Ruth Ladenstein:

raising standards of care for our young patients

Marc Beishon

Paediatric oncologists have a well-deserved reputation for collaborating and treating patients within trial protocols, but there are limits to what they can achieve alone. Leading practitioner Ruth Ladenstein is now calling on the EU and member states to commit to improving paediatric cancer care by providing specialist facilities and serious backing for research and data collection.

Of all the cancer specialities, some of the most spectacular gains in outcomes have undoubtedly been in paediatric oncology. Few could argue that an increase to about an 80% cure rate from less than 20% across the range of childhood cancers, albeit over several decades, is not a cause for celebration. Although these cancers are rare, there could be several hundred thousand people in Europe alive today who survived a cancer diagnosis when they were young.

However, as Ruth Ladenstein, president of Europe's Paediatric Oncology Society (SIOPE), points out, this success only highlights the need to maintain and improve the rigorous research environment that led to the gains, as there can be no relaxation of standards, while there are major challenges ahead. Around 15,000 young people, aged 18 and under, are diagnosed with cancer in Europe each year, and at present cure rates more than 3000 will die, making cancer the biggest cause of death in this age group for those above infancy. "We know that when children are treated outside clinical trial settings their outcomes are not nearly as good; survival is on average about 20% worse – a dramatic drop," she says. "And with a new drug in a trial setting we are looking for a 5% to 10% improvement."

This "life-saving factor" should be borne in mind, she says, when considering the impact on patients of the obstacles European Union regulation has placed on conducting trials, and indeed the lack of multidisciplinary paediatric oncology centres able to participate in this sort of research in many countries, particularly in eastern Europe.

"Integration of research and care is a hallmark of paediatric oncology," says Ladenstein, with about 80% of children now treated either in clinical trials or with prospectively monitored therapeutic protocols. But as childhood cancer treatments are firmly in the 'orphan' (more rare) disease category,

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thus attracting far less industry funding than the much larger adult cancer field, most of the research is reliant on investigators working in an academic setting, in often complex protocols, mostly with 'off-label' drugs – i.e. drugs that have never been trialled and approved for use in children. The European Clinical Trials Directive has had a dramatic effect on this already fragile research base – an impact even greater than in the adult tumour area.

"We estimate that the number of new trials has gone down by 70% since the implementation of the directive as there is just so much more funding and time now needed to deal with issues such as ethical committees around Europe and insurance in trials deemed to be high risk. Meanwhile we have virtually no funding or interest in running studies on existing off-label drugs, and these are classed in some countries as investigational medical products, which further adds to the administrative burden if we need to use them in trials. And of course because paediatric cancers are uncommon we do need multicentre, multicountry studies to accrue sufficient patient numbers."

As she adds, just as in adult cancer, the era of chemotherapy has largely run out of steam at the paediatric level, and the pursuit of translational research and new biological therapies is especially demanding for academic investigators short of funds. Then there is the paradox that this branch of oncology also contains – or should do – the most neglected group in cancer, namely teenagers and young adults. And all children with cancer need the major commitment of follow up through much of their lives to monitor the effects of treatment.

There are also urgent needs for gathering much better epidemiological data from various countries, for fostering multidisciplinary standards of care and for getting patients and families more involved in pressing for research. It's a huge agenda by any measure.

Ladenstein speaks from long-standing involvement in the paediatric oncology research community, specialising in neuroblastoma, and having spent her career working up to head the solid tumour unit at St Anna Children's Hospital in Vienna, Austria, and also holding an associate professorship at the University of Vienna. The St Anna Kinderkrebsforschung (children's cancer research institute) has long been a research hub in the German-speaking region and internationally, but it has really been put on the wider map with two recent EU initiatives that Ladenstein hopes will help to unravel the 'red tape' that she believes could seriously hold back progress in her speciality.

The first, now ended, was 'Overcoming cancer with research', a two-year communications project that aimed to raise public awareness of childhood cancer research. This media project, for which St Anna was the coordinating organisation, working with the German Childhood Cancer Foundation as a partner, has produced a comprehensive website (www.overcomingcancerwithresearch.eu), a film (Little Heroes – Great Opportunities), press conferences and other activities.

It also provides details of various paediatric research networks and other projects that have EU funding. One of these is ENCCA (European Network for Cancer Research in Children and Adolescents), a major €12 million initiative under the EU's 7th Framework Programme, for which Ladenstein is the coordinator. "It is a four-year project that started this year and our aim is nothing short of building a sustainable Europe-wide virtual institute that will unite the paediatric oncology community," she says.

Meanwhile, she adds, disparities in care standards are being addressed by SIOPE, which has drawn up 'European Standards of Care for Children with Cancer' for paediatric oncology, and a 'seven-point plan' for delivering the overall agenda (see p9), including a call for all member states to have national cancer plans that contain specific

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standards for age-appropriate treatment and care for children and adolescents with cancer.

