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The 44th Annual Meeting of the American Society of Clinical Oncology (ASCO) took place in Chicago, Illinois, USA (May 30–June 3, 2008). Robert Day-Webb, EJC's scientific editor, reports from the meeting

Vitamin D deficiency linked to breast cancer

Vitamin D deficiency has been linked to poorer outcomes in patients with early breast cancer (*J Clin Onc 2008;**26***: May Supplement. Abstract #511).

Canadian researchers found that women with vitamin D deficiency at the time of diagnosis are 94% more likely to experience metastasis and 73% more likely to die, compared to women with adequate levels.

The researchers studied 512 women diagnosed with breast cancer between 1989 and 1995 and followed their progress prospectively until 2006. At the time of diagnosis, 38% were classified as being deficient in vitamin D, 39% were classified as having insufficient levels, and only 24% were deemed as having adequate levels of the vitamin.

"Our results need to be replicated in other clinical studies," said lead author Dr. Pamela Goodwin, (Mount Sinai Hospital, Toronto, Ontario, Canada). "These data indicate an association between vitamin D and breast cancer outcome, but we can't say at this time if it is causal."

If these observations are confirmed in a second, ongoing study. Dr. Goodwin would like to see a new randomised clinical trial examining the effects of vitamin D supplementation on outcomes.

Experimental agent 'shows benefit' in renal cell carcinoma

A multicentre phase III trial has found that the experimental targeted therapy everolimus (RAD001) delays cancer progression in patients with metastatic renal cell carcinoma that has progressed despite treatment with other targeted therapies (*J Clin Onc 2008;**26***: May Supplement Late Breaking Abstract #5026).

The study provides convincing evidence that RAD001 is not only a safe and effective treatment for advanced renal cell carcinoma but that it also represents a new approach to cancer treatment by inhibiting the mTOR protein, a principal regulator of tumour cell division and blood cell vessel growth in cancer cells.

"This study has given us a new and clearly useful tool for treating renal cell tumours. It's an important step forward for patients living with this disease," said Dr. Robert Motzer, the study's lead author (Memorial Sloan-Kettering Cancer Center, New York, USA). "In the future, kidney cancer is likely to be managed as a chronic disease with treatments including this one."

The study randomly assigned 410 patients with metastatic clear-cell carcinoma whose disease had progressed while being administered sunitinib and/or sorafenib to receive best supportive care plus either RAD001 or placebo. After 6 months, 26% of the RAD001 patient group had not progressed compared to only 2% in the placebo group. The median progression-free survival for the RAD001 group was 4 months compared to 1.9 months for the placebo group.

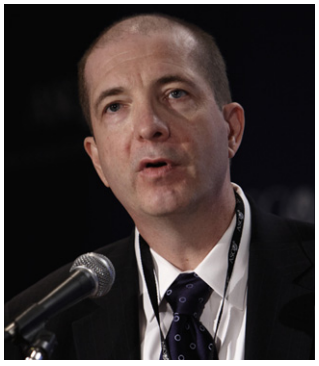

Photo courtesy of ASCO

Dr. Robert Motzer

RAD001 is the only agent with an established clinical benefit for the treatment of patients with renal cell carcinoma after vascular endothelial growth factor receptor-tyrosine kinase inhibitor therapy. Dr. Motzer suggested that it should be the standard of care in this setting.

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ASCO 2008

Gemcitabine 'doubles pancreatic cancer survival'

Gemcitabine more than doubles overall survival in patients who have undergone surgery for pancreatic cancer, a study found.

The CONKO-001 trial is the first large-scale phase III study to show a benefit for any adjuvant chemotherapy agent given to early-stage pancreatic cancer patients (*J Clin Onc 2008*;**26**: May Suppl. Abstract #4504).

Among the 368 patients who had their pancreas removed, 21% of those treated with gemcitabine (Gemzar) were alive 5 years later, compared with 9% of those who had surgery but no chemotherapy. Gemcitabine doubled the time patients were in remission, from a median of 13.4 months in the treatment group, compared with 6.9 months for those who had surgery alone.

