The knock-on effects of recognition?

On 24 March 2011, medical oncology became a recognised professional qualification in 18 of the 27 countries of the European Union. While this marks a legal milestone in the 30 year campaign to establish the recognition and free movement of medical oncologists around Europe, the nine nations opting-out represent a large proportion of Europe in which foreign oncologists may require intensive periods of re-training.

The European Society for Medical Oncology (ESMO) has been battling to have medical oncology recognised as a professional speciality since 1975. The barriers that have been overcome in 18 European countries have been significant. Håkan Mellstedt, professor of oncologic biotherapy at the Karolinska Cancer Centre in Sweden and ESMO president from 2006-2007, has been lobbying for the recognition of medical oncology since the 1990s. “When I started there was no specific training in Europe and a lot of other specialities were involved in the treatment of cancers – surgeons, pulmonologists and so forth - as treatments were limited. Patient handling was not optimal, yet there was a lot of resistance towards establishing medical oncology from other specialities as they felt we were taking patients away from them,” he says.

There is no obligation on the other nine countries – Austria, Germany, Sweden, Denmark, Finland, The Netherlands, Spain, Estonia and Malta – to accept the amendment to the law [EU directive 2005/36/EC], which grants the professional recognition on the basis of a minimum of five years of training.

The obstacles to acceptance in these countries arise from the heterogeneous way in which medical oncology has developed. Many of the countries such as Spain have training periods of different duration, in others such as the Netherlands, medical oncology contains four years of training in internal medicine, many more than in other countries. In Germany, medical oncology is included within three separate cancer specialities with training periods of different durations. “Swedish authorities feel they don’t have to recognise medical oncology as a speciality on its own because it is already within the speciality of oncology, a five-year training period which also includes radiation oncology. The situation is similar in Denmark,” says Mellstedt.

“It’s wonderful that medical oncologists can now move freely between countries. But we have a responsibility to ensure an identical level of care throughout Europe”
EUROFILE continued ...

On a practical level, medical oncologists trained elsewhere in the EU can still work in these countries if they are willing to make up areas of difference in their training. According to Mellstedt, in Sweden and Denmark this means up to six months of radiation oncology, generally determined at the discretion of a departmental head. He feels it a satisfactory solution.

However, in the Netherlands, it can take up to six months to determine what course of retraining is required. Gaia Schiavon graduated with a medical oncology degree from Italy in 2008 and spent two years conducting clinical research in America before accepting a combined research and clinical post at the Erasmus University Medical Centre in Rotterdam in 2010. "It took a total of six months before I had an answer on how much re-training I would have to do. My qualifications and month by month accounts of my training in Italy had to be translated and analysed," she says.

Schiavon agreed to a further two years of internal medicine with the intention of finishing her PhD during this time. But the nature of re-training has not allowed for this. "I had planned to spend three days a week on research but working 12-hour shifts means I have had to delegate my research to weekends," she says.

Tempted to take a position in the Netherlands after a short research period in 2010, Alberto Zambelli from the IRCCS Fondazione Maugeri in Italy was also prescribed a further two years' training in internal medicine. "Having qualified as a medical oncologist in 2004 and practised for 6 years in Italy, it would have meant working long shifts and a reduction in pay and position. I had a young family. I went back to Italy," he says.

Even within the 18 countries which have endorsed the law, its application is not without difficulties. Several such as Italy have only recently increased their training requirements to a five year minimum period so the legislation will only benefit younger specialists rather than those who have already qualified.

Despite supporting the legal recognition of medical oncology qualifications, eminent specialists predict a flow of expertise from poorer to richer countries in Europe. Studying mortality rates and the provision of cancer care in Eastern Europe, Stephan Tanneberger, professor and scientific director at the Fondazione ANT in Italy is concerned an East to West migration of specialists will lead to widening inequalities across Europe. "In Hungary, Czech Republic and Poland, cancer mortality is increasing dramatically. We have seen how much suffering is in countries where there are not enough human resources for taking care of patients and developing oncology. Salaries are low and medical oncologists are looking to leave for better opportunities. But sending people for long-term training is not the best way to build up oncology in a country because..."
there is a high rate of failure to return home, so the overall effect is negative," he says. "It's wonderful that medical oncologists can now move freely between countries. But we have a responsibility to make sure of an identical level of care throughout Europe."

