Unshackling progress in the care of childhood cancers

Marc Beishon

Young cancer patients face a specific set of problems that can only be resolved through a concerted and coordinated effort by national and EU policy makers, researchers, regulators, funders and service providers. A meeting held in the run up to International Childhood Cancer Day reviewed how well we are doing, and what is urgently needed to do better.

For anyone unsure that there really is overbearing regulation on cancer research in Europe, a visit to any gathering of paediatric oncologists and others involved with child cancers would soon put them straight. In the words of one senior clinician: "We have a clinical trials directive that allows national re-interpretation, no platform for European approval, one set of rules that applies to all types of study, no adaptation to risk, overwhelming bureaucratic burden and it has been conquered by regulatory fundamentalists."

So said Stefan Bielack, medical director of paediatric oncology at Stuttgart's Olga children's hospital, speaking at a stakeholder meeting held at the European Parliament in Brussels ahead of International Childhood Cancer Day, and hosted by Slovenian MEP Alojz Peterle, himself an adult cancer survivor who has helped restart the MEPs Against Cancer (MAC) group.

The fundamentalists, Bielack explained later to *Cancer World*, are those who strictly follow the regulatory rules to be above criticism, but grow at the expense of the 'rationalists', who exercise judgement in the pursuit of better progress. The terms, he adds, are those of David Stewart at the MD Anderson in the US, and colleagues, commenting on what they see as diminishing returns from the narrow and dysfunctional 'efficacy versus safety' approach in clinical cancer research in general (for more on this see Equipoise lost: ethics, costs and regulation of cancer clinical research *JCO* 28:2925–2935).

But for paediatric oncologists like Bielack, working in an even more complex regulatory regime than in the US, the straitjacket of clinical trial regulations has reached absurd proportions for childhood cancers, which rely almost totally on investigator-driven research, given that there is a limited market to interest pharmaceutical companies. "There is too much garbage to too many recipients," he said, in reference to the seemingly unending cascade of paperwork to meet the varied requirements of a wide range of organisations that can play by different rules.

Developing cancer drugs and refining their use in children is essential, said Gilles Vassal, head of clinical and translational research at the Gustave Roussy Institute, pointing to the major role that chemotherapy has played in reaching the 80% cure rate over the last 50 years. "We need to introduce more safe and effective drugs into standard care," he said, "and there are such drugs in development – about 800 now for adults – but children are denied

SIOPE

Drug A or drug B? Europe's paediatric oncologists are leading efforts to address the many obstacles to developing evidence on the best way to treat young patients like this one; most are still being treated with therapies that have never been approved for their particular indication

access to them, which is an issue not just for oncology but for all paediatrics."

This is not for lack of trying on behalf of the paediatric oncology community, commented Ruth Ladenstein, president of SIOPE, the European Society for Paediatric Oncology. The majority of European children with cancer are treated in trials, she said, and multidisciplinary approaches to treatment have been important in driving the cure rate to its present high level. "We have more than 250 specialised centres around Europe and we've been networking since the late 1960s. About 50% of children are treated in phase I to III trials and 30% in standard treatment approaches with prospective studies, but less than 5% are in pharma-sponsored trials." Also important, she added, are the many high-level research teams dedicated to tumour biology. "This is a unique situation for an orphan disease," she said.

The message is clear – that there are centres and networks across Europe which could do much more if they had access to more new drugs and improved profiling of the many unlicensed ones already used in paediatric oncology. Vassal talked about the hopes pinned on the European paediatric regulation of 2007, which requires pharmaceutical companies to submit new adult oncology drugs for paediatric investigation plans (PIPs) to the European Medicine Agency (EMA). "But four years later, where are we? Yes the process is in place, but only 23 oncology drugs have a PIP and not all of these will be completed. We are not seeing an increase so far in the number of drugs in early-phase paediatric studies in the European Union – there are fewer than ten now, while in the US there are more than 30."

No strategy for drug development

At present, pharmaceutical companies see paediatric development as a regulatory compliance issue in Europe rather than a strategic research priority, he said, and there is no role for cooperative groups beyond contributions from individual experts. "Europe lacks a strategy for drug development for children," he added, comparing the situation with the US, where since 1997 the National Cancer Institute

has funded a programme for drug companies to make products available to cooperative groups for paediatric trials. As a result, major opportunities to address childhood cancer through the PIP programme are being missed.

Childhood cancer researchers will push for more strategic use of the European paediatric regulation (and PIPs), and of course for the reform of the clinical trials directive, which should happen in some form next year. By coincidence, on the same day of the meeting in Brussels the European Commission issued a 'concept paper' containing a 'preliminary appraisal' of the most suitable ways to address some of the key concerns in the directive, such as how risk is determined.

Jan-Willem van de Loo, scientific officer for cancer research in the health section at the European Commission, was not able to comment on the directive's reform, but he did provide an overview of the EU's commitment to supporting research and care through the various framework programme (FP) projects and networks.

Most notable, in the area of paediatric oncology, is ENCCA (European Network for Cancer in Children and Adolescents), a four-year FP7 programme coordinated by Ruth Ladenstein that aims to build sustainable research via a 'virtual institute' across Europe (for more on both Ladenstein and ENCCA see *Cancer World* March/April 2011).

