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Calls for increased transparency at licensing bodies

The European Ombudsman, Nikiforos Diamandouros, has called on the European Medicines Agency (EMA) to give access to documents on suspected serious adverse reactions. The case could have wide-ranging implications for transparency at the agency.

Diamandouros became involved following a complaint by a man whose son committed suicide. EMA had refused access to documents relating to the acne drug isotretinoin, arguing that EU transparency rules did not apply to serious adverse reaction reports. Their release could result in circulation of misleading or unreliable data, EMA said.

However, the Ombudsman recommended that EMA review its refusal to grant this access and said that EMA could provide additional context to render such data and their significance more readily comprehensible by the public. EMA will respond by the end of July, 2010.

A Lancet editorial (*The Lancet 2010;375:1753*) stated transparency initiatives within EMA "might bring about more openness on licensing decisions and suspected adverse reactions.

"Since EMA plays an important part in the supervision and approval of medicines in the EU market for the benefit of public health, it should consider providing the widest possible public access to the requested reports in any form, including web-based resources, and pursue a proactive information policy for the public," the editorial states.

The sentiment is in keeping with moves at the US' Food and Drug Administration (FDA), which embarked on a major transparency initiative in 2009. Since then, according to Ms. Afia Asamoah (director of the FDA's Transparency Initiative) and Dr. Joshua Sharfstein (chair of the Transparency Task Force), writing in the New England Journal of Medicine (*doi:10.1056/nejmp1005202*), it has held two public meetings, multiple listening sessions, launched an online blog and set up a system for soliciting ideas from the public.

In May, 2010, its Transparency Task Force released a report containing 21 draft proposals for expanding the disclosure of information.

It includes measures such as elaborating on the FDA's decisions; providing increased access to important data, illuminating enforcement efforts and supporting innovation.

While not all of the proposals will necessarily be implemented, Ms. Asamoah and Dr. Sharfstein believe that implementing some would accelerate the development process for medical products by allowing companies to learn from the successes and failures of other products. "One proposal, for example, would allow the FDA to explain that an orphan drug whose application was abandoned or withdrawn by the sponsor for business reasons may nevertheless represent an important therapeutic advance for a rare disease," they write.

The information could encourage additional investment for development of that drug or provide another company with the incentive to purchase and continue with the application.

They conclude, "With the daily practice of medicine routinely affected by the decisions of the FDA, the medical community has a large stake in transparency at the agency."

The European Ombudsman's full recommendation: http://www.ombudsman.europa.eu/cases/draftrecommendation.faces/en/4810/html.bookmark

The FDA's draft proposals: www.fda.gov/transparency. Comments will be accepted until July 20, 2010

Capecitabine in gastric cancer

The UK's National Institute for Health and Clinical Excellence (NICE) has issued a final appraisal determination recommending capecitabine (Xeloda) in combination with a platinum-based regimen for the first line treatment of inoperable advanced gastric cancer.

Dr. Carole Longson, NICE's Health Technology Evaluation Centre Director said, "Oral capecitabine-based regimens are at least as effective as the other fluorouracil-based regimens currently used to treat gastric cancer."

The draft guidance is now with consultees and NICE's final decision is expected to be published in July 2010.

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Vitiligo and melanoma – two sides of the same coin?

Like many unexpected but welcome discoveries in the history of medicine, basic science may not always blaze a trail but it can put up sign posts to point the way. Such was the case when a study examining the genetic underpinnings of one skin disease, vitiligo, yielded insights about another, melanoma. The findings, published in the *New England Journal of Medicine*, suggest that vitiligo and melanoma might be opposite sides of the same coin, genetically speaking.

The genome-wide association study aimed at finding generalised vitiligo susceptible loci involved 1514 patients with vitiligo and 2813 people without, all of whom were of white European descent. Results turned up several genetic variants in nine chromosomal regions that further support vitiligo's link to other autoimmune diseases, and a genetic variant linked to lower susceptibility to melanoma. The current study comprises the first two phases of a three-phase international research effort called the VitGene consortium project, which aims to identify susceptibility genes for generalised vitiligo in white individuals, then extend the search to non-white individuals and examine gene–environment interactions.