Oncologists across Europe agree that encouraging more students to go to medical school is part of the solution. "Part of the reason for migration is the lack of supply. And getting undergraduates interested in medical oncology early, especially in richer areas of Europe, is essential" says Alexandru Grigorescu, professor at the Institute of Oncology in Bucharest, and vice-president of the National Society of Medical Oncology in Romania who has already lost two of his resident medical oncologists to France and America this year.

It is hoped that the legal recognition of medical oncologists will attract more medical students to the speciality. As a next step, Tanneberger and his colleagues in Romania, Hungary and Poland are urging the European Commission, ESMO and other organisations to collaborate to produce guidelines on minimum requirements for cancer care and the number of medical oncologists needed to adequately serve a given population.

But harmonisation is a problem which can't be tackled by the medical community alone, says Tanneberger. "If done rationally together with politicians who not only want to win the next election but want to develop Europe, we can achieve a lot in 10-15 years. We haven't alternatives."

Saffina Rana
Brussels
The new one-stop-shop for cancer information: ecancerHub.eu

Gordon McVie (European Institute of Oncology, Milan), is a co-founder of ecancermedicalscience, which is one of the partners involved in eurocancercoms. It was awarded a European grant under the Framework-7 Programme to address bottlenecks in communication between different interest groups in cancer in Europe. The resultant website, ecancerHub, is to be unveiled at the forthcoming ECCO Congress in Stockholm (September 24-27, 2011).

Why was eurocancercoms set up?
The stimulus was the Eurocan+Plus report to the European parliament in 2008, which highlighted bottlenecks in cancer research and its translation into better cancer care in all European states. The FP7 project Eurocanplatform came out of it: top cancer institutes in Europe will share a platform for genomics, clinical trials, epidemiology, and so on, and thereby accelerate the rate of progress in translating ideas from lab to clinic.

The other product of Eurocan is eurocancercoms. We consulted groups of people – patients, relatives, basic scientists, the cancer societies representing different disciplines etc – on barriers to cancer research progress in Europe. Near the top of everyone’s lists was a failure of communications, and there was a cry for a simple system like nci.gov and clinicaltrials.gov for Europe. We wanted a one-stop-shop providing reliable information that is easily understood, and accessible to patients, scientists or clinicians.
INTERVIEW continued.

Are communications worse in cancer than in other medical specialties?
Cancer is not a single disease. Cancer scientists often work on a single gene or pathway, or a single imaging technology, and so on, and they don’t communicate with each other. The MRI people don’t know what the PET people are capable of, basic scientists don’t usually know a great deal about clinician’s work, and vice versa; many people only know their own bit of the cancer business. On top of that is the disease specificity. The end result is that we have communication channels which are internally effective but only used by a small number of people; they work well within each little silo, but the cross-communication between fields is minimal. By definition that’s a barrier to research.

The ‘people on the street’ are overwhelmed by the abundance of information, and almost none of it carries any trademark of quality. It’s frequently irrelevant to the problem that the particular patient or their relatives are facing. Information might be too generic, geographically irrelevant, or too difficult to understand.

So what is the solution?
Eurocancercoms partners (18 in number) have developed a flexible platform called ecancerHub, which is showcased on ecancer, and we’ll be unveiling the beta version of the programme at ECCO in Stockholm. It is totally open, there are no barriers to patients, scientists, healthcare professionals or policy makers and it uses up to date social media technology. The open space will be monitored by experts. We’re not producing any content ourselves; ecancerHub simply finds and signposts the content our experts consider to be the best on the web.

The search tool itself is the latest version of a Google search tool – a sort of cancer-Google search tool! It can be customised by any user, so you enter the site, say what your personal or professional interest is, and that immediately takes you into a particular area. You can look at European tools, such as the European Medicines Agency (EMA)’s EUDRACT, or globally at the entire inventory of NCI tools (caBIG), for example. You can upload and share your own content: audio, video, blogs, risk-calculating or genomic tools. And you can find information by a variety of tags. So with a geographic tag, you put in your postcode or zipcode and the platform takes you to the nearest cancer specialist unit is, allows you to find out which doctors deal with particular cancer types, what clinical trials could be available to you, and so on. These tools already exist but people can’t find them.

