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Opposition to ESMO decision grows

Key opinion leaders in medical oncology have expressed their unhappiness at the ESMO Board's decision to withdraw from FECS (*see EJC News, 2006;***42**:*7*). The decision was taken after the ESMO General Assembly at ECCO-13 in Paris last year. It was communicated to members on 28th December, 2005 in an email from Professor Paris Kosmidis, who was ESMO President at the time.

Professor Kees Punt, medical oncologist at the Radboud University Nijmegen Medical Centre, The Netherlands, wrote objecting to the move, and copied his email to some 60 medical oncologists from all over Europe. "These are among the key opinion leaders in Europe, and I received positive support from a great number of them. There was not one single negative comment," he said.

In reply to Professor Punt's email, the current ESMO President, Professor Häkan Mellstedt (Cancer Centre Karolinska, Stockholm, Sweden) wrote, "The future of ESMO has been discussed repeatedly by the ESMO Board and at several meetings with key opinion leaders and the National Representatives during 2005 and GA [General Assembly]. The decision taken by the ESMO Board was based on what has been expressed by the majority of members as well as taking into consideration the possibility for ESMO to survive as a strong, independent and prosperous society for medical oncology." The ESMO Board's decision followed an announcement by the FECS Council that the Federation is to allow organ-based societies to become members; and that it is not, for the time being at least, to move towards becoming a member-based society. "At the ESMO General Assembly, the FECS model was declined by an overwhelming majority," he wrote.

Professor Punt, who attended the General Assembly, disputed that, and believes the decision was top-down. "There was a heated discussion at the General Assembly", he said, "but the main topic was the ESMO proposal to change its name into European Society of Multidisciplinary Oncology which was strongly opposed by the majority of attendees. As a result, this proposal was withdrawn by the ESMO board during the meeting. However, ESMO members have never received a full account of the discussions during this meeting. So the majority of European oncologists don't know what is going on, and probably don't care. The FECS and the ESMO Board may have lost contact with society members. FECS appears to have realised this since its current president, Prof. John Smyth, clearly said in Paris that it is investigating how it can perform better. I acknowledge the great difficulty in leading a society whose members have such diverse professional circumstances in a fully democratic way. But with its recent decisions the ESMO board is seriously risking alienation from its members."

ESMO has decided to allow non-medical oncologists to join as full members. But Professor Punt said it would be naïve to think radiotherapists and surgeons will do so on a large scale and leave their own society, certainly after ESMO has dissociated from FECS. "It is clear to every oncologist that the future of oncology is multidisciplinary. Every cancer patient deserves to have the opinion of all relevant specialists in the field. The structure of the societies representing the relevant disciplines should follow that strategy. Every discipline in oncology should have its own society to guarantee its specific interests, to support its specific needs, and to facilitate its development. But the societies of the respective disciplines should closely collaborate in order to reflect the multidisciplinary practice of oncology. The fact that one society has now withdrawn itself from such collaboration is the wrong signal and will weaken the status of oncology in Europe."

Professor Mellstedt wrote that FECS' intention to host an annual ECCO meeting would prevent ESMO from having its own large congress and it would only be able to hold small discipline meetings: "ESMO cannot survive in that way," Professor Mellstedt wrote. "The changes in FECS would very much threaten the survival of ESMO."

"I really don't see that threat, and in my opinion ESMO has not presented any convincing arguments to support this view to its members" said Professor Punt. "This decision, in which ESMO members surprisingly were not involved, could lead to the situation where there are 2 European conferences a year: ESMO's and FECS' ECCO. This will dilute the scientific impact of either meeting, and will be a waste of money as well. Oncology in the Western world benefits from general high-quality meetings in both Europe and the US. What we need in Europe is one such meeting a year, and for this we need the support from all relevant disciplines."

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Teenage cancers and possible causes

A newly-identified group of 'true' teenage cancers may help researchers discover and understand the causes, according to Professor Jillian Birch (University of Manchester, UK). Speaking at the 4th International Conference on Teenage and Young Adult Cancer Medicine, London, 29–31 March, 2006) she outlined a group of cancers that have a main peak of incidence in teenagers and young adults.