It's a familiar story in European oncology: many interest groups have realised recently that there is much to be gained by combining the efforts of national societies and institutions to gain scale for research and to lobby and network more effectively at both European and state levels. As Ladenstein adds, "While there has been effective networking in childhood cancer – indeed more so historically than in most adult tumours – efforts have largely been focused on specific diseases such as neuroblastoma."

Now it's vital to unite research networks and lobbying work, she believes, and Ladenstein finds herself at the head not only of one of oncology's most important European societies, but also a key project in ENCCA, given the impact it could have on issues such as the Clinical Trials Directive.

Her path into medicine was almost preordained – "It was what I wanted as a little girl" – and she found herself drawn to paediatrics despite a conscious choice to resist it, as she felt women too often find themselves earmarked for the speciality. "But I loved it," she says, "and I did all my standard paediatric training at St Anna. In fact despite moving into oncology I'm still a practising general paediatrician, as when I'm on call in the hospital I see all children, not just those with cancer."

It was early in her career when her chief, Helmut Gadner – one of the pioneers of the BFM (Berlin-Frankfurt-Münster) leukaemia protocols developed in Germany, who recently retired from St Anna – pointed her in the direction of oncology. "We had just started to treat children with cancer then, and he gave me a paper to study on sarcoma patients, and from that we started the first Austrian sarcoma study."

Ladenstein says that far from childhood cancer being a daunting area, "it's exciting because we have a 40% better chance of curing them than we do with adults. Some types of paediatric tumours respond much better to chemotherapy and children are wonderful patients to be with. They understand a lot when you explain properly and it makes them mature in a very short time. It's a pleasure to be with them and their families at a critical time, and now I also see them as grown-ups with their own children." But of course there is great sadness when treatment fails in some. "I especially feel for teenagers – you should never die when you have hope for the life ahead of you."

As she adds, it is the right place to be for those who want to be rewarded in terms of outcomes and scientifically. "We are on the edge of a fast-moving field and there is so much research to be done."

Needing more research experience herself, and the recipient of an Austrian award, Ladenstein cast around for a project abroad, landing in Lyon, France, at the Léon Bérard Centre. France has been a European cradle of paediatric oncology, and she was quickly immersed in analysis of data on neuroblastoma transplants, and also on Ewing tumours and lymphoma patients around Europe. She also studied mechanisms in neuroblastoma cells in the laboratory, and went on to work and study further in Paris.

Neuroblastoma is the most common childhood solid tumour outside of the brain, and the most frequent of all under the age of five – in fact it is the second most common cause of death in children after domestic accidents. As a neuroendocrine disease it often develops from the adrenal glands. Ladenstein explains that it also has a wide spectrum of risk, and stem cell transplants are given after high-dose chemotherapy treatment for overcoming tumour cell resistance in the more severe cases. But low-risk disease often regresses to a benign state without any treatment, and identifying how best to apply high-dose regimens became a particular goal for her following her return to Austria.

"It is one of the most fascinating of cancers because it is completely driven by tumour biology, as we have been discovering," says Ladenstein. "We

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have learnt that neuroblastoma in infants can even regress from the metastatic stage and does not need chemotherapy, unless there are specific risk factors that do require intensive treatment. So far we know half of patients need little or no chemotherapy and can be spared high-dose treatment, and we have improved outcomes in the high-risk group from 20%–35% to more than 50%, which is quite an achievement. It is knowing early on who has an unfavourable profile that improves outcomes."

Ladenstein has been at the centre of both local and Europe-wide neuroblastoma research that has found prognostic markers for risk and developed new treatments and protocols, and she is the co-ordinator of the SIOP European Neuroblastoma Research Network (SIOPEN-R-NET) and chair of SIOPE's neuroblastoma group (the research network was funded by the EU's Fifth Framework Programme, but continues to operate today). "The history of paediatric oncology is that we run one protocol after another and make slight progress by optimising treatment plans over many years, but we have learnt so much more now about prognostic markers, stratified treatment and biology in most child tumour types.

"In neuroblastoma, a key focus now is still on the high-risk group and we have a huge trial running that has accrued more than 1500 children across 20 countries and we are getting exciting results from the randomisation, which we will be taking to the ASCO conference in the US this year. We will show that a European protocol we have developed is performing better than the best American standard."

She says the Children's Oncology Group in the US had demonstrated a significant improvement for neuroblastoma immunotherapy using a monoclonal mouse-human chimeric antibody (ch.14.18). The SIOPEN group then undertook to provide access to this antibody for neuroblastoma patients in Europe via the trial, but this work illustrates well the difficulties that paediatric oncologists face in pursuing new treatments.