How can you be sure that all the sites you’re linking to will give out bona fide information?
Quality control is key, but we’re not fazed by that, we deal with quality control every day in publishing journals, and agreeing guidelines.

What is ecancerHub’s approach to guidelines?
Many sets of guidelines are completely inaccessible to patients, particularly those put together by clinicians for clinicians. There’s no reason whatsoever why someone with breast cancer can’t inspect the 50 or 60 sets of accredited guidelines on how to treat breast cancer – and ecancerHub will allow this in time – but we feel that guidelines are
INTERVIEW continued.

mostly helpful and relevant on a geographic basis. The Hub will signpost people according to their geographic location so they can access the guidelines for their region or country.

Shouldn’t guidelines be the same for everyone regardless of where they live?
You do need guidelines adapted for regions or countries. If there isn’t a linear accelerator in your region, or the capacity for robotic surgery, there’s not much point in guidelines based on this equipment. Guidelines may recommend drugs which are not available in certain countries, or not prescribed by doctors there for a variety of reasons.

Will ecancerHub cover oncopolicy?
The Hub is going to portray issues such as ageism in oncology, and affordability of care, how we could share policies which might help to keep the cost of cancer care under control. We will showcase themes and invite people to contribute, to add in guidelines, information about clinical trials which at present we can’t access through EUDRAC or clinicaltrials.gov. Doctors and scientists tend to be slow to add information via blogs or twitter, but we’re hoping that demands from patients and patient groups will stimulate responses from healthcare professionals. All of these cancer communities will be integrated on ecancerHub.

What sort of obstacles have you faced in getting ecancerHub up and running?
Fundamentally, we believe that all information should be accessible by everybody; there should be no firewalls. But in our discussions about EUDRAC, we found EMA is having problems taking down the firewalls within its system. It will happen – there’s no shortage of goodwill – but firewalls built at the insistence of Pharma still have to be dismantled. It’s hard work finding a specific trial for a specific disease type; doctors can do it but it might be 8 or 9 tiers down in the website. We want to make sure that everyone can access EUDRAC through ecancerHub.

Are there downsides to losing the firewalls?
One of the first countries to remove them was Italy, which has one of the few national clinical trials websites. Every clinical trial in Italy is accessible via the Italian website run by the Istituto Superiore de Sanita. There was sensitivity initially – not about the big phase III trials which are advertised – but about phase I studies. Pharma was concerned about losing commercial advantage by letting it be known publicly that they were putting a particular drug into a clinical trial of a particular clinical disease. But the Italian Department of Health held firm and in fact, everybody we have spoken to so far has welcomed the idea. There has been no resistance from Pharma so far, or from the medical profession.

How optimistic are you that you will get enough money for ecancerHub to continue over the long term?
Very. There is a wave of expectation from the general public; a feeling that we have rights to information. A lot of cancer patients are upset that they have to go to clinicaltrials.gov to find out about trials in Europe. And there are hordes of trials that are not on clinicaltrials.gov and never will be. If via ecancerHub, we can give access
INTERVIEW continued.

with one click of a button to Europe’s cancer trials buried within EUDRACT, to clinicaltrials.gov, and to the Italian national register trials, that will be a tremendous service.

Where do you see the ongoing challenges? We’re using hot off the shelf technology, and it’s impressive, but development won’t stop and I suspect that within a few years there’ll be something far better. You’ll be able to personalise more of your needs and so on. This is just the first step, and it’s overdue, but absolutely necessary in the era of the multidisciplinary approach to individualised care.