Gemcitabine is the standard treatment for inoperable pancreatic cancer. However, previous results from this study (presented at ASCO 2005) had already shown that adjuvant gemcitabine improved disease-free survival. These latest findings now confirm the benefits of gemcitabine earlier in the course of the disease, with adjuvant treatment significantly improving both disease-free and overall survival. Gemcitabine was well-tolerated by patients in the study group.

"The ultimate goal of adjuvant therapy is improving the cure rate, and we have shown that this treatment more than doubles the overall survival 5 years after treatment," said Dr. Hanno Riess, leader of the CONKO study group (Charité University Medical School, Germany). "Based on the earlier results of this study, this regimen is already more widely used in both Europe and the United States. These findings can reassure physicians that the drug is also extending lives."

Narcolepsy drug 'alleviates fatigue'

The narcolepsy drug modafinil can help treat severe cancer-related fatigue, a phase III study has revealed (*J Clin Onc 2008*;**26**: May Supplement Abstract #9512).

The randomised trial included 642 patients undergoing chemotherapy for a variety of cancers. Half of the patients were given modafinil and half were given a placebo. Modafinil is a stimulant thought to promote wakefulness without interfering with sleep or causing addiction concerns because it is cleared from the body in about 12 hours. It is currently approved by the US' Food and Drug Administration for the treatment of narcolepsy, sleep apnoea and other sleep-related problems.

Patient fatigue, sleepiness and depression were evaluated by survey and were assessed twice – first at the time the trial started (during the second cycle of chemotherapy) and again during the fourth cycle of chemotherapy.

Results showed that patients who had the most severe fatigue at the beginning of the study demonstrated significant improvement from taking modafinil, compared to those in the placebo group. Patients with mild or moderate fatigue did not see the same improvements. The drug also had a significant beneficial effect on sleepiness but had no effect on depression.

"Although this drug did not have a positive effect for everyone, until now there was nothing reliable to prescribe for people who are most severely fatigued," said Dr. Gary Morrow, the study's lead author (University of Rochester Medical Center, USA).

Vaginal brachytherapy: New treatment of choice for endometrial cancer?

Vaginal brachytherapy is as effective as external beam radiation therapy at preventing the recurrence of higher-risk endometrial cancer, according to a new study (*J Clin Onc 2008*;**26**: May Supplement. Late Breaking Abstract #5503).

Between 2002 and 2006, the phase III study randomised 427 patients to receive either brachytherapy – in which a radioactive cylinder is inserted into the vagina – or external beam radiation therapy. The treatment was given after removal of the uterus and ovaries.

At 3 years of follow-up, vaginal relapse rates were 0.9% and 1.9% for brachytherapy and external beam radiation therapy respectively. Overall survival and relapse-free survival rates were similar in both groups. Patients receiving brachytherapy reported fewer side effects with only 6% reporting diarrhoea compared to 22% in the external beam radiation group.

"Based on this study, we expect that vaginal brachytherapy will be adopted as the new standard of care for patients with this type of endometrial cancer," said lead author Dr. Remi Nout (Leiden University Medical Center, The Netherlands). "This treatment is simpler and just as effective as external beam radiation, and it allows patients to have a better quality of life both during and after treatment. This new strategy will make treatment and recovery for many patients much more manageable moving forward."

Photo courtesy of ASCO

Dr. Remi Nout

ASCO 2008

Zoledronic acid 'benefits women with early breast cancer'

Zoledronic acid may offer a significant anticancer benefit to pre-menopausal women with hormone-sensitive, early stage breast cancer, Austrian researchers say.

Results from the major phase III trial showed that the addition of the bone protective agent, zoledronic acid (Zometa), to hormone therapy significantly prolonged both disease-free and relapse-free survival compared to hormone therapy alone (*J Clin Onc 2008;**26***: May Suppl. Late Breaking Abstract #4).

The trial, conducted by the Austrian ABCSG-12 group, enrolled 1803 pre-menopausal women after surgery. They were treated for 3 years and observed for an additional 2 years.

The addition of zoledronic acid to hormone therapy (either tamoxifen or anastrozole) increased disease-free and relapse-free survival by 36% and 35% respectively, compared to hormone therapy alone. A positive but non-significant trend towards an overall survival benefit was also seen in patients who received zoledronic acid.

