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Update on ATAC

Updated data on the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial provides support for the initial promising results. Presented at the Breast Cancer Symposium (San Antonio, Texas, USA, December, 2002), the new data extends the median follow-up in the ATAC trial to 4 years.

Researchers say that, among postmenopausal women with early breast cancer, anastrozole continues to show statistically significant benefits in efficacy over tamoxifen. A number of tolerability benefits have also been identified and no new safety issues have emerged since the first results were presented at the corresponding meeting the previous year (San Antonio Breast Cancer Symposium, Texas, USA, December 2001).

'WE NEED TO CONTINUE THE STUDY'

ATAC includes 9366 postmenopausal women with early breast cancer. They had all completed primary therapy of surgery, chemotherapy or both. Radiotherapy could be given after randomization.

The updated analysis found that anastrozole significantly prolongs disease-free survival compared with tamoxifen. Among all patients, risk of recurrence was reduced by 14% among patients treated with anastrozole rather than tamoxifen. Among those with hormone sensitive tumours—the target population for the therapy—it was reduced by 18%.

Benefits of anastrozole included a reduced risk of endometrial cancer, vaginal bleeding and discharge, cerebrovascular and thromboembolic events, and hot flushes. Tamoxifen showed tolerability benefits in terms of musculoskeletal disorders and fractures.

Commenting on the results, ATAC Principal Investigator Professor Michael Baum (University College Hospital, London, UK) said, "These updated results confirm that our initial optimism, expressed after the primary analysis, was justified. Anastrozole represents new hope for postmenopausal women with early breast cancer."

Another investigator, Professor Jeffrey Tobias (University College Hospital, London, UK) said, "News from last year's analysis was very encouraging, but we have been waiting for data on longer-term benefits. Now from these latest results, it really does look likely that anastrozole will prove to be a better drug than tamoxifen , the most widely used hormonal treatment for over 20 years, and we are still noting far fewer troublesome side effects."

However, Professor Jack Cuzick (Cancer Research UK) stressed the need for longer follow-up. "The additional follow-up continues to support the belief that anastrozole may be better than tamoxifen for the treatment of early, hormone-sensitive breast cancer. We need to continue the study, however, to establish whether anastrozole can prevent the disease from spreading to other sites in the body and, crucially, whether it can keep women alive long-term.

"Tamoxifen is currently the best available treatment for many women with breast cancer and is the main reason for the fall in deaths from the disease over the last decade, so any further improvement would be a very significant advance."

Anastrozole has been approved for use in postmenopausal women with early breast cancer in UK, US and Japan.

Baum's honours

Professor Michael Baum gave the prestigious William Maguire lecture at the San Antonia Breast Cancer Symposium, in which he presented the new data from the ATAC study.

Earlier in the year, (October 30, 2002), he won the annual award from the UK charity, HealthWatch, which aims to promote consumer protection. Professor Baum was chosen for his outspoken views on informed consent in breast screening.

Professor Baum believes that the benefits of the UK national breast screening programme for women aged 50 to 64 are marginal at best. They are even less marked for the under-50s and it is unethical for private clinics to promote screening for this group, he says. He also claims that latent cancers detected by screening may be sparked into invasive life by the surgery that is designed to cure them.

Professor Baum said, "A woman screened for 15 years has only a one-in-a-thousand chance of benefiting, yet women are summoned for screening with leaflets that deny them that information and distort the facts.'

He believes that money spent on screening should be channeled into improved access to specialist units and clinical trials on new treatment. "I would like the Government to realize that better treatment holds more hope for women than better screening."

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Call for mutual recognition of CME credits

Cancer specialists are calling for the mutual recognition of credits in continuing medical education (CME) between European countries.

A survey conducted by the Federation of European Cancer Societies (FECS) on the needs in CME in oncology in Europe concludes that health professionals almost unanimously (96%) believe that a system of mutual recognition of CME credits between European countries is needed. Health professionals in oncology strongly requested the development of such a system when questioned about their main wish in CME. Half the respondents from Central and Eastern Europe consider the fact that CME credits are not recognised in their country as a main weakness. This view is shared by a quarter of respondents from EU countries.

'MOST FAVOURED ACCREDITATION OF CD-ROMS AND WEB-BASED PROGRAMMES'

A large majority (80%) of respondents from EU countries would be in favour of the accreditation of enduring materials (CME journals, CD-Roms, web-based programmes, etc.) while this is supported almost unanimously by respondents from Central and Eastern Europe.