Professor Birch analysed a new data set provided by the UK National Cancer Intelligence Centre (Office for National Statistics, London). It included more than 1.6 million cases of cancer in people aged up to 79 years between 1995 and 2003.

It was previously known that the most common groups of cancers in teenagers and young adults are lymphomas, germ cell tumours, leukaemias, brain tumours, bone tumours and soft tissue sarcomas. "However, unlike the childhood embryonal tumours, these groups of cancers can be seen at all ages. This new research shows that there are specific types of cancers within these groups that show a main peak of incidence in 13 to 24 year olds," she said.

The cancers are Hodgkin lymphoma, osteosarcoma, Ewing sarcoma, certain rare soft tissue sarcomas, germ cell tumours of the testis and ovary and germ cell tumours in the brain. "These can be regarded as 'true' teenage and young adult cancers that typically occur specifically in this age group, rather than being either the tail-end of childhood cancers, the majority of which occur below the age of 10, or the unusually early development of cancers typical of older ages," said Professor Birch.

The data was analysed according to the types of cells and tissues involved in the cancers, Professor Birch said, rather than the site in the body at which the cancer occurs.

The findings imply that infections, adolescent growth spurts, hormones and other growth and development factors are among the probable causes of cancers in this age group, Professor Birch said.

An 'historic moment' in myeloma therapy

The addition of thalidomide to standard chemotherapy for elderly people with multiple myeloma is an effective first-line treatment, say Italian researchers. Patients given thalidomide had higher response rates and longer event-free survival than those who received the standard treatment alone (*Lancet* 2006;**367**:825–31).

Conventional chemotherapy with oral melphalan and prednisolone (MP) has remained the treatment of choice for people over 65 years since 1960. Younger patients benefit from high-dose chemotherapy with haemopoietic stem-cell support but this is not considered suitable in the older age group.

The new multicentre trial was run by the Italian Multiple Myeloma Network (GIMEMA). It included 225 patients who were older than 65 years (or younger but unable to undergo transplantation). They all received MP; the experimental group also received thalidomide (MPT). The median follow-up from diagnosis was 17.6 months.

The overall rate of complete response to MPT was 15.5%, nearly 5 times greater than that to MP alone. Event-free survival, another primary endpoint, was significantly improved by thalidomide; it was 16 months longer in the MPT, compared with the MP, group.

However, the MPT group had a higher proportion of early deaths from adverse events early on and the survival advantage was not evident in the first 9 months after randomisation. "Thereafter a trend toward a survival advantage became evident", the authors say.

The study protocol was amended almost 2 years after the study started, to include anticoagulation prophylaxis with enoxaparin, which significantly reduced adverse events.

"After 50 years of unsuccessful attempts to find new and more effective treatment approaches suitable for most patients with myeloma, our results lend support to the use of thalidomide in the initial treatment of elderly patients with multiple myeloma," the authors conclude.

The adverse effects associated with thalidomide remain an important consideration. A US study, also published recently, included patients aged 75 years or younger with newly diagnosed multiple myeloma (*NEJM* 2006;**354**: 1021–30). They all received 2 cycles of intensive melphalan-based chemotherapy, supported by autologous haemopoietic stem-cell transplantation. Half received thalidomide from the outset; half did not.

This study again found that thalidomide increased the frequency of complete responses. Event-free survival rates at 5 years were increased from 43% to 62%. "The drug failed, however, to prolong overall survival and was associated with considerable adverse effects," the authors wrote.

Relapses in the thalidomide group appeared to be more drug-resistant than relapses in the control group. A higher failure rate with salvage therapy and shorter survival after relapse partially explained the similar overall survival rates.

The US researchers note that another group, the InterGroupe Francophone du Myélome, reserved thalidomide for maintenance therapy after transplantation, which has advantages: "Resistance may be avoided; the risk of thromboembolic complications can be reduced, since this risk is highest during induction therapy, when the burden of tumour is high; and the incidence of neurotoxic effects should be reduced with the later introduction of thalidomide at lower doses during maintenance therapy."

An editorial (*Lancet* 2006;**367**:791–2) was ebullient, commenting, "This is a historic moment in myeloma therapy." It notes that ongoing trials with the thalidomide analogue lenalidomide, the proteasome inhibitor bortezomib, and replacing melphalan with cyclophosphamide "will likely redefine initial therapy for myeloma in the near future."

