

European Leukemia Network: making fragmentation a thing of the past

→ Marc Beishon

Efforts to improve the care of Europe's leukaemia patients have been boosted by a highly-motivated, well-focused network that is integrating the work of trial groups and partner groups, involving diagnostics, treatment, registries and guidelines.

While debate about how to fix the fragmented nature of European cancer research continues, there is one group that has been quietly getting on with the job of transnational collaboration. The movers behind the European Leukemia Network ('European LeukemiaNet' or ELN; www.leukemia-net.org), now in its fourth year, have a justifiable claim to be running one of the most far-reaching oncology networks to date. As of January this year it has brought together national leukaemia study groups comprising 147 institutions in 28 countries, more than 1,000 researchers – and potentially tens of thousands of patients.

So far, achievements include an annual symposium with a growing attendance, implementation of new treatment guidelines, progress with standardising monitoring techniques

and the start of a number of clinical trials and registries for certain leukaemias.

However, the ELN is a product of the European Commission's Sixth Framework Programme and has limited funding – the challenge will be to secure cash to sustain it after the official project end in 2010. The signs are that it may succeed, thanks to partnerships with industry and other funding sources – as evidenced by a tie-up with Novartis for one of the most advanced categories, chronic myeloid leukaemia (CML). Progress so far has been all the more notable because the initial proposal to the EC for a 'network of excellence' was met with only a fraction of the funding asked for – €6 million instead of €30 million.

The ELN is coordinated by Rüdiger Hehlmann, professor of medicine at the Mannheim Medical Faculty of the University of Heidelberg, and a CML expert. It is modelled on a German Compe-

tence Network for acute and chronic leukaemias, funded to the tune of almost €12 million since 1999 by the country's Ministry of Research and Education.

The Competence Network – there are two others for cancer in Germany, for lymphomas and paediatric oncology – was formed to address a number of deficiencies in research and care, including incomplete identification of the country's population of leukaemia patients, duplication and fragmentation of clinical trials (and missed opportunities to recruit into trials), and lack of definitions and standards for diagnostics and therapeutic criteria.

As Hehlmann and colleagues wrote in an editorial in *Leukemia* (2004, 18:665–669), the aim of the Competence Network is to support excellence in care and research, and also "incorporate insights from gene array research into clinical practice...and to migrate rapidly to molecular classification of



Fitting the pieces together. The ELN connects 95 leukaemia trial groups covering 147 institutions, and 102 interdisciplinary partner groups involved in diagnostics, treatment, registries and guidelines for six different types of leukaemia across 28 countries, offering an impressive role model for those aiming at a more general integration of Europe's cancer research efforts

leukaemias... The network offers a competitive advantage for participating doctors and scientists from Germany and neighbouring countries." Now, with the ELN, that advantage looks to be spreading to many more countries, and it is just the kind of collaboration for less common tumour types that many senior oncologists feel Europe is uniquely able to exploit.

For the relatively low funding the ELN started with, the programme looks hugely ambitious. In keeping with European Commission parlance, it comprises a number of 'work pack-

ages' – 16 in total – with the initial objective of integrating 95 leukaemia trial groups covering all leukaemia types, their 102 interdisciplinary partner groups (involving diagnostics, treatment, registries and guidelines) and industry.

There are six work packages for clinical trials for the disease types – acute lymphoblastic leukaemia (ALL), acute myeloblastic leukaemia (AML), chronic myeloid leukaemia (CML), chronic lymphoblastic leukaemia (CLL), chronic myeloproliferative diseases (CMPD) and myelodysplastic syndromes (MDS).

The other packages support interdisciplinary topics such as registries, gene profiling and guidelines. In addition, there is a network management centre and support for communications and information technology.

A CRITICAL MASS

According to Susanne Saussele, a haematologist-oncologist at the University of Heidelberg, and the ELN's scientific network manager, the roots of the project also lie in existing European groups, such as that for CML, but the ELN has widened the number of countries taking

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part. "We have over 20 now for CML, more than double the original number, and the new participants include several from eastern Europe," she says. Indeed, the ELN as a whole also embraces participants from Russia, Turkey and Israel as members.

There has been more long-standing international cooperation generally in rarer cancers because of the need to assemble a critical mass of patients and knowledge, says Saussele. Each disease group operates independently and is a network in its own right. Leadership of the work packages is distributed around Europe, although the core activities, including the network management centre, are based in Germany.

The various leukaemia groups have continued existing trials and started new pan-European ones using common data sets, response criteria and diagnostic standards established by the ELN (although as Saussele comments, the different national interpretations of the European Trials Directive has slowed progress).

There is a strong focus on the diagnostic and treatment side, such as the growing use of molecular monitoring and gene profiling, and a number of therapeutic guidelines have been published. Cooperation with other bodies, such as the European Organisation for the Research and Treatment of Cancer (EORTC) and the European Group for Blood and Marrow Transplantation (EBMT), is ongoing. A European leukaemia registry is an ultimate goal of the ELN, and most registry progress so far has been with CML and MDS.

The CML group has received a major boost with a joint ELN/Novartis

European Treatment and Outcome Study (EUTOS). This, as the name suggests, is aimed at improving and standardising treatment of CML in Europe, given the effectiveness of the Novartis 'blockbuster' drug, Glivec (imatinib).

The challenge with CML is to treat it before it enters an acute, often fatal stage, which, without treatment, almost everyone with the disease will progress to. Some 5,000–10,000 people in Europe are diagnosed each year with CML, and about 60,000 are living with the disease.

The dramatic improvement in outcomes for CML came about once the mechanism of the Philadelphia chromosome abnormality was understood, and five-year survival rates have increased to 90% with Glivec's inhibition of the process of leukaemia cell proliferation – up from the 60% achievable with interferon or bone marrow stem cell transplantation. Today, all patients with a major molecular response – eliminating virtually all the tumour cells – are alive after five years.

The challenge now is to raise the bar in treatment standards across Europe, including routine use of PCR (polymerase chain reaction) testing, which is the molecular test for determining whether minute levels of cancer cells remain in the blood, and is more precise than cytogenetic testing from bone marrow or blood samples, which in turn is superior to basic blood analysis.

Building a network of labs that can carry out tests to a reference standard is one of the aims of EUTOS. These tests could include monitoring blood levels of Glivec – not least for adherence with taking this expensive drug. Building a

European registry of CML patients is also part of the project. Among other aims, this will help quantify much more accurately just how many cases there really are, and answer patients' questions on outcomes with more certainty. Education for healthcare professionals is another part of EUTOS (as it is for all of the ELN).

EUTOS is also mooted as one of the first genuine cooperations of its type between academia and industry. For Novartis it does of course potentially widen the market for its drug, but it also opens pathways to faster development for new agents, and several other drugs (for example, for patients resistant to Glivec), are also becoming available. But the input from Novartis is substantial – the company is putting €14 million over three years into the ELN.

Saussele stresses that the network is strongly protective of its independence – researchers around Europe will not cooperate without mutual trust, she says. Various other funding sources are being explored, and the ELN is considering establishing a foundation that would accept contributions from industry and other parties.

Certainly, what the ELN has in abundance is open access. A good deal of effort has gone into developing a content management system for its website to allow all the project details – trials, papers, reports, contacts etc – to be easily obtainable. Those not involved in leukaemia may gain useful insight into this model for transnational collaboration, not least from reading the original proposal to the EC.

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