Others include collaborative research projects such as PROTHETS, which looked at prognostic markers and therapeutic targets in Ewing's sarcoma, and PanCare, which is building a database on long-term childhood cancer survivors to look at trends such as late-effects.

Van de Loo highlighted the explicit focus in FP7 on investigator-driven clinical trials, and on trials to obtain marketing authorisation for paediatric use of off-label drugs – a big gap in the recent EU paediatric regulation according to Ladenstein. One example is the work of the European Paediatric Oncology Off-Patent Medicines Consortium (EPOC), which is examining the pharmacokinetics of doxorubicin – a drug that is widely used in paediatric oncology, despite the scarcity of data on correct doses for young children.

Another helpful development has been the establishment of a European Network of

A success story. Diagnosed quickly, referred to the right specialist centre, treated effectively – Olivia Ferrary described her experience of having a rare kidney cancer to show the meeting what all child cancer services should aspire to

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The ear of the President. Jerzy Buzek, President of the European Parliament, was among those attending the SIOPE conference. He is pictured here (right), with fellow Poles Sidonia Jędrzejewska MEP (centre), and child cancer specialist Piotr Czauderna (left)

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Paediatric Research run by the EMA, and tasked with promoting collaboration, as it is primarily a 'network of networks'.

Funding remains a barrier

But oncologists such as Vassal are sceptical that the current framework programme will deliver more 'calls' for cancer research funding, and Richard Sullivan, from the Centre for Global OncoPolicy in London, noted that a new report he has co-written on the state of child cancer research in Europe (see box) shows that funding remains short-term and 'fragile', and support in some member states is poor. "New mechanisms are needed for complex translational research infrastructure – we need to innovate all the time," he said.

The need to unshackle the research effort is, however, only half the story. Jerzy Kowalczyk, from the children's hospital in Lublin, Poland, talked of the need to improve the standards of care across Europe. A symposium in Lublin two years ago laid the basis for SIOPE to draw up a set of minimum European standards of care for children with cancer, and a project to identify best healthcare practices in paediatric oncology has now started under the auspices of the European Partnership for Action Against Cancer. Next steps include preparing national versions of the standards, convincing national agencies and the EU to issue regulations, and building a registry of child cancer centres.

Kowalczyk expressed disappointment that "politicians showed little interest" in the 2009 meeting, but there is an opportunity to put that right at the European Standards of Care for Children with Cancer conference on 20–21 October in Warsaw this year, led by the Polish Ministry of Health under Poland's EU presidency. Jolanta Kwaśniewska, President of the Communication without Barriers foundation, and a former 'first lady' of Poland, is a leading supporter of the meetings and of child cancer clinics in her country.

Present at the Brussels meeting were representatives of the thousands of child and teenage cancer survivors and their parents for whom good-quality services and unhindered progress in developing new therapies are so important. Olivia Ferrary talked of her experience of being successfully treated for a rare form of renal cell carcinoma at Great Ormond Street hospital in London. A video was also shown of teenagers, which came from Jimmyteens.tv, a project started at St James's hospital in Leeds, UK, where young people with cancer are given cameras to record their experiences. There are 600 such videos now from the UK and Ireland, and the producer, Claire Pope, is looking to include more from other countries.

The term 'therapeutic orphan' was first coined back in 1968 to describe the lack of drug development for children, but there does finally seem to be concerted action to improve matters substantially.

The state of paediatric research

'The state of research into children with cancer across Europe: new policies for a new decade' is a research report with input from more than 30 leading European paediatric oncologists, led by past SIOPE president Kathy Pritchard-Jones, and funded by the EU Eurocancercoms project. It looks at the funding and extent of paediatric oncology in European countries and also compares the effort with the rest of the world.

Findings include:

- In Europe, Sweden and the Netherlands have done the most basic paediatric oncology research but the differences between countries are not large
- Papers from the Netherlands are the most cited, followed by those from the US, the UK and Sweden
- There is relatively little collaboration between North America and Europe. However, EU member states are collaborating increasingly with each other, especially Germany and the Netherlands, and also Switzerland with France, Germany and Italy
- In most European countries except Spain, private non-profit funding sources outnumber government support, but almost half the papers bore no acknowledgement – "a marker of fragile, short-term funding"

The report includes snapshots of countries from experts, finding for example that no international trial has opened in Poland since 2007; in Italy efforts are being made to cut down the large number of centres (54) seeing child cancer, some of which have fewer than 10 patients a year; and those countries that do have strong government funding include France and Germany, whereas the UK and Sweden rely more on charitable organisations.

A survey of opinion leaders done for the report revealed the following to be priorities:

- Adequate EU funding to support a Europe-wide clinical trials network to assist with testing and dissemination of novel therapies and techniques
- A reduction of EU trial bureaucracy/regulations to remove barriers to investigator-led clinical trials, which could include a European trials bureau
- Better understanding by regulatory policy makers of the level of risk for children participating in trials (currently overestimated by insurers as well)
- The creation of a European parent/survivor organisation and a common European information portal
- The creation of a European childhood cancer epidemiological registry
- EU support for harmonising of treatments through pan-European guidelines.

The report is at www.eurocancercoms.eu