The discussion in the *NEJM* paper was more cautious, pointing to the "potential of the newer agents for irreversible and incapacitating chronic adverse effects". Acute complications and chronic sequelae may be minimized by combining "old" and "new" therapies, it stated, "especially since the genomic heterogeneity of multiple myeloma may require a multifaceted approach to treatment to achieve lasting control."

Chernobyl: 20 years on

Radioactive fallout from the Chernobyl accident in 1986 did not increase the incidence of thyroid cancer among children and adolescents in Finland, researchers say (*But et al., EJC, this issue, page 1167*). 20 years after the nuclear power plant exploded, the report provides some reassurance about the extent of the health problems it caused.

So far, the only established long-term health consequence has been increased risk of thyroid cancer in the population of the regions adjacent to the reactor. Previous studies have reported dramatic increases in thyroid cancer among young people in Russia, Southern Belarus and Northern Ukraine, and established a dose-response relationship between radiation and risk of thyroid cancer. The risk of radiation-induced thyroid cancer peaks 15–25 years after exposure, remains high for 10–20 years and then declines gradually, which means that further sharp increases in this cancer, as a result of Chernobyl, are unlikely.

The Finnish study used the Finnish Cancer Registry to identify 479 cases, diagnosed between 1991 and 2003. The population was divided into 2 exposure groups, based on an estimation of the thyroid dose received in 1986. At the time of the accident, most of the population lived in the more exposed Southern and Central Finland.

Thyroid cancer incidence was lower in the more exposed population. Increased incidence may reflect an increased number of diagnostic investigations and improved detection of the disease, but the researchers note, "Both localised and non-localised thyroid cancers seem to be detected more in the less exposed area than the higher exposed area."

Other studies conducted outside of the former Soviet Union have failed to demonstrate an elevated incidence of thyroid cancer. Similarly, this report concludes, "No increase in thyroid cancer was found in the population more affected by the Chernobyl fallout."

MEPs against Cancer

A campaign to tackle the differences in survival rates across EU member states has been launched by Members of the European Parliament (MEPs). The all-party group, called MEPs against Cancer, says that the EU can do much more to prevent the predicted cancer epidemic. So far, 44 MEPs have pledged to support the campaign.

The group is calling for the European commission to set up a Cancer Task Force and to promote the European Code Against Cancer. Further, it wants member states to implement the 2003 Council Recommendation on Cancer Screening for colon, cervical and breast cancer.

At the group's first conference, Liz Lynne, MEP and co-chair of MEPs against Cancer, said, "With an ageing population, the need for concerted action has never been more urgent. Member states are ultimately responsible for health policy, but there are strong initiatives which can be taken at an EU level and we could be doing much more. Unequal survival rates across Europe are unacceptable.

"Cancer professionals know what needs to be done, and it is up to us to ensure they can do it."

From left, Alojz Peterle, MEP and co-chair of MEPs against Cancer; Lynn Faulds Wood, President of European Cancer Patients Coalition; Adamos Adamou, MEP and co-chair of MEPs against Cancer; Liz Lynne, MEP and co-chair of MEPs against Cancer; Markos Kyprianou, EU Commissioner for Health and Consumer Protection.

The Nice Manifesto

The Nice Manifesto, a commitment from doctors, nurses, patients and advocates to support breast cancer research and improve patient care, was presented at the 5th European Breast Cancer Conference (EBCC-5, Nice, France, 21–25 March 2006).

The manifesto was endorsed by the 3 organisations which hosted EBCC-5: Europa Donna – the European Breast Cancer Coalition; the European Organisation for Research and Treatment of Cancer (EORTC); and the European Society of Mastology (EUSOMA). The conference therefore represents the views of all the major breast cancer advocacy groups and institutions.

Conference chair, Dr Alberto Costa, and co-chair Dr Stella Kyriakides, said that the Nice manifesto is "a promise to improve breast cancer care" for women in Europe. "It is a basic right for patients to expect the best care and the conference pledges to meet the challenge."

