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Cancer 'should be a Millenium Development Goal'

Cancer leaders have called for non-communicable diseases (NCDs) to be included in the Millenium Development Goals (MDGs) as a matter of urgency. Waiting until 2015 when the MDGs expire and successor goals are implemented will be too late, they say.

The heads of the Union for International Cancer Control (UICC), Lance Armstrong Foundation (LiveSTRONG), International Network for Cancer Treatment and Research (INCTR), and the American Cancer Society (ACS), say there has been global neglect of the cancer epidemic in low and middle income countries.

In a Comment in *Lancet Oncology* (*doi:10.1016/S1470-2045(10)70228-X*), the groups claim that the exclusion of NCDs from the millennium goals has led to a "skewed distribution of oversees development aid, with less than 2% of more than $44 billion actually helping developing countries in their fight against NCDs."

The NCD Alliance, which is pushing for correction of this 'oversight', was formed in 2009 when UICC joined forces with the International Diabetes Federation and the World Heart Federation.

It wants to see all countries develop and implement a national NCD plan; fully implement the Framework Convention on Tobacco Control; agree on cost-effective interventions for the early detection, treatment and palliation of NCDs; and build NCD management into global targets for the future.

"Millions will die unnecessarily if we do not include NCDs in the MDGs now," the *Lancet Oncology* Comment concludes.

NICE says no to trabectedin and ofatumumab

The UK's National Institute for Health and Clinical Excellence (NICE) has not recommended trabectedin (Yondelis) for relapsed ovarian cancer; or ofatumumab (Arzerra) for lymphocytic leukaemia that is refractory to fludarabine and alemtuzumab.

On trabectedine, NICE cited continued concerns over how well the drug works in relapsed platinum-sensitive ovarian cancer compared with the re-use of platinum-based chemotherapy.

For ofatumumab, NICE said the benefits it may provide compared with best supportive care 'does not justify the extra cost the Health Service is being asked to pay.'

See http://guidance.nice.org.uk/TA/Wave19/47 for draft guidance on trabectedin; http://guidance.nice.org.uk/TA/Wave22/7 for draft guidance on ofatumumab.

Synthetic lethality in a nutshell

The concept of synthetic lethality, which provides a new approach to drug development and is the mechanism of action by which the PARP inhibitors work, is explained in a review in this issue of *EJC* (*doi:10.1016/j.ejca.2010.07.031*).

Researchers adopting this approach are aiming to find secondary pathways which are essential for the survival of cancer cells but not normal cells. Corresponding author Professor Marco Foiani (IFOM & University of Milan, Italy) stressed its essential features in an interview with *EJC News*: "Where we have a well-defined oncogene, the standard approach is to inhibit the oncogenic process. But in a way, that's not sufficient. What you need to know is what is keeping this particular cell alive.

"With synthetic lethality, you are aiming to identify – through blind genetic screens – the other pathways in the cell which are essential to its survival. So we need information on top of what we already know about the oncogenic process; we're looking for these secondary pathways which work in tandem with the defective oncogenic path. And they will become new targets.

Professor Marco Foiani

"You could imagine that a cancer cell is a chair with 3 legs, the normal cell has four. The idea is to kill one leg in both cells so the normal cell survives because it still has 3 legs. The cancer cell with its 2 remaining legs falls over."

Continued over

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ESMO rewards outstanding contributions

ESMO is to honour eminent cancer specialists for their contributions to the advancement of medical research. The awards will be presented to Dr. Alberto Costa, Professor Bengt Glimelius and Professor Hilary Calvert at the 35th ESMO Congress (Milan, Italy, 8–12 October, 2010).

Dr. Alberto Costa will receive the 2010 ESMO Award for his role in the development of international guidelines for breast cancer and his ongoing commitment to the education of oncologists. Dr. Josep Tabernero, chair of ESMO's Fellowship & Award Committee, said: "Professor Costa is a leader in his field and has changed clinical standards."

He participated in the Milan trial (local control and survival in early breast cancer), the St. Gallen Consensus Report and in the development of chemoprevention. He has emphasised scientific communication, and supported patient advocacy groups, including Europa Donna.