Helen Saul and Olivia Law
Leukaemia news from ASCO

Novel combinations for traditionally difficult-to-treat leukaemias were presented at ASCO (Chicago, Illinois; 4-8 June, 2011). One involved an interesting approach to induction chemotherapy in acute myeloid leukaemia patients aged between 62 and 86 years (abstract # 6505). This age group is the focus of much current investigation to find less toxic regimens than those tolerated by younger patients. The incidence of AML increases over 60 years, and prior myelodysplasia and abnormal karyotypes are among the reasons why inducing remission is more difficult, and why new regimens are eagerly awaited. Daniel Pollyea for the Stanford group presented the study. Using azacytidine, in a fixed dose, followed by lenalidomide in escalating doses in a Phase I trial in 18 patients, researchers observed a 44% response rate. This included 4 complete remissions, one of which was a complete cytogenetic remission, achieved without the typical marrow aplasia. The median remission duration was 6 months and was more common in those with less than 50% marrow blasts. Only 28% of these older patients had disease with adverse karyotypes, and the patients whose leukaemias showed pre-treatment hypermethylation were less likely to respond to the regimen, which is based on a hypomethylating agent. To estimate the chance of response in this age group treated with other regimens for comparison, the authors used the AML score, available online (www.aml-score.org), and found the remission rate they observed was comparable to other regimens, but with a significantly lower early death rate.

In refractory acute lymphoblastic leukaemia, Elias Jabbour from the M.D. Anderson group reported on 60 adults and children (25% were over 60 years old) treated since June 2010 with inotuzumab, a CD22 antibody bound to calicheamycin (abstract # 6507). Oncologists may recall that gemtuzumab, a CD33 antibody for AML was also linked toocalicheamycin; gemtuzumab was withdrawn from the market in 2010 for toxicity without superior benefit to other agents. Inotuzumab was chosen because of early data showing 20-40% response rate in indolent and aggressive lymphomas. It was given to most patients at a dose of 1.8 g/M² i.v. every 3 weeks for up to 8 cycles. Of 46 evaluable patients, with median follow-up of 4 months, overall response rate was 61%, which included 9 complete remissions. Perhaps most interesting was the finding that 16 patients with abnormal karyotypes achieved full cytogenetic remissions (out of 18 evaluable from the total 34 with abnormal karyotypes in the study), and that 18 of 28 evaluable for minimal residual disease showed none. These remarkable results did not, however, correlate with prolonged survival, which was 4.5 months overall in this heavily pre-treated group. A correlation between drug plasma levels and response has prompted the authors to explore other dosing regimens. Dr. Jabbour suggested that in the M.D. Anderson experience this agent was the most active single agent tested in refractory lymphoid leukemia. Certainly, 4 month follow-up is short, and many patients are not yet evaluable, but the data suggests there is dramatic cell kill when CD22 is targeted, and that when therapeutic drug levels are established and the drug tried in combinations, it may be a useful agent in inducing remissions in refractory disease. The hepatic toxicity seen with the CD33 antibody in acute myeloid leukaemia will be a concern in ongoing trials, particularly in patients in whom transplant after remission is considered.
Leukaemia at ASCO continued.

In chronic lymphocytic leukaemia, John Byrd reported for a consortium of U.S. investigators on a Phase 1b/II study begun in March 2010. The group used PCI-32765, an inhibitor of Bruton’s tyrosine kinase, a B cell receptor signaling kinase, which was found to induce apoptosis, decrease CLL cell migration and adherence to stroma, and block B-cell receptor signaling (abstract # 6508). The drug has a long half-life and can be given once daily orally. The trial population included 23 symptomatic, previously untreated patients and 27 relapsed/refractory (2 to 12 prior regimens) patients given the 420 mg/d dose, and a more recent cohort of 33 relapsed or refractory patients who received 840 mg/d, evaluable only for early toxicity. The main toxicity was infectious, typical of CLL and not associated necessarily with neutropenia, as there was little myelosuppression induced by this agent. Diarrhoea and nausea occurred in almost half, and muscle spasms in approximately 17%, all of which typically decreased on continued therapy. An overall response rate of 67% was observed in previously untreated patients, mostly partial remissions, and 19% nodal responses. Among the refractory/relapsed patients, overall response was 48%, nodal response in 41%. The pattern of response was an initial increase in lymphocytes and dramatic decrease in lymphadenopathy, followed by a drop in lymphocytes. Also seen were increases in haemoglobin and platelets among those who had been anaemic and thrombocytopaenic prior to initiation of PCI-32765 therapy. Dr. Byrd said it was “quite amazing” that at a median of 6 to 8 months, 81 to 85% were still on study in both groups, without progression, “feeling wonderful and continuing to improve”.