According to the study by Ying Jin and colleagues, the immune system might be upregulated in vitiligo and downregulated in melanoma. A genetic glitch in the protein (tyrosinase) that makes melanin causes it to produce a variant in vitiligo, which the immune system seems to identify and attack more easily. "So the same people who easily develop an autoimmune disease, vitiligo, because the immune system attacks pigment cells, may find that they are less likely to get melanoma since early melanoma cells are more efficiently attacked by the human body, which easily recognises the same antigen sign posts", explains Robert Brodell (Northeastern Ohio Universities College of Medicine, Warren, OH, USA). "However, no large patient study to date shows a protective effect of vitiligo against melanoma", suggests Brodell. "Now, that this study suggests the possibility, perhaps such a study will be done."

"It is intriguing that an alternative polymorphism of tyrosinase is associated with melanoma, suggesting that these distinct allelic linkages correlate with greater or diminished immune-recognition of tyrosinase and melanocytes", comments David Fisher (Harvard Medical School, Boston, MA, USA). He predicts that "these findings could lead to the better identification of [patients with melanoma] who will respond to immunotherapeutic regimens, and may help to establish better early detection or prevention strategies".

'THIS MAY EXPLAIN WHY SO MANY MELANOMA IMMUNOTHERAPIES HAVE BEEN SO DISAPPOINTING'

For vitiligo researchers and clinicians from the immunological camp, the new findings reassuringly fuel the concept of vitiligo as an autoimmune disease. "Patients or family members with vitiligo have a higher percentage of autoimmune disease, so it's guilty by association", says Raymond Boissy (University of Cincinnati College of Medicine, Cincinnati, OH, USA).

Now this study offers a solid genetic basis for that association. "The findings highlight that vitiligo shares risk genes with the other autoimmune diseases with which it is epidemiologically associated (particularly autoimmune thyroid disease, type 1 diabetes, rheumatoid arthritis, psoriasis, pernicious anaemia, systemic lupus erythematosus, and Addison's disease), only about half of which have thus far been extensively studied from the genetic standpoint", explains study co-author, Richard Spritz (University of Colorado School of Medicine, Aurora, CO, USA).

'THE SHARED SUSCEPTIBILITY GENES MAY HIGHLIGHT NEW TARGETS FOR THERAPEUTICS'

"The results are especially important for the melanoma field", says Estela Medrano (Baylor College of Medicine, Houston, TX, USA), who is cautiously optimistic about the study's clinical implications. "The hypothesis that a defective tyrosinase variant (402Q) may be poorly antigenic due to its reduced expression may help explain, at least in part, why so many attempts to target melanoma by immunotherapies have been disappointing so far." She adds that further research would help to determine "whether presence of the 402Q variant in individuals with primary non-invasive melanoma may have predictive value for tumour invasiveness and poor responses to immunotherapies".

The findings fit with longstanding studies in patients with melanoma, particularly those who might develop vitiligo in the course of their treatment. "Interestingly, melanoma patients with metastasis who respond well to immunotherapy and experience tumour regression actually develop vitiligo, which is a sign of good prognosis", says Boissy. Some case studies have also shown prolonged survival in patients with melanoma metastases and vitiligo.

"There's the general idea among those who treat melanoma that if you develop vitiligo, then your prognosis is better", says Delphine Lee (David Geffen School of Medicine, UCLA, California, USA). "It could be that their vitiligo is a clinical manifestation of a physiological response to abnormal melanocytes and it could be protective for those individuals".

"Ultimately", says Spritz, "these shared susceptibility genes may highlight pathways and targets for therapeutics that may thus be effective in several [autoimmune] diseases".

Angela Pirisi

For more on the study by Ying Jin and colleagues see N Engl J Med 2010; 362:1686–97

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EUROFILE

Health ministers ready to fund Partnership program

Health ministers across Europe are ready to put up half the cost of a 7.5 million euro proposal on collaborative cancer work if the European Commission matches their offer.

The 3 year proposal has been developed by countries and organisations taking part in the EU Partnership for Action Against Cancer – launched by the European Commission in September 2009. It was developed during preparatory meetings in January and February 2010, and suggests activities in all areas of the Partnership: collection and analysis of comparable data, best practice in cancer related healthcare, prevention and research.

The proposal has been submitted as an EU Joint Action and, if approved, funds put forward by member states would be matched by the EU's Health Programme budget.