Dr Alberto Costa

Professor Bengt Glimelius

Dr. Costa (Maugeri Foundation, Pavia) played a key role in the creation of the Italian School of Senology in 1984, and of the European Institute of Oncology, in 1994.

Professor Bengt Glimelius (University of Uppsala and Karolinska Institutet, Stockholm, Sweden) will receive the Hamilton Fairley Award which recognises achievements in science and clinical/laboratory research.

He has worked on malignant lymphomas, gastrointestinal cancer, radiotherapy and psychosocial care. According to ESMO, he has been instrumental in the substantial improvements in loco-regional control of rectal cancer through a systematic approach to staging, treatment and long-term follow up, of metastatic gastrointestinal cancer patients by using systemic chemotherapy in randomised trials.

The 2010 ESMO Lifetime Achievement Award will go to Professor Hilary Calvert (University College, London, UK) in recognition of his 'seminal work' on the introduction of carboplatin as a major anti-cancer agent, the development of a dosing formula based on its pharmacokinetics and its subsequent clinical use in ovarian cancer.

More recently, his work in the molecular pathology of human cancer, defining targets and developing specific drugs, has included research into the role of PARP inhibitors.

Professor Hilary Clavert

"We have amazing technologies that allow us to characterise gene expressions, mutations, translocations etc, at an unprecedented rate," Professor Calvert said. "The challenge is that many of the most promising potential targets for drug design are regarded as intractable (or undruggable). We need to develop techniques to approach these targets."

Synthetic lethality in a nutshell *Continued*

The PARP inhibitors are a well-known group of drugs which act via synthetic lethality, he said. Where there's genomic instability, a normal cell uses at least two independent repair processes: base-excision repair and homologous recombination, and problems can be fixed without consequences for normal cells. But patients with BRCA mutations may have cancer cells which cannot be repaired through homologous recombination so they rely entirely on base-excision repair. The PARP inhibitors specifically inhibit repair of this mechanism, so that cancer cells die. Normal cells with functional BRCA can rely on homologous recombination and survive.

As discussed in the *EJC* review, other classes of drugs have retrospectively been found to work through synthetic lethality. But in future, synthetic lethality will be used in drug development, and for that the secondary pathways have to be identified so they can become new targets. Professor Foiani said that powerful new technology is making this a reality; for example, robotics that can handle RNAi interference approaches are using model cells that mimick tumour cells with a particular genetic defect. The aim is to identify pathways that extend viability genetic approaches, and then develop drugs against those pathways.

"I'm optimistic that this might not be such a long haul," Professor Foiani said. "And that there will be other benefits. For example, in my lab, we're looking at drugs which are routinely used in the clinic and searching for genetic mutations which either sensitise the cells to the drug or make the cell resistant to the drug. It's exactly the same concept. We will learn why those drugs are effective in certain contexts and not in others. In the end, it's all a genetic problem."

EUROFILE

New moves to revamp the clinical trials directive

The European Commission is actively considering measures to improve the conditions for hosting academic pan-European clinical trials. Proposals suggested by the research community were put forward at a meeting held by the EORTC in Brussels, on 2 September 2010. Commission officials stressed that they were listening to academia, and open to suggestions. "We know what the problems are," said Stefan Führing, involved in the revision of the clinical trial directive at the Commission's department for Health and Consumer Protection: "Please come forward with concrete ideas and recommendations. The time to come forward is now."

Problems raised included the increased insurance burden for the sponsor, the divergent assessment of multinational trials and SUSAR (suspected unexpected serious adverse reactions) reporting to ethics committees, and the fall in trial numbers in Europe since an EU directive seeking to harmonise disparate clinical trials procedures came into force in 2004.

One of the largest difficulties facing non-commercial investigators is the requirement that a single sponsor must accept the legal and financial responsibility for running a trial across all study sites, and the cost of risk insurance. Having previously shared the costs for non-commercial pan-European trials, research institutions have found the requirement prohibitive.

