Europe's rare cancer community calls for a more radical approach

Anna Wagstaff

The genomic era offers enormous potential for patients with rare cancers, but progress is being held back by structures that separate research from care, regulatory practices that penalise small patient populations, and rules that restrict close working between researchers, companies, patients and regulators.

"Nobody wants to be an orphan," commented EMEA's Kerstin Westermark, at a conference last November on Addressing the Challenges of Rare Tumours. The reference was to the orphan status the European Medicines Agency confers on novel medical products intended for use in certain rare – or 'orphan' – diseases. The point she was making, however, was that patients with rare diseases are the orphans of healthcare systems throughout Europe, which are failing to take responsibility for their needs.

EMEA defines a disease as 'rare' if it affects fewer than 5 out of every 10,000 people. More than 6,000 diseases fall into this category and, strangely, taken collectively, they are really quite common. An estimated 1 in every 10 people in Europe suffers from some form of rare disease, making a total of around 32 million.

These 32 million people have a number of problems in common. Because their disease is rare, delayed diagnoses and misdiagnoses are frequent. Once they are diagnosed, patients and their doctors may struggle to find the information they need about the disease, how it will affect them and what are their best treatment options. Because specialists are few and far between, treatment may require travelling very long distances – possibly even abroad. Treatment options are themselves often very limited. The evidence base may be very poor, because it is hard to organise clinical research for a small and scattered patient population. The multidisciplinary approach to treatment – so important in complex diseases like cancer – may not be available, because specialist teams are hard to sustain when patients are few. Diagnostic and therapeutic medical products simply do not exist for many rare diseases, because the market is too limited to provide an adequate return on investment. When new orphan products do make it through EMEA's central marketing approval procedure, decisions on pricing and reimbursement can delay

patient access for several years.

As a consequence, patients are frequently treated with therapies that have never been properly studied or approved for their disease. To add insult to injury, even this option may not be open to them, as public health systems may refuse to reimburse drugs used on an off-label basis.

Having the odds stacked against you in this way must be hard for any patient. For patients with chronic and debilitating conditions, it is terribly frustrating. When that disease poses an immediate threat to life, it becomes the stuff of nightmares.

Sandy Craine, co-founder of the CML Advocates Network and secretary of the European Cancer Patient Coalition, will never forget the nightmare feeling she had on being diagnosed with chronic myeloid leukaemia 10 years ago, aged 50. She was told she had only 12 months to live unless she agreed to undergo a stem cell transplant. Aware of the risk involved and the high rates of mortality and morbidity from this procedure, she was left frantically searching for an alternative.

"There is a great sense of urgency. What you want to do is survive, but you feel you are wasting time every day, because you are aware that newer, more effective drugs are in the pipeline, but you don't know how to get them, and you don't know how or where to get the information. Your doctor doesn't know…" And all the time the clock is ticking.

She found her way, via an online patient group, to the phase II imatinib (Glivec) trials in the US. This drug brought her progressive disease under control and bought her valuable time. But even when Glivec became available in Europe, she had to organise a campaign against an early decision in the UK not to reimburse the drug for patients in the chronic stage of CML.

As she learned more about the disease and as new treatment options developed, Craine was able to find a solution despite developing a resistance to Glivec. Following a reduced-intensity stem cell transplant six years ago, she is now fit, healthy and devoting time and energy to helping ensure that other patients don't

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The orphan drugs regulation shows what can be achieved with a unified European approach

face similar nightmares alone.

Patients should not have to battle to get the care they need, argues Craine. "People like me continue to work and pay our national insurance. Like all insurance, the idea is that the risk is pooled. Not everyone claims. But if and when you do need therapy, you expect to get it. It's reasonable isn't it?"

In the year 2000, the EU went some way towards endorsing this position. Regulation 141/2000, which introduced the 'orphan' designation to encourage pharmaceutical companies to invest in rare diseases, recognised that "patients suffering from rare conditions should be entitled to the same quality of treatment as other patients..."

The purpose of last November's Rare Tumours conference – convened by sarcoma specialist Paolo Casali of the European Society for Medical Oncology, and shaped by representatives from clinical specialists, industry, patient advocacy, the regulators and EU policy makers – was to reach a consensus on what needs to be done by whom to turn this 'entitlement' into reality.

From rights to reality

The need to pool knowledge, expertise and research resources and to draw in a critical mass of patients to sustain specialist treatment centres, makes a coordinated European approach essential in addressing the challenge of rare diseases. The challenge is how to achieve this when health policy is decided independently in each of Europe's 27 Member States.