It involves the production and distribution for clinical testing of this 'chimeric' (combination) antibody for use in the high-risk trial – but so far this is an entirely academically driven effort, with all that means for pressure on funds to bring a new drug to market. "It is very unusual for us to attempt drug development without industry support – but we have obtained about €2 million through our own fundraising efforts. Even so, we only have a limited amount of the drug for the controlled trials, and we are hoping to find an industrial partner and also greater government support for drug production, especially in the UK, so we can open up more trials."

She also mentions another drug that could improve outcomes when given in combination, by promoting white blood cell production, which is being used in trials in the US, but is simply not available in Europe. "We eventually tracked down a potential 'importer' supplier in Switzerland, but the pharmaceutical licence holder wasn't interested in making it available," says Ladenstein. "It's very hard when parents read about our trials and ask why we can't give these drugs to all children. I have to explain we are not a drug company, that the drugs aren't mature enough yet to be on the market and there can be concerns about toxicity, and simply that we do not have enough of them, such as the chimeric antibody, and we are not allowed to offer the drug outside a controlled trial setting."

The antibody in question was first researched some 20 years ago for adult and childhood cancers, but as Ladenstein points out, children in Europe have been "extremely poorly served" in access to innovative drugs that have been investigated and developed for adults. She is encouraged, however, by a recent initiative that could help children gain better access to new drugs, namely the requirement for pharmaceutical companies to develop paediatric investigation plans (PIPs) for new adult drugs, where appropriate, under the recent EU Paediatric Medicine regulation, which also aims to promote safe and effective treatments in general.

HOW WELL DOES YOUR COUNTRY SERVE ITS YOUNG CANCER PATIENTS?

SIOPE has drawn up this seven-point plan as a guide for policy makers on how to upgrade paediatric cancer services.

1. Cancer plans. Every country should have a national cancer plan that contains specific standards for age-appropriate treatment and care for children and adolescents with cancer.

2. Registries. Every country should support prospective registration of new cases and outcomes of all cases using the International Childhood Cancer Classification scheme, extended to include adolescent cases.

3. Access to specialists. Every country should have defined referral pathways so that each patient is managed at an age-appropriate specialist treatment centre that works within a national or cross-border network structure and can have access to innovative therapies in development when needed.

4. Multiprofessional teams. Every child and adolescent with cancer should be treated by a multiprofessional team which has a sufficient volume of activity to maintain expertise and which participates in audit and accreditation schemes.

5. Specialist training. Specialist training in paediatric haemato-oncology should be recognised in every European country.

6. Family support. The crucial role of parental/family support should be recognised as critical to treatment outcome and survival of the young cancer patient.

7. Research. Greater EU and national support is needed for investigator-led clinical and translational research, to reverse the recent decline in participation in clinical trials, which, to date, has greatly benefited the development and delivery of 'best practice' of care for young people with cancer.

The benefits, however, won't be felt for a long time, she says. "We may see an impact from the crossover from adult drugs in 10 to 20 years time. There are only a few that are ongoing at present, but it is a move in the right direction." The regulation also fails to resolve the major problem of getting approval for drugs that are already widely used off-label. "There is not yet any investigational process or funds for us to do this."

About 80% of drugs used in paediatric oncology are used off-label, and even those that are approved are not often labelled appropriately for certain age groups in terms of dose calculation, for example. "We need to take steps to ensure all the drugs we use for children are safe and effective – but despite a backwash of 30 years of clinical trials we still have this huge burden of off-label drug use and barriers to moving forward, such as the continued classification of many of our drugs as investigational medical products in some countries, despite their long use." If drugs are treated as investigational, they require 'expedited' reporting to the European Medicines Agency, EMA, and Ladenstein fears that much of these data, which could be valuable for knowledge about say toxicities in multiagent trials, are disappearing into a 'black hole'.

There are funds available from the EU's Framework Programmes for drug development that could help investigate the pharmacokinetic/dynamic behaviour of off-label drugs in children and so move towards approval, but as Ladenstein points out, the only way for academics to access these funds is to compete against one another, which means many will simply waste a lot of effort writing applications.

"We need dedicated funding to investigate the older drugs we use, and there is a feeling that some should be entered into randomised trials, which would be very costly. However we do need to charge experts to do the work on correlating drugs properly in terms of their behaviour with the course of a disease and the dose, as clearly children are different

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from adults. We could certainly aim now to get that 80% off-label figure down to 40% in five years' time." If standard chemotherapy protocols can be optimised, Ladenstein says that adding new drugs could then add another 10% benefit in outcomes.