The manifesto comprises 7 goals:

- Improve the number and quality of European screening programmes
- Support breast cancer research
- Rethink the breast cancer staging system
- Define metastatic breast cancer guidelines
- Increase the number of breast care nurses
- Expand the Breast Unit accreditation process
- Recognise the essential role played by charities in independent breast cancer research

Targeting Cardiovascular Complications

The development of targeted treatments for cancer has been widely welcomed as a major breakthrough in improving outcomes, but do these advances come at the cost of adverse effects on the cardiovascular system? Evidence is growing that the actions of highly selective targeted agents—ie, that of switching key processes in the cancer-cell growth cycle on or off—also affect non-cancer cells that share the same signalling molecules.

Trastuzumab, a humanised monoclonal antibody against ERBB2, has shown efficacy in reducing risk of recurrence and increasing short-term survival in women with early and advanced ERBB2-positive breast cancer. However, Kenneth Chien (Massachusetts General Hospital Cardiovascular Research Centre and Harvard Medical School, Boston, MA, USA) noted recently that heart failure has emerged as a serious side-effect, occurring in 1–4% of patients treated with the antibody; 10% of patients show a decrease in cardiac function (*N Engl J Med* 2006;**354:**789–90). "The biological principles of cell growth, death, and survival are as important in the onset of heart failure as in tumour progression", he explains.

Another cardiovascular adverse effect—hypertension—is emerging as one of the most common side-effects of a different group of targeted cancer drugs, the angiogenesis inhibitors. In a recent small study, treatment with sorafenib

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(an inhibitor of RAF kinases, vascular endothelial growth factor [VEGF] receptor 2, and angiogenesis) was associated with a significant and sustained increase in blood pressure. 15 of 20 patients treated with sorafenib had an increase of more than 10 mmHg in systolic blood pressure. 12 of these patients had an increase of 20 mmHg in systolic blood pressure, with a mean increase for all patients of 20.6 mmHg ($p < 0.0001$) after 3 weeks of treatment (*J Clin Oncol* published online Jan 30 2006; DOI: as10.1200/JCO.2005.02.0503).

One of the researchers, Keith Flaherty (Abramson Cancer Centre, University of Pennsylvania, Philadelphia, PA, USA) says: "Angiogenesis inhibitors all cause hypertension. Increased [blood pressure] has been described for each of the drugs in this class". Evidence suggesting a link between impaired angiogenesis and hypertension is growing. "The most likely link is a change in nitric oxide production", he suggests. "[Nitric oxide] production is well known to be downstream of [mitogen-activated protein kinase] and other signalling molecules. VEGF also affects [nitric oxide] levels."

Another possibility is that hypertension results from depressed angiogenesis at the microcirculation level, a phenomenon known as rarefaction (ie, a reduction in the density of microvessels). This reduction in vascular surface area leads to increased peripheral vascular resistance, which increases blood pressure.

The good news is that the cardiovascular side-effects of targeted drugs seem to be manageable. Hypertension caused by angiogenesis inhibitors responds as effectively as essential hypertension to standard antihypertensive treatments such as calciumchannel blockers and thiazide diuretics, notes Flaherty. Moreover, a recent study of early ERBB2-positive breast cancer found that trastuzumab alone as the first treatment, rather than at the same time or after anthracylines (drugs which are known to be cardiotoxic), was associated with lower frequency of heart failure than had been noted in previous trials (*N Engl J Med* 2006;**354:**809–20) .

Chien proposes that the risk of heart failure associated with trastuzumab was negated because cardiac-stress signals had not been activated by anthracyclines. He suggests that pathological stimuli causing biomechanical stress (such as exposure to anthracyclines) activate pathways that lead to the death of cardiomyocytes. The irreversible loss of viable cardiac muscle is usually prevented by the

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concomitant activation of pathways that promote cardiomyocyte survival, including those involving gp130 cytokines and neuregulin. Inhibition of the ERBB2 receptor by trastuzumab leads to a loss of the neuregulin-dependent pathways that promote survival of cardiac myocytes. In most patients, activation of other survival pathways is sufficient to prevent loss of viable muscle cells and onset of heart failure. However, in a subgroup of patients, loss of the ERBB2-dependent survival pathways promotes the cardiotoxic effects of anthracyclines.