The Commission's Health directorate has been overwhelmed by the scale of the proposal. "It includes the participation of virtually all member states," says an official in the Commission's directorate for health and consumers. "Member states are ready to put up half the money and in these economic times, that's no small statement."

However, it also costs more than the Commission had originally envisaged – around 2.5 million euro according to

'IT INCLUDES THE PARTICIPATION OF VIRTUALLY ALL MEMBER STATES'

Partnership stakeholders. "We have an extremely limited budget in the Health Programme and I don't think we are going to be able to find the money to support everything, but we are really making an effort to find the money to support as much as we possibly can," says the official. The EU's Health Programme has a budget of 321.5 million euro for 2008–2013 to cover public health projects across the board.

The Partnership proposes a series of work packages, each conducted by a consortium. Main partners – interested countries and organisations – had to commit to funding 50% of the work package. Italy has chosen to be the main partner for a work package on health information, gathering epidemiological indicators for cancer in Europe – incidence, prevalence, mortality, survival, costs in terms of burden, and patterns of care.

The Italian ministry of health appointed Milena Sant (Fondazione IRCCS Istituto Nazionale dei Tumori, Milan) scientific co-ordinator of the EU Eurocare project on cancer survival, to lead the work. "The aim is not to produce anything new, but to put together data that are already out there, hard to find or hard to access," she says. "We will make it available in the most accessible way, for example through a website for the public, stakeholders, scientists and patients."

Other committed partners include IARC, the Italian National Institute for Health, the UK Department of Health, the European Society for Clinical Nutrition and Metabolism (ESPEN) and countries: France, Portugal, Latvia, Hungary, Netherlands and the UK. The package has been costed at 500, 000 euro. "It's quite low, as our task is to collate the information, not produce it," says Sant.

Malta has taken on national cancer plans, aiming to establish the state-of-play in the EU, evaluating the content and efficacy of existing plans and ultimately transferring knowledge and expertise between member states. A source close to the package said there is little consistency across the EU. "Some countries are revising existing plans, some are developing their first plans and some haven't even started yet. The proposed work will also look at the content: how the programmes will be put into practice, and with what resources." Partners include Belgium and Ireland.

Prevention would be led by the European Cancer Leagues (ECL). Key elements include communication of the European Code Against Cancer and targeting specific populations. "We will do this by determining the baseline situation and developing strategies through surveying our members. We also propose to relaunch the European Week Against Cancer from 2011, and develop tools to evaluate public awareness and changes in behaviour," says ECL President, Tezer Kutluk. "Targeting populations includes specific actions aimed

'WE WILL SUPPORT AS MUCH AS WE POSSIBLY CAN'

at young people, using social networking media such as Facebook and Twitter," he adds. These would include campaigns on sun safety, alcohol consumption, and smoking for 13–25 year olds, evolved with their help. Partners include IARC, AIM, UICC, the European Cancer Patient Coalition (ECPC), and Schools for Health in Europe (SHE).

The ECPC proposed a Virtual Partnership – an interactive website (www.cancerpartnership.eu) which would allow ideas and documents to be shared between the work packages, and provide a networking platform for patient organisations, nurses, academics, pharmaceuticals sectors, and journalists. The work will be led by Slovenia, as the ECPC could not commit to funding 50% of the work. "However, the lead partner could subcontract the ECPC," says Jan Geissler, ECPC Director. "I think the budget [for the virtual partnership] will be cut down considerably, and we think we can do it on a low cost-low effort basis." The ECPC will host a conference in October 2010, to get the data co-operation going in areas of strong commitment.

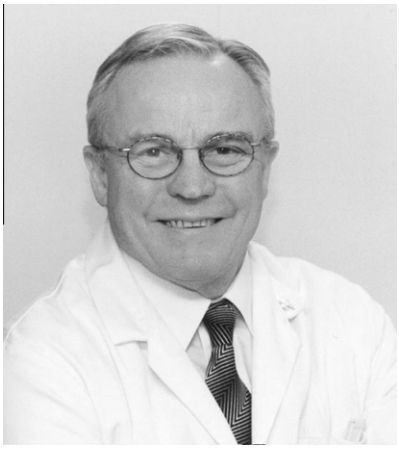
The Commission will decide which activities will be funded by November, enabling work to start by the end of 2010.