Lobbying from SIOPE will continue on this issue, as it is not explicitly part of the work programme for ENCCA. "In the new project, though, we will be aiming to influence the Clinical Trials Directive so it is more feasible for paediatric oncology, such as by developing a contract framework that allows academic institutions to become coordinating pan-European trial sponsors, delegating tasks to national bodies so we can share the burden. We are also looking to use a not-for-profit insurance organisation, maybe insuring studies through national health services." (Both Ladenstein and the previous SIOPE president, Kathy Pritchard-Jones, have written about the absurdities of the Clinical Trials Directive, which include the stipulation that crushing tablets in trials to enable children to swallow drugs is not allowed as it is deemed a 'manufacturing' process – *EJC* 44:2106–2111.)

The clinical trials work package of ENCCA (just one of 18 'work packages' tackling various challenges in paediatric oncology) will also aim to streamline childhood cancer trials by using standard templates and datasets; determining just what an investigational medicine should be; and cutting duplication and fragmentation by promoting more multinational trials.

"In other work packages we want to explore how we can build better registry data for childhood cancers, and how we can improve long-term survivorship as children grow up to become adults, by following up late-effects of treatment. One idea is for them to carry a survivor's passport that contains updated information and is always with them. Another project is PanCare, which focuses on long-term effects. The challenge is that this is not like caring for those with just diabetes or a heart condition – we will still need multidisciplinary teams throughout."

It seems from existing data that paediatric cancers are not increasing in overall incidence, but if national registries improve, Ladenstein says, trends in certain tumours and leukaemias may become apparent at a European level. At present, she adds, only localised events such as Chernobyl and other pollution in some countries appear to have given rise to higher than usual rates of childhood cancers. "We also need very long observation times concerning treatment – for example it took 30 years for us to see the higher incidence of breast cancer in those who had been diagnosed with Hodgkin's lymphoma and had been given certain drugs and radiotherapy."

The biggest work package, in terms of 'person months', is on networking among preclinical research groups to create common data sharing and bio-information tools, and Ladenstein notes that an overall aim of ENCCA is to bring researchers together across the range of paediatric cancers, to possibly identify shared biological pathways, for example.

More funding is likely to come from pressure from advocacy groups, she believes. "SIOP [International] has a committee working with the International Confederation of Childhood Cancer Parent Organisations, which can be a strong voice for us. I know from speaking to people at the US National Institutes of Health that funders are driven much more by parents than by doctors."

She hopes that SIOPE will benefit from increased membership as a result of ENCCA, as people recognise the importance of integrated working. The European branch of the society has around 900 members and could do with more interest from national organisations, but Ladenstein says there is difficulty in getting people to commit to additional membership fees. "But we have a strong European agenda that ENCCA will increase further – and I hope it will show people what they are missing."

SIOPE is a founder member of ECCO and runs a paediatric stream at the conference. It joins

the SIOP International congress when it convenes outside Europe (this year it will be in New Zealand). But as Ladenstein adds, it is important that networking continues in countries that are most underrepresented in membership and that have more trouble meeting standards of care, such as in eastern Europe. "SIOPE has a partnership with the national society in Poland, and we jointly drew up the European Standards of Care for Children with Cancer," she says.

A survey of the state of regulations and standards of children's cancer care in 27 European countries conducted in 2008 by Jerzy Kowalczyk, of the Children's Hospital in Lublin, Poland, revealed that only Austria, Belgium, France, Germany and Italy had officially recognised regulations in place, with the most comprehensive in Germany.

SIOPE's European Standards of Care, which were developed from this, are described by Ladenstein as guidelines on the minimum requirements for bringing children and families through intensive treatment, "on factors such as access to drugs and protocols, sufficient team members, how children are looked after in the wider context such as schooling, and so on."

Given the importance of trials and protocols for best outcomes in paediatric oncology, having dedicated cancer centres for children is also critical, adds Ladenstein, but it can mean travelling and staying a long way from home. And at primary care level, those countries that have paediatricians who see children as they grow up are also in a better position than those where children mainly see general practitioners.

"You need a lot of expertise with children to suspect the symptoms of cancer early on. For example, a child needs to be undressed completely to see possible swelling associated with neuroblastoma, which would more commonly be attributed to a condition such as gastroenteritis. Similarly, tiredness and swellings can be associated with leukaemia. These are things I teach my university students in basic oncology classes. I do feel that children should be looked after by paediatricians throughout their childhood and not just referred to specialists."

She has been fortunate, she adds, to have worked with mentors such as Gadner in Vienna and Thierry Philip in Lyon, and notably Olivier Hartmann at the Institut Gustave Roussy in Paris, "a fantastic personality", who died in 2009.

Despite her workload, Ladenstein, who has a teenage daughter, has many hobbies, including mountain hiking, sailing, diving and ballroom dancing. She may need all her nifty footwork skills in dancing the tango with the powers that be to achieve the establishment of the European virtual institute for paediatric oncology, which is one of key aims for the next few years.

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