More than half of the respondents both from the EU and Central & Eastern Europe indicate they would like to see the development of web-based programmes.

The survey was conducted between October 2001 and September 2002 and gathered the views of 910 health professionals in the field of oncology worldwide including 553 from EU countries and 111 from Central and Eastern Europe. The questionnaire was handed out during the European Cancer Conference (ECCO 11) in Lisbon in October 2001 and mailed with the newsletters of FECS' member societies. Approximately 20,000 questionnaires were distributed.

The survey is part of a Leonardo da Vinci project aimed at raising the standards in CME in oncology in Europe. The project includes 2 main components: the development of a European accreditation system for CME activities in oncology including new quality evaluation methodologies, and the development of new educational materials. The project has been carried out with the support of the European Community. The content of this project does not necessarily reflect the position of the European Community, nor does it involve any responsibility on the part of the European Community.

'MUTUAL RECOGNITION OF CME CREDITS WAS STRONGLY REQUESTED'

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Bowel cancer awareness

Too few people are aware of the symptoms of bowel cancer, family doctors in the UK say (*Colorectal disease* 2003, **4**: 483–485).

In the week following Bowel Cancer Awareness Week in the UK, 77 patients attending non-emergency clinics completed a questionnaire. Only 44% could name a symptom of colorectal cancer, compared with 85% who could name a breast cancer symptom. Colorectal symptoms may be more vague than those of breast cancer, but patients identified more sources of information for breast cancer and the authors said lack of publicity might be partially resposible.

Cognitive follow-up for ALL children

Children in remission from acute lymphoblastic leukaemia (ALL) are at risk of cognitive impairment and daily life difficulties, Italian researchers say (*Cancer* 2002; **95**: 2562-70). Even the new treatment protocols which avoid cranial radiotherapy increase the risk, and children need a detailed follow-up of their cognitive functioning, they say.

The study comprised 32 children treated for ALL between 1984 and 1988 at the Catholic University of Rome, Italy. They had been in continuous complete remission of disease for between 4 and 11 years after diagnosis. They underwent neuropsychologic tests, brain MRI and CT scans.

Cognitive sequelae were common in the past when patients were routinely treated with high doses of radiotherapy. Most patients now receive intrathecal and systemic high-dose MTX and no radiation at all. However, multiple intrathecal injections of MTX may have a substantial neurotoxic effect, they found, especially among girls. Total and verbal intelligence, attention and praxic abilities were reduced.

Calcifications were often detected by CT scans, and white matter alterations by MRI scans. Calcifications were related to reduced performance intelligence quotient (PIQ), visual attention and visual-motor integration (VMI). White matter alterations, found in half of the children, also related to poor VMI test results.

The neuropsychologic assessment picked up subtle problems in some patients which would not have been revealed by the scans alone. These included mild intellectual decline and nonverbal abilities such as visual attention. Verbal abilities were less affected and the researchers suggest the children may have a specific cognitive defect involving fine psychomotor performance, attention and concentration abilities.

They conclude, "Our study stresses the importance of extensive neuropsychologic testing because some children treated for ALL present subtle cognitive difficulties that can be detected only by appropriate tests. Early detection of learning disabilities may be advantageous in providing early adequate support in school."

EUROFILE

Informing the consumer

The European Union will soon have the fastest drugs approval process in the world, following a vote in the European Parliament on October 23, 2002, which handed important new powers to a centralised authority. But the parliament voted against plans to allow pharmaceutical companies to provide information on request about specific products. The proposal to allow limited "direct to consumer" was the most controversial measure in the EU Pharmaceutical Review, which set out to reform the workings of the European Medicines Evaluation Agency (EMEA).

A 5-year pilot scheme covering AIDS, diabetes and asthma was to have been used as a test case for DTC. This attracted criticism from all sides: the pharmaceutical industry arguing that it did not go far enough, and consumer groups seeing it as the thin end of the wedge on the road to US-style medicines advertising and soaring healthcare costs. Before the debate got off the ground, the issue was further confused by a translation error in the English version of the proposal, which appeared to allow the provision of advertising rather than information. The European Commission, which drafted the plans, was forced to admit that this was not its intention and many believed that it wanted the whole idea quietly dropped.

'IT WAS NOT KNOWN WHAT PATIENTS THINK'

This turned out not to be the case, however, and the Commission has said it will continue pressing for the pilot scheme. But, such is the opposition from all sides, it seems unlikely to go through in its current form.