The Commission has already discarded the idea of excluding non-commercial trials from the scope of the law. "We will have no schemes for different types of sponsor," Führing told delegates, "The same rules will apply to all. We are happy that the public consultation has confirmed this viewpoint. The question today is whether the legislation today takes care of the risk. If it doesn't we will go back to the drawing board."

Liselotte Højgaard, chair of the European Medical Research Council and the newly appointed chair of the scientific advisory body on clinical research in Framework 7, called on the Commission to adapt the regulation to a risk-based assessment of trials. This would result in lower insurance costs for many of the trials sponsored by academic institutions, since they predominantly correspond to research associated with a lower risk, such as studies using marketed drugs within their labelled indication for therapy optimisation.

However, it's an approach the Commission is reticent to take. "It's not easy to enshrine risk-based assessment in legislation," said Führing.

Instead he is keen for the Commission to cost the viability of an EU clinical trials compensation fund, proposed by Marcel Kentner from CCMO, the central committee on research involving human subjects in The Netherlands. "A small amount of trial funding could go towards the fund, and any claims could be dealt with from this," said Kentner. "Then there would then be no need for insurance."

"We should see how much it costs. This is exactly the sort of concrete idea we need now," said Führing.

Newly compiled Commission statistics presented by Führing at the meeting showed a 10% drop in the number of clinical trials applied for in the EU, from 5028 in 2007 to 4491 in 2009. A much greater drop is apparent in the planned number of participants in clinical trial applications during the same time period. They fell from 535,481 in 2007 to 358,429 in 2009.

Führing flagged the migration of trials to non-EU countries as "a highly political issue." EORTC director general, Françoise Meunier, told the Commission that the migration of trials was due in part to insufficient EU funding opportunities for large international phase 3 trials. "The Framework research programme covers phase 1 and maybe even phase 2 trials, but not phase 3 trials which cost millions and are going to answer big questions. This falls between industry and government."

Meunier proposed the creation of a European Investigator-driven Clinical Trial Fund at European level, equivalent to the European Research Council which funds investigator-driven basic research from the EU Framework budget. "It would have a common pot to best allocate scarce resources to a number of international academic clinical trials in all disease areas every year, through a competitive process targeting scientific excellence and public added value," she said.

Meunier's idea is supported by the European Medical Research Councils. "Make it a private-public partnership," said Højgaard.

Silvio Garattini, director of the Mario Negri Institute in Italy proposed a model based on a current Italian scheme which could be scaled up for EU use. Pharmaceuticals companies in Italy are obliged to pay a small percentage of their profits to the Italian drugs agency, which is then used to support investigator-driven clinical trials. "Set up 5 years ago, this now funds 75 long-term trials. Spain has also done this type of thing," he said.

When it comes to streamlining the assessment procedures for pan-European trials, "The regulatory goal is to establish a single opinion valid for all member states," says Ruxandra Dragia-Akli, director of the health directorate at the Commission's department for research. "There is also general agreement that SUSAR (suspected unexpected serious adverse reactions) reporting to ethics committees needs to be changed, but how to do this has not been discussed," said Draghia-Akli. "We hope it is not going to take another four years to change this directive."

But Alice Nemcova a delegate from the Czech Republic clinical trials unit thinks it might. "There's a lot of politics involved with ethics committees, and no one is willing to give up their say," she said.

The Commission intends to have the revision of the directive complete by autumn of 2011, after which it will be up to national governments to consider.

Saffina Rana
Brussels

Lifelong battle for childhood cancer survivors

Although 80% of children treated for cancer survive, many have special medical needs for decades afterwards, according to new Australian data. As they become adults, childhood cancer survivors face an almost a five times greater risk of a second cancer compared with the general population and are 7.5 times more likely to die prematurely; similar results have been recorded in studies done in the USA and Europe.