"This study is the first large-scale trial to demonstrate the significant antitumour benefit of zoledronic acid," said lead author Dr. Michael Gnant (Medical University of Vienna, Austria).

There were no serious side effects and in particular, no confirmed cases of osteonecrosis of the jaw, a complaint which has previously been reported in cancer patients treated with intravenous bisphosphonates, including zoledronic acid.

Photo courtesy of ASCO

Dr. Michael Gnant

Zoledronic acid is currently prescribed for reducing or delaying bone complications, such as fracture, in people with cancer that has spread to the bone or who have multiple myeloma. "It's very exciting to find that in addition to preventing bone loss in women undergoing adjuvant endocrine therapy for breast cancer, zoledronic acid can also reduce the likelihood that breast cancer will return in some women," said Dr. Gnant. "Future research will focus on optimising the administration schedule and the dose, and determining which patients will benefit the most from treatment with zoledronic acid."

Blood test may detect lung cancer

A blood test has been developed which may identify outwardly healthy smokers who will go on to develop lung cancer on the basis of genetic changes, German researchers say (*J Clin Onc 2008;* ***26***: May Supplement Abstract #1509).

A preliminary study suggests that the blood test is sensitive and specific for detecting early-stage lung cancer in smokers. The test uses an RNA "fingerprint", created by comparing the blood of lung cancer patients to a control group of people without the disease.

The researchers assessed the blood test in smokers who developed lung cancer within 2 years of joining the European Prospective Investigation on Cancer and Nutrition, as well as in a set of matched controls. They concluded that a lung cancer-specific gene expression profile present in peripheral blood can be used to predict prevalent disease with an accuracy of 88% and incident disease within 2 years with an accuracy of 80%.

Urgent need for action' on colorectal cancer

Europe and Australia have both failed to prioritise a 'potentially preventable and curable cancer', according to the authors of a comprehensive report on colorectal cancer (CRC) care.

A team from the London School of Economics used a 'scorecard' of positive indicators (factors which improve CRC care) and negative indicators (which create barriers to best care) to demonstrate what countries do well and where they could improve.

A minority (including Denmark, France, Germany, Italy, Netherlands, UK and Austria) scored more than 50%, but none scored more than 75%, suggesting that each country has room for improvement.

Overall, the report found that data collection is poor, which makes planning difficult. Only a minority of countries have formal screening. All countries reported issues with access to all types of CRC treatment modalities. Many countries have no treatment guidelines, and only half of those that do, monitor their use. The numbers of patients with access to novel therapies is limited.

Lead author Professor Panos Kanavos said, "This report is the first to give healthcare providers, policy makers and patient groups the detailed evidence needed to create and deliver sustainable standards and plans that will ensure people throughout Europe affected by this devastating cancer have equal access to a better future."

The report calls for greater pan-European cooperation and delivery of a concerted, integrated prevention programme, including screening and treatment of CRC. Jola Gore Booth, founder of patient advocacy group Europacolon, said, "Compared to other high incidence cancers CRC has been largely ignored. That is why we see so much variability around Europe in the diagnosis and care of people with this common and highly treatable cancer".

'Colorectal Cancer in Europe and Australia: Challenges and Opportunities for the Future, a survey of 21 countries' is available at http://www.lse.ac.uk/collections/LSEHealth/

EUROFILE

Towards a more effective EU legal framework

Current European biomedical research legislation adversely affects pan-European clinical research activities. The Clinical Trials Directive 2001/20/EC has prompted a fall in newly activated academic clinical trials; ongoing translational research activities have exposed critical legislative gaps at the European level. The academic research community and pharmaceutical industry agree that substantial amendments to the EU Directive are required.

Academic researchers and legal experts took part in a recent one day workshop, *Biomedical Research in Europe: Challenges and Solutions for Academic Sponsors (EORTC Headquarters, Brussels)*. The objective of this meeting was to coordinate the ongoing efforts of four groups (EORTC, ECRIN, ICREL, CONTICANET) working to improve current clinical research legislation.