The orphan drugs regulation offers a good example of what can be achieved when a unified European approach is possible, as well as of the obstacles that arise in the absence of a coordinated strategy. The regulation, which applies across the EU, offers 10 years' market exclusivity to any preventive, diagnostic or therapeutic product developed for an indication that is life threatening or seriously debilitating, where there would be no sufficient return to justify the necessary investment by the sponsor and where no satisfactory alternative is already on the market. It also cuts the costs associated with the marketing application procedure.

Prior to the legislation there was little interest in developing drugs for rare diseases in Europe. In the nine years since the legislation was passed, applications have been received for 865 experimental drugs to have orphan designation and 573 of these have been approved – 44% to treat rare cancers. Of these, 15 cancer orphan drugs have already received marketing approval, including four for CML and two for multiple myeloma. A success by any standards.

The problem is what happens next. With each Member State using its own system for deciding what price they are prepared to pay for the new drug, and whether all patients or only some (e.g. those in the late stage of the disease) – or none – will be eligible for reimbursement, it can take up to six years for these vital new therapies to reach all of Europe's patients. Many of them won't survive the wait.

While this delay is common to all newly approved therapies, Yann le Cam, chief executive of EURORDIS, the European umbrella advocacy group for patients with rare diseases, says it is exacerbated with orphan products.

"There are two problems. On the one hand, many Member States, especially small or medium-sized states, don't have the medical expertise [in rare diseases] to carry out the health technology assessment, so they wait for other states to do it first. On the other hand, in the area of orphan drugs, there tends to be more small and medium-sized companies, and they do not have the resources and competencies of big pharma to place the product in the 27 countries immediately. On average, the newly approved product is introduced into six or seven main markets, and then progressively into three to four additional markets each of the following years."

EURORDIS has fought a long campaign to reduce this delay by 'completing' the EU policy on orphan drugs to cover post-approval assessment of clinical value. 'Common assessment reports' of this clinical added value of orphan drugs would be done at European level, by EMEA, drawing on the data already submitted as part of the orphan designation and marketing approvals procedures and paediatric investigation plan.

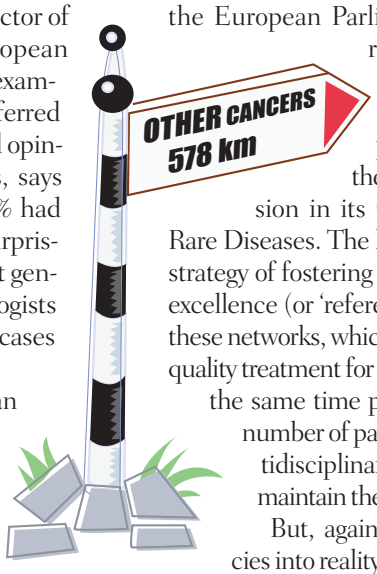
Member States have always jealously guarded their right to determine their own economic, social and health priorities, but Le Cam believes this proposal goes a long way to addressing their concerns. "The scientific and clinical data do not change from one country to another. What changes is the economic environment and willingness to pay and how it is distributed – through hospitals or pharmacies. These are reasons that can justify different approaches in different

Member States. Providing a common assessment of clinical added value could at least provide a way to speed up decision makers at a national level."

Last year this policy was endorsed by the EU high-level Pharmaceutical Forum, which has representation from all Member States, and in the EC Communication on Rare Diseases issued by Health Commissioner Androulla Vassiliou in November. Movement on this issue therefore seems to be a possibility.

Access to best care

Lack of coordination also accounts for the high levels of misdiagnoses and inappropriate treatment of rare cancers. Jean Yves Blay, network director of CONCATINET, the European sarcoma network, cites the example of sarcomas. Of cases referred to their network for a second opinion over the past two years, says Blay, between 20% and 25% had been misdiagnosed. Not surprising, perhaps, given that most general practitioners and pathologists come across only one or two cases during their careers.



Inclusive pan-European networks are the way to improve care in rare cancers, argues Blay, not just to give smaller centres access to second opinions, but to pool existing knowledge and expertise, to gather, classify and make sense of new molecular and clinical data, and to use the new knowledge to draw up treatment guidelines. Making this new knowledge accessible to patients is also essential to equip them to take informed decisions on treatment options – particularly important in the absence of evidence-based guidelines.