"Physical late effects must be prevented, or diagnosed at an early stage; the psychological and social evolution of each patient needs to be addressed by close collaboration between paediatric oncologists, adult oncologists and primary care, nurses, psychologists and social workers", says Jose Sanchez de Toledo (Hospital Universitario Vall d'Hebron, Barcelona, Spain). Spain and 25 other European countries are now contributing to PanCare, an initiative founded in 2008 that aims to improve care for all childhood cancer survivors. PanCare's 180 members are drawn from European health professionals, survivors, and their families, and have just met to discuss pressing issues (Mainz, Germany, Sept. 15–17, 2010). "Currently, our priority is to develop pan-European projects to follow up and characterise a large European cohort of former childhood cancer patients", explains Desiree Grabow, responsible for long-term surveillance at the German Childhood Cancer Registry (Mainz, Germany). After that, infrastructure for clinical follow-up needs to be improved. "These patients no longer belong in the paediatric unit but adult oncology units often do not feel responsible for them and do not have information about their former treatment", she highlights.

Adverse late effects seen in childhood cancer survivors are due to the long-term effect of radiotherapy and chemotherapy regimens, which often need to be aggressive to cure the original cancer. "The effects vary depending on the type of treatment used, the age and sex of the child when they are treated and also on the body region targeted", explains Patricia Ganz (Jonsson Comprehensive Cancer Center, Los Angeles, CA, USA). Ganz points out that although some patients cured by surgery alone tend to have few problems, children treated intensively with radiotherapy and chemotherapy can be at very high risk for organ toxic effects (heart, lung, kidney) and are more likely to develop additional cancers. "The most serious complications are second primary cancers followed by cardiovascular disease", agrees Raoul Reulen (Centre of Childhood Cancer Survivor Studies, University of Birmingham, UK). "In particular, women treated with chest irradiation during childhood (mainly for Hodgkin's disease) are at increased risk of developing a second primary breast cancer and heart problems. Specific chemotherapeutics agents, specifically the anthracyclines, have been associated with cardiomyopathy and congestive heart failure."

'ALMOST 75% OF SURVIVORS OF CHILDHOOD CANCER HAVE LATE EFFECTS'

Helena van der Pal and colleagues (Academic Medical Center in Amsterdam, the Netherlands) have shown that almost 75% of survivors of childhood cancer have late effects; a quarter has more than five different adverse effects, and 40% have one or more adverse event that is severe or life-threatening. "Apart from cardiovascular disease and second malignancies, these [events] also include orthopaedic, neurological, kidney damage, endocrine disorders and fertility problems. And, although most are not life-threatening, [they] can give a high burden of disease", she comments. Radiotherapy is particularly associated with growth disorders, cardiovascular, endocrine, and neurological events, and second malignancies, and with psychosocial and cognitive events, especially after CNS irradiation. Alkylating agents can cause fertility problems in male survivors and kidney toxic effects. "Whether there is a synergistic effect or an additive effect when both treatments are used remains the focus of research", notes van der Pal.

"The literature and our clinical experience also indicate substantial psychological problems in many childhood cancer survivors, usually related to their burden of physical problems", comments Ganz. Any chronic illness can create disruptions in normal social and educational development for a child and the more serious the persisting long-term effects (eg, chronic pain, scars, body image changes, fatigue), the more different many young adults feel. "The health insurance system in the US presents particular problems, but we hope this situation may be improved with the new health-care legislation", she adds.

'THE LITERATURE INDICATES SUBSTANTIAL PSYCHOLOGICAL PROBLEMS IN MANY SURVIVORS'

Lesley Ashton (Children's Cancer Institute Australia, Sydney, Australia), a coauthor of the recent Australian study, highlights that determination of the incidence and risk of the late effects of cancer treatment is the first step towards characterisation of the genetic factors involved. Specific variants in DNA repair genes are known to be associated with an increased risk of radiation-induced damage to normal tissue, whereas gene variants in the folate pathway have also been shown to influence the efficacy of some cancer drugs, such as methotrexate. "Ongoing research in this area is needed to refine existing cancer therapies, to develop systematic age appropriate longitudinal health care, and to enhance primary prevention campaigns encouraging cancer survivors to modify their lifestyle", concludes Ashton.