Françoise Meunier, Director General of the EORTC, reiterated the need for collaboration to identify concrete solutions, develop new models of research funding and convince policymakers that European academic clinical research is essential and not simply a luxury.

As part of the ICREL (Impact on Clinical Research of European Legislation) project, the EORTC is actively collecting pre- and post-implementation metrics on cancer clinical trial activity,

'EUROPEAN ACADEMIC CLINICAL RESEARCH IS NOT A LUXURY'

work force, and financial costs to demonstrate the direct and indirect burdens of the Directive.

The Connective Cancer Tissue Network—CONTICANET, launched in 2006 through the 6th Framework (FP-6) and dedicated to research on the diagnosis and management of connective tissue tumours, seeks to promote better understanding of these rare tumours, and to harmonise and optimise their treatment across Europe. The Network has also identified multiple clinical research barriers under the current legislation. Human tissue research is yet to be regulated. National regulations differ on informed consent for human tissue sampling; tissue exchange transfer rights, industry collaboration and financial implications; drug availability, off-label usage, reimbursement; and non-commercial trials. CONTICANET is meeting with health authorities, detailing specific problems with the legislation and ethics, and proposing strategies for improving harmonisation.

The collaborative one-year ICREL project was initiated under FP-7 to examine the Directive's impact on industry and academic clinical trials, regulatory authorities, ethics bodies, pharmacovigilance systems, research funding and infrastructure. ICREL is currently conducting a longitudinal, retrospective observational and comparative study, collecting detailed metrics and surveying all major pan-European research stakeholders to provide fact-based data. This work will help determine the most relevant pathways for improvement of the Directive. ICREL will discuss its fact-based results at a workshop in Brussels on December 2, 2008 and prepare a list of recommendations for changes to the current Clinical Trials Directive.

The European Clinical Research Infrastructures Network (ECRIN), also funded by FP-6 and FP-7, is aiming to facilitate multi-national European clinical research by integrating EU research capacity and public funding and by harmonising tools, training, practice and legislative systems. ECRIN's research shows that the first challenge to multi-national clinical research in Europe is patient access, despite a population of over 500 million. There is a lack of integrated research funding and a paucity of quality research infrastructures, namely established clinical research and trial centres, disease-oriented networks and national coordination. ECRIN identified bottlenecks in multi-national research cooperation, then defined procedures and guidelines for EU studies and is currently working towards building a European clinical trials and biotherapy infrastructure that will provide high-quality services to multi-national clinical research. Significant improvement in the legislative framework is without doubt a critical element to the success of this program and the ECRIN findings add further weight to the argument for revising the EU Clinical Trials Directive.

Recent debate on ethical and governance issues of human biological tissue research has uncovered gaps in legislation at the national and European level. Human tissue research falls outside of the Clinical Trials Directive but is an integral part of current cancer

'THERE IS A LACK OF INTEGRATED RESEARCH FUNDING'

clinical trials. Legal experts differ in their opinions on the adequacy of international conventions, treaties, national laws, professional guidelines and recommendations on tissue research but agree that the way forward must strike a fair balance between the interests of all stakeholders. Any future governance should encompass strict privacy protection, transparent basic principles for research projects, methods for disseminating research results, conflict of interest policies, and intellectual property rights while at the same time allowing sufficient flexibility. Researchers together with patient organisations are best suited to develop this research governance and a proactive approach will avoid repeating the experience of the Clinical Trials Directive.

The consensus from the Brussels meeting was that academic researchers from all disciplines will strengthen their cooperation, speak with one voice and collaborate to define an improved directive that should achieve the original goals of the Clinical Trials Directive and ensure a level playing field for all European clinical researchers.

Colette Lukan, MD, FRCPC
for the EORTC, Brussels, Belgium

For further information, see www.eortc.be; www.conticanet.eu/html; www.eortc.be/services/doc/highlights/ICREL.html; www.ecrin.org

PODIUM

Oestrogen: A new chemopreventive agent for prostate cancer?