Saffina Rana
Brussels

For more information see Eurofiles: EJC 2009;45(8):1327 and EJC 2009;45(14):2441

PODIUM

Chemotherapy in breast cancer: the final hurdle?



Professor Trevor Powles (Emeritus Professor, Institute of Cancer Research, and lead clinician, Parkside Oncology Clinic, London), led the Royal Marsden Hospital tamoxifen chemoprevention trial (Lancet 1998, 352; 98–101), one of the four large randomised studies of tamoxifen use in healthy women at high risk of breast cancer. Tamoxifen was approved as a preventive agent in the States by the Food and Drug Administration in 1998, but a recent paper (Cancer Epidemiol Biomarkers Prev 2010 19(2) 443–6) found that fewer than one in a thousand women aged between 40 and 79 actually take the drug.

Why is the figure so low?

The figure is lower than was anticipated in the US, and the reasons for that are difficult to pin down. They probably come down to concern about the safety of tamoxifen and an effect on risk reduction that was considered to be relatively small. But these fears are not well-grounded. We've done a meta-analysis and found that the safety of tamoxifen is very high by comparison with most drugs, and that it reduces the risk of breast cancer by about 40%, which is significant.

What is the position in Europe?

Tamoxifen hasn't been licensed in any European country for risk reduction of breast cancer. It was only approved for this indication in the US.

Is the situation likely to change?

Promotion of tamoxifen could change things, but because it's off patent, and not being sponsored by a pharmaceutical company, that's probably not going to happen. Another approach would be to look at newer selective oestrogen receptor modulators (SERMs) and this is where there's been most activity over the past 10 years. Raloxifene shows a similar, or possibly less, reduction in risk of breast cancer compared to tamoxifen and also reduces the risk of vertebral fractures. It also has a lower toxicity profile and doesn't increase the risk of endometrial cancer in the way tamoxifen does. That makes it an attractive option for the subpopulation of patients with an increased risk both of breast cancer and of osteoporotic fractures through having a low bone mineral density. But because raloxifene is no better than tamoxifen at reducing the risk of breast cancer, and not as good as the bisphosphonates at treating osteoporosis, its use in chemoprevention has not taken off. It has also not been aggressively marketed, and has only another year or so under patent.

Wouldn't public health bodies be more able to afford prevention drugs if they're off patent?

That's correct, but if a drug is within patent, it has all the machinery of a big pharma company to encourage its use. Without this, it's a different model altogether. You can still do it – it's been done with low dose aspirin – but the momentum is of a different scale.

What other drugs are on the horizon?

We've reported on two more drugs recently. One was the PEARL (Postmenopausal Evaluation And Risk reduction with Lasofoxifene) trial, which compared two different doses of Pfizer's lasofoxifene with placebo; it wasn't studied in direct comparison to tamoxifen. It had a high efficacy in reducing risk of breast cancer; there was a 70% reduction in risk of oestrogen-receptor positive (ER+) breast cancer. At the same time, it reduced the risk of vertebral fractures and of non-vertebral fractures – hip fractures – which is important. It reduced risk of major cardiac events and of stroke (*NEJM 2010 362:686–696*). This drug has not been approved in US at the moment, but has been approved by the (European Medicines Agency) EMA for risk reduction of fractures, though not for breast cancer prevention.

This drug is probably as good as we're going to get with drugs like tamoxifen. It has multiple outcome efficacy and a low toxicity profile. One unexplained aspect of the data is an increased mortality at the lower dose of lasofoxifene; there was an increase in all-cause mortality of about 10% which was just significant. But there was no obvious reason for it; it didn't fit in with the toxicity profile. There was not a significant increase in mortality for the higher dose, which was also most effective in reducing risk of breast cancer and fractures etc. But that has held up the FDA's approval. The EMA considered the mortality data an aberrant chance event.

And the other drug you mentioned?

The other drug was Eli Lilly's arzoxifene, which again significantly reduced breast cancer risk and, again, the risk of vertebral fractures. Unfortunately, it didn't have a significant effect on non-vertebral fractures and its toxicity was similar to tamoxifen. Eli Lilly thought it was going to be the next generation SERM; after these results, they pulled the rug on it. But it does give yet more evidence that these drugs reduce the risk of breast cancer.

PODIUM

Lasofoxifene seems to have a wide spectrum of benefits: breast cancer, bone health and vascular improve-ments. Why is there still reluctance to license it as a preventive agent?