Kathryn Senior

For more on childhood cancer survivors in Australia see Med J Aust 2010;193:258–61

For more on PanCare see http://www.pancare.eu

This article originally appeared in Lancet Oncol 2010;11:924

PODIUM

A new network for translational research in ovarian cancer

Professor Hani Gabra is director of the Ovarian cancer action research centre at Imperial College London, UK. He is president of the newly-formed EUTROC (European Network for Translational Research in Ovarian Cancer) which will hold its first symposium on October 23rd, 2010, at the International Gynecologic Cancer Society's 13th Biennial Meeting (Prague, Czech Republic).

What exactly is EUTROC?

EUTROC has grown out of conversations over the last two years, based on an understanding of the unmet needs in ovarian cancer, which has a poor prognosis and is relatively rare. In order to carry out meaningful research, you have to bring together people from different centres.

EUTROC is a multi-disciplinary, trans-national framework for ovarian cancer which will bring science and translational research into the clinical environment. It's built on a group of centres which each had expertise in the systematic collection of frozen cancer tissues at the time of diagnosis. Most of these centres are linked through the TOC (Tumorbank Ovarian Cancer) Network, based in Berlin. Because the research groups in these centres were interested in the same questions, were carrying out similar research projects and were essentially collecting identical types of tissues, it seemed natural to expand TOC into a wider consortium. We want to develop predictive and response biomarkers in prospective clinical trials.

This has been more difficult to achieve than one imagines because of the resource implications. It also requires centres to have an interest in, and a capability for, fairly complex research that can be built into clinical trials. These are not standard phase II trials in which response or progression free survival (PFS) are the principle questions. More, they are complex translational phase II clinical trials, typically involving 80–120 patients, which cannot be conducted by single centres; they need a hardcore of interested co-investigators to take them forward.

Is this work more difficult in ovarian than other cancers?

Only in the sense that there aren't so many cases. In the more common cancers, 1–2 centres could team up to do this kind of work but you need more with such a rare tumour.

Despite the optimism that novel targeted therapies will substantially improve clinical outcomes in ovarian cancer, no predictive markers have been identified to select the patients most likely to benefit. One reason for this is the lack of systematic linkage of clinical and translational studies.

How many centres are involved in EUTROC?

About 15 centres across Europe – including Eastern Europe – which already map to the TOC network, are interested. We would like to develop biomarker type studies and then expand them into the type of clinical trials I have described. Within EUTROC, there are partners who are not clinicians, and that's one of our strengths; we have translational scientists and scientists with backgrounds in medicinal chemistry, biology and genomics who are integrated with the clinical centres. Ours is a comprehensive network which covers basic biology and drug development, right the way through to clinical trials.

We're a young group driven by a common vision and the enthusiasm of our members and we hope to do great things.

Is there a specific trial or project ongoing?

One area is the AKT pathway; we're looking at it in the context of response biomarkers and predictive biomarkers. We are having dialogue with several pharma companies at the moment about potential clinical trials that we'll take forward.

What do you hope to achieve as President?

My role is to bring together these centres in a single vision of translational research and clinical trials. We need coherence – for instance with common standard operating protocols between the centres so that what's done in one centre is equally quality controlled at another and that people move in a co-ordinated way through clinical trials. The idea is to bring seamlessness to a group of investigators who are already enthusiastic. It's taking the next step from single institutional enthusiasm to coordinated and purposeful activity across multiple centres in different countries. That's a challenge which depends on the willingness of the individuals to work together.

What sort of barriers do you anticipate?

Many! But, in particular, the regulatory hurdles for conducting clinical trials involving individual national institutions. We are hoping that, as a single entity, we can interact with pharma on European-wide studies. We will look for pharma to sponsor the trials to ease the regulatory issues but we would expect to discuss and develop protocols jointly with them. We have to ensure that we have access to data and that there is a commitment to publication and holding data.

How do you see the group in 3 years time?

We hope that we will have a vibrant organisation that is delivering change to patients. We want an end to the blunderbuss approach to treatment and to make personalised medicine that improves the targeting of patients a reality. That way, we can improve the difficult prognostic outcomes in ovarian cancer.

Helen Saul