"In rare cancers," says Blay, "research helps structure good routine clinical practice, and the two activities need to be carried out within a single network." He cites, as a good example, the European Leukaemia Network, which is compiling a molecular database to map the genetic profiles of leukaemia across Europe, while also supporting clinical practice through exchange of information, facilitating second opinions, and developing guidelines, and at the same time working with patients and industry to monitor and improve outcomes from established treatments.

These sorts of 'European reference networks' were endorsed at the level of the European Parliament, in its 2008 resolution on Combating Cancer in the Enlarged European Union and by the European Commission in its Communication on Rare Diseases. The latter also endorses a strategy of fostering European centres of excellence (or 'reference centres') within these networks, which would ensure high-quality treatment for each patient, while at the same time providing a sufficient number of patients to enable multidisciplinary teams to build and maintain their specialist expertise.

But, again, turning these policies into reality will require commitment from Member States, because responsibility for funding healthcare is the preserve of national governments. EC funding is available only for the research side of these networks, and even then, only on a project by project basis, which takes months to secure and lasts for a limited period. This sort of funding has been important in getting networks like CONCATINET and the European Leukaemia Network up and running, but it is not a long-term solution. One option may be for governments to use some of the funding they get for healthcare through the EU structural fund, but international structures are not always a high priority, particularly when recession bites and healthcare resources are under pressure.

National governments also hold the purse strings for reimbursing treatment carried out abroad, which may mean some patients with rare cancers will not have access to the proposed European reference centres. The draft directive on cross-border healthcare, which is expected to be put to the vote in the full European Parliament in April or May, specifies that governments will be required to reimburse treatment only to the level that would have been spent had the patient been treated in their home country. If this provision is not amended, rare cancer patients in many countries of Europe may find treatment at a specialist centre is ruled out.

Refocusing on research

Important though it is, access to the latest drugs and high-quality care can only do so much when there is no effective therapy – sadly still the case in many rare cancers. Patient advocates from the rare cancer community feel that the right to 'the same quality of treatment as other patients', enshrined in European legislation, is betrayed by cancer control policies that focus predominantly on prevention, screening and promoting healthy lifestyles – all of marginal relevance to rare cancers, which are predominantly genetic in origin.

Denis Strangman of the International Brain Tumour Alliance is concerned about

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Patients and researchers alike believe what is needed is a massive change in gear

FROM RIGHTS TO REALITY

Thirty-nine recommendations were agreed by the clinicians, researchers, patients, regulators, policy makers and companies who participated in the November 2008 conference on Rare Tumours convened by the European Society for Medical Oncology. Among them were the following:

Research and treatment structures

- Local, national and European centres of expertise should be integrated into European networks.
- Centres and networks of expertise should receive appropriate and permanent funding, acknowledging the extra medical and institutional resources needed to manage patients in a collaborative manner and to develop institutional multidisciplinary expertise.
- Network-based clinical databases and tissue banks should be developed.

Access to high-quality treatment

- Innovative approaches should be used to raise awareness about rare cancers among general practitioners and pathologists.
- Easy-to-understand, comprehensive, balanced and high-quality information about rare cancers and their treatments should be made widely available.
- Immediate referral of all suspected cases of rare cancers to centres of expertise should be mandatory.
- European clinical guidelines should be developed.
- The reasons behind the high level of off-label prescribing should be investigated and the extension of drug labels for use in rare cancers should be facilitated.
- Conflict of interest considerations should not be allowed to present a barrier to ensuring the best possible clinical decisions.
- Issues surrounding social justice, solidarity, equity and the interests of patients with rare cancers should be included when setting public health priorities.
- EMEA should be given responsibility for conducting a non-binding assessment of orphan drugs as a guide to facilitate national pricing and reimbursement for innovative medicines in rare cancers.
- Meaningful and transparent dialogue should take place between Member States and pharmaceutical companies to speed up access to treatments for rare cancers.
- Governments should shift from risk aversion to a risk management strategy when assessing new medicines for rare cancers.

Drug development

- A higher degree of uncertainty should be accepted for regulatory as well as clinical informed decision-making.
- The research community should consider testing new agents in rare cancer patients as an essential part of the clinical drug development process of new drugs.
- The research community and regulators should consider using a Bayesian approach for the design/evaluation of clinical trials.

For the full list of recommendations, see Improving Rare Cancer Care in Europe at www.esmo.org

what he sees as a growing trend for cancer control organisations and policies to move away from their original remit, "which was to have a broad concern about all cancers and not just those that are amenable to screening and so forth."

"Ten years ago," he says, "there would not have been so much interest in joining hands with the National Heart Foundation to promote a campaign over childhood obesity. I can see the link, but it's a bit remote from what I believe should be their basic orientation."

