated from the Academic Hospitals of Lyon.

(50% cure rate), medulloblastomas (50% overall survival), metastatic neuroblastomas (25% cure rate) and high-grade gliomas (<5% cure rate) fall into this category.

Progress in supportive care has rendered immediate complications manageable, mainly reversible alopecia, nausea and vomiting, pain and blood cell alterations. Long-term toxicity has to be balanced with the risks of disease relapse. Specific toxicities include cardiac toxicity with anthracyclines, deafness with platinum salts, lung toxicities due to radiation therapy and bis-chloroethyl nitrosourea (BCNU), neurocognitive damages with radiation therapy (especially in children below the age of three years), renal toxicity with ifosfamide, methotrexate and platinum salts, sterility and the risk of second tumours (especially with alkylating drugs).

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Children with refractory tumours are the subjects of advanced and carefully designed research throughout treatment. While fewer than 20% of adult patients are enrolled in clinical trials attempting to improve current treatment modalities, most, if not all, paediatric patients are treated at some point in their disease with experimental strategies, ranging from new combinations of known drugs to experimental new molecules. Overall, research in paediatric cancers aims to answer one of two questions. First, why does a cell become cancerous? Answering this question requires innovative research tools at the gene or protein levels, e.g. wide-array genomics and proteomics that have benefited greatly from the recent progress in molecular biology and bioinformatics. These strategies aim at identifying not only diagnostic and prognostic markers, but also – and most importantly – targeted therapies that counteract a specific deficient molecular pathway within the tumour cell itself. Second, why is a cancer cell not eliminated from the body? The answer lies in the field of immunology and its upshot, immunotherapy, which is not widely developed in children with cancer, despite promising prospects.

As childhood cancers are rare, progress can proceed only with collaborative efforts at national and international levels. In fact, numerous prospective clinical trials are planned by several national scientific societies, including the French Society for Paediatric Cancers (SFCE), the UK Children's Cancer Group (UKCCG) and the International Society for Paediatric Oncology (SIOP). Transatlantic co-operation is under way between the main European childhood cancer societies and the US Children's Oncology Group (COG). Recently implemented EU regulations now directly or indirectly govern (via national regulatory agencies) paediatric biomedical research, including prospective clinical trials. Paediatric oncologists in Europe have united to form the Innovative Therapies for Children with Cancer (ITCC) network, which is dedicated to bringing new anticancer drugs to highly selected children. With direct input from the industry, several drugs have already gone through ITCC's pipeline and reached phase III studies. Recent legislation (passed by EU and US governing bodies) encourages the pharmaceutical industry to provide new molecules to paediatric oncology consortiums. Under these specific regulations, pharmaceutical companies are given incentives to facilitate paediatric assessment of drugs approved in adults. The most obvious incentive for pharmaceutical companies is the possibility of extending the duration of patent protection on their drug portfolio.

Beyond this pragmatic (albeit contemptuous) reasoning, childhood cancers evoke a strong emotional reaction, and in the age of corporate cynicism several pharmaceutical companies have begun generously supporting paediatric oncology, not solely because it is appropriate, but mainly because childhood cancer is a model for all cancer.

Treatment protocols are developed in two stages. First, consensually designed recommendations are made by renowned experts in the field. However, these should not deter individual physicians from relying on their own experiences to adapt each treatment to a particular patient. Second, prospective treatment protocols are carefully designed and approved by national and transnational regulatory agencies after thorough review by ethics and parents' committees. This prospective approach has clearly demonstrated its formidable impact on the overall paediatric cancer cure rate, which has risen from a discouraging 0% in the 1960s to over 75% nowadays. Insurance companies, pharmaceutical drug companies and, above all, regulatory agencies have respected the high ethical principles, scientific independence, optimal healthcare expenditure and excellence in the standard of care provided by paediatric centres involved in clinical research. Not only do these centres implement good and approved clinical practices, they also provide supportive care adapted to suit individual children. As such, areas of research for further improvement include nutrition, psychosocial factors, education and pain management, to cite only a few aspects of multidisciplinary patient care now in place in most, if not all, specialised centres throughout developed countries.

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Finally, paediatric oncology illustrates the gap between developed and developing nations. While more than 75% of children with cancer in developed nations survive, the majority of children from developing countries succumb due to lack of access to appropriate care. Western paediatric oncologists are increasingly lobbying for the launch and fostering of outreach programmes to help local physicians gradually raise their standard of care and offer a chance of survival to the many children affected by cancer around the world. ■

The Hague, The Netherlands, 10-12 September 2008

ESSO 2008

14th Congress of the European Society of Surgical Oncology

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