There's a real problem in promoting drugs with multiple beneficial outcomes; in selling to the public, to marketing people and to licensing agencies. All of the models we use for evaluating drugs weigh up a single beneficial effect against side effects. Pharmaceutical companies are set up with cardiovascular divisions, oncology divisions, and so on. The same goes for regulatory bodies. So when you have multiple outcomes they get unbelievably confused. I've done presentations on breast outcomes of drugs to a scientific advisory committee composed entirely of experts on bone health – oncologists were not brought into it and knew nothing about the drug because it came under women's health.

The second problem is that these drugs only work on ER+ breast cancers. We ought to know the risk factors for ER+ breast cancer, but we don't; we're always looking for risk factors for all breast cancers. Only 75–80% breast cancers are ER+ so you get a dilution of the effect. If you reduce ER+ breast cancer by 70%, you only reduce the risk of all breast cancers by 50%. We really need to more accurately identify the risk for ER+ positive breast cancer.

Is that going to happen?

Genetic work is identifying SNPs or commonly occurring polymorphisms which indicate risk for breast cancer. About 12 of them have been identified, and a paper just out in *Nature Genetics* identifies another five (*doi:10.1038/ng.586*), picked up by the human genome project. Although each of these loci is low risk, some will relate to oestrogen, and they probably interact with each other and with some environmental factors. We can also look at clinical factors which we know are hormone-driven, such as radiological breast density and blood hormone levels.

If we were able to more accurately identify women who had, say, a lifetime risk of getting ER+ breast cancer of 1 in 5 or even higher, the case for chemoprevention would start to get compelling. At the moment, we're looking at women who have a risk of something like 15 to 20 per 1000 over 5 years. There's a lot of work going on at the moment into identifying more accurately the risk factors for ER+ breast cancer, and I think that's what's needed to take the next step forward.

Are there any other reasons to believe we're close to seeing chemoprevention become routine in practice?

When we originally carried out the Royal Marsden Hospital tamoxifen trial, we found that tamoxifen reduced the risk of breast cancer more decisively during follow up – when we'd stopped the tamoxifen treatment – than during the treatment period. We now have 20 years' follow up – the trial is still blinded – and it looks like this spill-over benefit could even be a lifetime effect. The curves are still separating at 15 years.

If this turns out to be the case, someone taking tamoxifen, or lasofoxifene or another drug, for five years could be looking not at reduced risk of breast cancer over a five year period, but protection that could go on for twenty or thirty years. The case for chemoprevention then becomes much more compelling.

Putting these two advances together – identifying women at high risk of ER+ breast cancer and looking at the long term effects – it could be that these drugs will offer a lifetime reduction of 60–70% in ER+ breast cancer. Once we're at that point, I think taking 5 years of a drug will become a much more acceptable proposition to healthy women.

Will this happen in the next five to ten years?

I think it will happen before then; the risk factors for ER+ breast cancer are going to become much more robust in the next two or three years. Combined with that, we are in the process of a meta-analysis – with longer follow up than in previous analyses – on the spill-over benefit. If it confirms what we suspect, we will be able to say that the benefit continues over the longer term, and make this a much more attractive modality of treatment.

Do you see any difference in the attitude towards chemoprevention among European women compared to Americans?

I don't think so. I can't base this on practice because tamoxifen is not licensed here. But at the Marsden, a single centre, we recruited 2,500 women into the tamoxifen trial over a period of 10 years. The uptake for that trial was better than probably any trial we've done. It was purely because women were saying that we ought to be able to prevent this disease and they were therefore enthusiastic about doing a trial in order to get there. That's an important clue to say – if we can show that it works, within the constraints we've discussed – that the uptake here will be as good or better than in America.

It's an exciting time for such a common disease?

It is. And I'm surprised there hasn't been a more positive response to the results we already have. We have included 100,000 women in the trials of SERMs for the prevention of breast cancer. We have got strong evidence that we can reduce risk of ER+ breast cancer substantially and that the spill-over benefit continues afterwards. I'm surprised that there hasn't been more impetus for getting chemoprevention into clinical practice.

But I think we're almost there. If we can identify the risk factors for ER+ breast cancer and really get over the message that there's a long term benefit from a short term treatment, I think we'll see it happen.

Helen Saul