*Professor Emeritus Louis Denis (Oncology Centre Antwerp, Belgium) was an academic urologist who introduced transrectal ultrasonography to Europe. He was EJC's first managing editor, is a past president of EORTC and secretary of the patient advocacy group, Europa Uomo. He is interested in new drug development and clinical research in urological oncology; one of his interests is the chemoprevention of prostate cancer. (See also EJC 2008;***44***(7): 928–36)*

How strong is the evidence that oestrogens may play a role in prostate cancer?

The story is both old and new. Ten years ago, it had already been suggested that the male foetus may be influenced by the mother's oestrogen during the first week of foetal life and that this foetal imprinting may be involved in the development of prostate cancer decades later. Foetal imprinting has been accepted as a concept since it was discovered that the daughters of women who took diethylstilbestrol while pregnant were much more likely to develop vaginal cancer – which is extremely rare – 25 years later.

Similarly, in prostate cancer, differences in pregnant women's oestrogen levels could possibly explain why African American men in the States have more disease than Caucasian men.

Recently it was reported (*J Natl Cancer Inst 2008;***100**:815–25) that gene alterations do not occur in all patients but a large amount of information on more than 6.000 genes implicated oestrogen as part of a molecular pathway that results in the fusion of two genes promoting prostate cancer. These fusions (TMPRSS2/ETS) were found in up to 60% of patients and were associated with an aggressive clinical phenotype.

This scientific argument will be easier to check than foetal imprinting, and it suggests that oestrogen might be a target in prevention of prostate cancer.

Isn't this counterintuitive, since oestrogen has long been considered to be protective?

No, it is a question of dose. Oestrogens are powerful drugs and control prostate cancer growth. However in this case they act by lowering serum testosterone via the hypothalamic pituitary hormonal axis. Other hormonal treatments also have this effect; they act by lowering or blocking the male hormones in prostate cancer patients. Another successful chemopreventive agent is finasteride (which blocks the conversion of testosterone to the more potent dihydrotestosterone). In a US National Cancer Institute (NCI) sponsored trial, the Prostate Cancer Prevention Trial (PCPT) finasteride was tested against placebo in more than 18,000 men aged 55 or over. The original trial was stopped in 2003 because it looked like finasteride was encouraging high grade cancers. However a recent reanalysis found no support for this thesis and confirmed that the drug reduced prostate cancer risk by up to 25% in tumours with Gleason scores 5, 6 and 7.

Ongoing studies with dutasteride, blocking the two isozymes of 5 alpha-reductase, are promising in terms of future treatments (REDUCE trial).

How seriously are these suggestions being taken?

At the moment, something like 1250 studies on prostate cancer are in progress. This includes about 70 randomised trials on all kinds of drugs, most of which are not hormone therapies. And these therapies are not anti-oestrogens. The NCI is sponsoring 17 prospective randomised Phase II and III trials on prevention, and only one (GPX-006) is studying an anti-oestrogen.

How advanced is other work into the chemoprevention of prostate cancer?

In 2003, the European code against cancer (*Ann Oncol 2003;* **14**(7): 973–1005) written by Peter Boyle and a total of 42 experts concluded that there was no convincing evidence of effective chemoprevention in prostate cancer. The American Institute for Cancer Research's 500 page report, *Food, Nutrition, Physical Activity and the Prevention of Cancer: a Global Perspective (April, 2008)* lists the activities and drugs that might increase or decrease the risk of each cancer. But in prostate cancer they don't believe that anything works apart from the general advice on physical activity and diet that would be true for any cancer. Lycopene (in tomatoes), selenium and vitamin E have been suggested but there's no conclusive truth that they are effective. We have to look for the active agents in our nutrition. Chemoprevention in prostate cancer is clearly underutilized and extensive research is needed to confirm the circumstantial evidence hypothesis of the promising agents.

Will this new suggestion give research a real boost?

All chemopreventive agents that have any effect seem to have some hormonal activity, but solving prostate cancer isn't going to happen in a single quantum leap. The first problem in chemoprevention is that although by age 50, 50% of Western men have an indolent prostate cancer – and by the age of 80, it's 80% – only 10% ever develop a clinical cancer in their lifetime. There's a real danger of over-treatment and we can't embark on chemoprevention unless we have an extremely safe product that will do the trick. Furthermore, studies usually last 15 years, so nothing is going to change overnight.

Helen Saul