Strangman believes a major factor behind this trend is the way funding is allocated. "I know how governments work and how you apply for funds on the basis that this is a cost-effective proposal. I can see how preventing lung cancer or detecting breast or colorectal cancer early works from the point of view of cost-effectiveness. It's within that trend that I see the less common cancers as fading into the background and not fitting the mould."

The irony is that this perceived trend coincided with the period when developments in cancer research finally began to favour rare cancers. When the dawn of the genomic era opened up the potential for targeted therapies, the rare cancer community was the first to run with it. Unburdened by traditional paradigms based on massive clinical trials, they have been blazing a trail that researchers in the more common cancers will probably follow, as all cancers become broken down into smaller groups based on molecular signatures.

So it was that the first breakthrough for targeted cancer medicines, Glivec, was in the rare cancer, chronic myeloid leukaemia, at the end of the 1990s. The first confirmation that a genetic signature

could be more relevant than traditional pathological and organ-based classification also came from Glivec, when it was found to be effective in an even more rare cancer – GIST, a solid tumour of the gastro-intestinal stromal tissue that shares with CML the c-kit gene mutation.

Over the past 10 years, as a small minority of CML patients and many GIST patients developed resistance to Glivec, this rare cancer community – patients, clinicians, basic scientists and industry researchers – has been at the forefront of developing new ways to work together. This includes collecting blood and tissue, reporting symptoms, comparing molecular and clinical responses, analysing data, working on new compounds and ways to use them, taking some through the approval process and onto the market – trying to stay ahead of the disease as the clocks tick for the patient population.

But while this work has provided a glimpse of what may be possible, those involved with other rare cancers – brain tumours among them – are still waiting for that breakthrough. Patients and researchers alike believe what is needed is a massive change in gear. Not just more funding for reference networks and their tissue banking and research activities, but cutting the time and the cost of the whole research and development process.

This means much more than cutting the notorious bureaucracy associated with clinical trials. Filippo de Braud, of the clinical pharmacology and new drugs development unit at the European Institute of Oncology in Milan, for instance, is among those arguing that where patients are few and the need is great it should be easier to get permission to research the effect of a drug in rare indications for which it has not been approved.

"Where we have a drug that has already been proved to be safe, we should improve our regulatory procedures using the market, and try to share with companies the experience in the market," he argues. He also proposes examining ways in which patients with rare cancers could have access to drugs being trialled for other cancers, "soon after their phase I development," as a routine part of the clinical drug development process.

Another key to cutting time and costs is shifting the research methodology away from the traditional reliance on showing statistically significant effect in successive trial stages, towards the more flexible 'Bayesian' methodology, which allows the results of each new stage of a trial to be evaluated in the light of 'prior probability' based on what is already known. As Bayesian procedures are notoriously complex, this would require a determined effort on behalf of the research community as well as a willingness from the regulators to accept studies conducted in this manner.

There are also calls for a paradigm change in the traditional approach to handling conflicts of interest in disease areas where expertise is concentrated in the hands of a very small community. This is something Novartis – drawing on its experience with Glivec – considers essential, and the company strongly supported ESMO's Rare Tumours conference as a potential step in this direction. Guido Guidi, head of the European Oncology division of Novartis Oncology, argued that 'conflict of interest' rules can prohibit the experts who advised and assisted in the early part of a drug development from involvement in designing and conducting the clinical trials, leaving this to be carried out by clinicians less familiar with the disease.

He would like the rare cancer community – patients, researchers, companies and regulators – to explore ways in which the traditional conflict of interest barriers designed to protect the highly confidential drug development procedures against inappropriate influence could be replaced by less restricted collaboration carried out in a far more transparent environment.

Seize the moment

Taken together, what the rare cancers community is calling for is a fresh look at how we organise our research and care, and how we conduct the relationships between researchers, companies, patient groups, regulators and reimbursement authorities in order to realise the huge potential of the new era of molecular biology.

"Cancer in the genome era is a steep learning curve for all of us," said Sandy Craine, herself a survivor of the first cohort of Glivec patients, speaking at ESMO's Rare Tumours conference. "But too many people are still dying. We need a more radical approach. We have great potential in Europe for clinical and translational research. Let's take this opportunity to change the way we look at health and the costs of providing healthcare in our societies. We need to redesign research methodologies and turn the knowledge we have now, and are accruing all the time, into effective therapy, and deliver those new therapies to patients much, much faster.

"We are living through transformational times, and I believe we need to grasp this opportunity and transform the vision of this conference into concrete actions."

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