Chien argues that the cardiovascular effects observed with targeted drugs in oncology provide new insights into cardiovascular disease. "Given the similarity between signalling pathways in cancer and those in the heart, there is a strong possibility that clinical observations made in large-scale clinical oncology trials will uncover unsuspected modifiers of cardiovascular disease." He concludes: "One of the most exciting aspects of this new era of biologically targeted therapy is the increasing number of new fundamental scientific insights that are being generated by clinical trials in oncology".

Susan Mayor

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PODIUM

One in a Million!

Professor Nicol Keith

Nicol Keith is Professor of Molecular Oncology at the University of Glasgow, UK. His research focuses on the mechanisms underlying cancer cell self-renewal, which incorporates the key strategic areas of cellular immortality, cancer stem cell biology and chromatin regulation of gene expression. He is the Guest Editor of EJC's forthcoming Special Issue "Cancer Stem Cells: Opportunities for novel diagnostics and drug discovery."

What is a cancer stem cell?

It is the cell that initiates the process of cancer development. It is not a normal cell; it has been changed and is a target for transformation by carcinogens. Stem cells are rare: there might only be one for a million other cells in the tumour. They are identified by their behaviour: if you put a mass of cancer into tissue culture, most cells will not grow, but stem cells will.

The concept of such cells is a relatively old one; what's new is the discovery of these cells in solid tumours. People working in haemopoietic disease have been aware of cancer stem cells for some years; the cells have also been seen in animal models. But actually finding the stem cell in solid tumours and proving that it's the cell that gives rise to the full tumour has been a long drawn-out process.

Are stem cells at the root of all cancers?

Not necessarily, but they've now been found in breast, prostate and brain cancers. They are providing a new way of thinking about these tumours, for looking for prognostic markers, and therapeutic targets.

What has prompted the recent increase in research?

Over the past 5 years, there has been a gradual acceptance that these cells actually exist. There's been a convergence of technologies which has allowed the cells to be isolated. The field is developing in parallel with, and learning from, other areas such as embryonic stem cell research, adult tissue stem cell research, drug development, work on genes such as telomerase. The next 5 years will be important in establishing how we can use our knowledge in a positive way.

You don't face the same ethical issues as your colleagues from other fields?

The ethical issues surrounding embryonic stem cell research and tissue regeneration do not apply to cancer stem cells, which generally arise in adult tissues and have limited potential to differentiate. They are fundamentally different.

How could cancer stem cell research be used in the clinic?

We need to know whether the presence of cancer stem cells determines the clinical outcome. It could be that the patients who do badly have more stem cells, or that those they have carry more mutations. This work is in the early stages, but if it is the case that cancer stem cells fuel cancer growth, then identifying these cells will be helpful in giving information about the cancer: how aggressive it is, whether it will respond to therapy, and so on. If you have the means to detect the stem cell, it should also allow you to follow up patients after therapy to determine the presence or absence of stem cells and predict whether the individual will remain disease-free. We don't have good markers for this in many disease types.

How far do characteristics of the stem cell determine the type of cancer?

We don't know whether the molecular profile of a breast cancer stem cell is the same as that of a prostate cancer stem cell. If there are common factors across all cancer stem cells, we may be able to use the same target to tackle different cancers. But we may be looking at specific targets for each cancer type.

How will the research contribute to new drug development?

The first task is to see whether current drugs target stem cells; Glivec probably targets stem cells in chronic myeloid leukaemia (CML) and other drugs may do the same in other cancers. In future, stem cell research may lead to new classes of drugs, but for the time being we need to use a best guess approach. For example, we know that some cancer stem cells contain telomerase, so we could be looking at developing telomerase inhibitors.

Where do you expect the field to be in 5 years' time?

Publishing activity has exploded over the past 5 years as this "new" concept has generated a lot of interest. It will be tested over the next 5 years. We'll begin to sort out the molecular profiles of the cancer stem cells and hopefully, come up with proof of concept by showing we can target cancer stem cells in a therapeutically-useful way.

What do you hope the EJC Special Issue will achieve?

I've been pleased to be able to bring together authors from quite different fields who have given their opinions on the problems we're up against. These are fresh opinions that haven't been heard before, from experts from many different backgrounds asking, "How can I apply my knowledge and technology to this problem?" Sometimes whole areas of research can become dominated by a small group of people very quickly: if this Special Issue is anything to go by, it won't happen in cancer stem cell research.