Two posters concerned potential treatments for refractory AML or ALL patients who are eligible for transplants and need bridge therapy to decrease leukaemic burden prior to transplant to increase the chance of post-transplant disease-free survival. Both posters studied common leukaemia agents prepared in liposomes, which allow increased doses with less toxicity. An international study presented by Schiller (abstract #6527) included 65 heavily pre-treated adults with ALL. They were given liposomal vincristine weekly at 2.25 mg/M² and 20% obtained complete remissions or complete remissions with incomplete haematologic recovery. Eleven were able to undergo stem cell transplants, 7 of whom had had prior transplants, and were thus at particularly high risk for complications. Three of 11 were still alive 28 to 35 months after transplant. The liposomal preparation delivered individual VCR doses from 2.8 to 5.5 mg. of dose-intensive drug, without apparent dangerous toxicity.

A small Phase I study (abstract # 9521) of clofarabine and liposomal daunorubicin, a regimen found effective in paediatric ALL, was undertaken in 9 relapsed or refractory paediatric AML patients. Three obtained complete remissions and were able to proceed to stem cell transplants. Liposomal daunorubicin was given at 60mg/M² days 1, 3, and 5, with two different doses of clofarabine (30 mg/M²/day x5 escalating to 40 mg/M²/d x 5), without the maximum-tolerated dose of clofarabine being reached.

Abstract e19649, accepted for publication only, highlighted a source of line infection which may be under-appreciated. K.R. Wells et al. reported on a collection of mycobacterial line infections due to M. mucogenicum, an organism first characterized about 5 years ago. Of 56 cases of this infection in adults after stem cell transplants, approximately half were found on central catheters and half on PICC lines. Important
Leukaemia at ASCO continued.

features of this study were that 37% of transplants had been autologous, myeloma was as common as leukemia as the underlying disease, and overall mortality was 30%. Infection was successfully treated with line removal, amikacin, and a macrolide, and rates decreased with HyTape wrapping and decrease in capping of lines. This study reminds us that new and worse infectious agents are coming along all the time, and that even patients receiving their own cells, who are presumed to be less immunocompromised than allogeneic recipients, are at risk for fatal infections.

Finally, a plenary paper compared regimens in use for over 30 years in lymphoid leukemia. The optimal use of “intensified methotrexate” was the focus of a Children’s Oncology Group study (AALL0232) of 3154 children and adults under 30 with pre-B acute lymphoblastic leukaemia (abstract #3). Focusing on the rising CNS relapse rate despite 75-85% survival, they compared the high-dose MTX/leucovorin regimen of Djerassi, in use since 1968, to the Capizzi regimen of escalating doses of i.v. methotrexate followed by 2 doses of pegylated L-Asparaginase, originally designed in 1978. This was a randomisation of patients in remission after the consolidation period, the so-called “interim maintenance #1” phase of their augmented BFM protocol. All patients continued to get protocol intrathecal methotrexate and the “Capizzi regimen” in another protocol segment. A reduction in both isolated CNS relapses and marrow relapses was seen, along with improved event-free survival (82% v 75%) for the high-dose MTX/LV regimen, with less febrile neutropenia. The difference was particularly among those patients considered “slow early responders” (79% v. 65% EFS), who had slow marrow response by day 15 or minimal residual disease on day 29. Essential points were not addressed in the presentation. Cranial irradiation (1200 cGy) was administered subsequent to this phase to the slow early responders, who constituted over half the patients, but the potential influence of RT was not discussed. Cranial RT is not routinely given to adults, so it is critical to provide the number of patients in the young adult age group, and their results, in view of the controversy about whether young adults should be treated on adult or paediatric regimens. Presumably, the complete data will be published in the near future.

Isabel Cunningham, MD