What do patients think in this debate? Until recently, it has been difficult to find out. But an interesting study carried out by PatientView and the International Alliance of Patients' Organisations (IAPO) presented at the European Health Forum, Gastein, in September, gave an overview of a survey of 146 patient and umbrella organisations across Europe. The umbrella groups represented some 6000–7000 patient groups, and the individual groups some 6–15 m people, making it the largest such survey carried out on the question to date. Responses were received from groups in each EU member state, though numbers varied considerably, from only 2% in Italy and Luxembourg, to 33% in the UK.

Ms Alexandra Wyke, Managing Director of PatientView, a market research agency specialising in patient issues, presented the findings, which had already been seen by EMEA, the Commission, and the G10 group, she said.

For the purposes of the survey, a patient group had to have patients as members or on the Board; no pharmaceutical industry funding for core activities; and be engaged in advocacy. There was a 30% response rate from the organisations selected. All disease areas were represented, with a high representation from groups specialising in HIV, cancer, diabetes, asthma, psoriasis, and rare diseases. 72% of respondents said that the patients they represented took medicines on a regular basis.

'CANCER PATIENTS ARE NOT TOLD THE WHOLE TRUTH'

To the question "Should the EU legislate to allow pharmaceutical companies to supply the public with significantly more information about prescription medicines?" 33% replied, "Yes", and 17% "Yes, but with strict limitations". 25% believed that the Commission should study the matter further; 16% replied "possibly/it depends"; 9% said no.

Patient View is due to publish a report analysing the responses from cancer patient groups. The results obtained from 11 of the key cancer patient groups across the EU clearly indicate that patients would like more information about their treatments. But they were more cautious than other patient groups about the idea that pharmaceutical companies should supply that information. Only three (27%) of the cancer patient groups gave unqualified support to the idea; a further two (18%) believed that industry should supply the public with more prescription drug information subject to certain limits; and two thought that the EU should 'possibly' pass legislation along these lines. Four groups thought that the European Commission should study the matter further.

The main reason why cancer patients supported the idea that greater prescription drug information was needed was that they felt they were not told the whole truth about the medicines they were taking. "The side effects. . .. are denied by GPs and specialists", said one group. Patients not in possession of information on side effects and changes in lifestyle required as a result of treatments, could not make informed choices, they said.

Cancer patients are more active at seeking out alternative sources of information on their treatments than patients with other diseases, says the study. 82% of the respondent groups said that the patients they represented got 'most' or 'some' of their prescription drug information from friends, relatives, and other patients, as opposed to 73% reported by respondents in all disease groups.

So what influence will this have on the Commission's next steps? Even though it was unhappy with the original proposals, it was clear from the debate that the European Parliament wants change. Patients want it, and so does industry. The Commission wants it too. How it will reconcile so many conflicting interests is anyone's guess—but at least it now has a properly representative overview of what patients think.

Further information on the report is available at www.patient-view.com or info@patient-view.com

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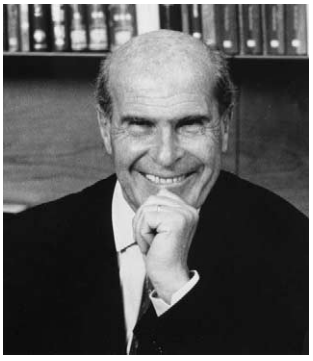
King Faisal International Prize Awarded

The 2003 King Faisal International Prize for Medicine has been jointly awarded to Professor Axel Ullrich (Max-Planck Institute for Biochemistry, Germany) and Professor Umberto Veronesi (European Institute of Oncology, Milan, Italy). The 2003 prize was earmarked for excellence in the field of breast cancer and the winners will share US$ 200,000.

Professor Ullrich is widely regarded for his outstanding contribution to the study of the molecular biology of breast cancer, the announcement says. Over the last 20 years he and his colleagues have demonstrated the role of tyrosine kinase receptors as growth promoters for cancerous cells.



Professor Umberto Veronesi

Their discovery of the HER-2 oncogene in 1985 led to the subsequent description of its amplification.

In 1990, his description of a monoclonal antibody to the HER-2 receptor led to the development of Herceptin, the first clinically effective monoclonal antibody, now in use worldwide. More recently, his research has extended to other areas of receptor target interactions of relevance to angiogenesis.

Professor Veronesi has pioneered a revolution in the management of breast cancer over the past 3 decades, according to the announcement. His pivotal role in demonstrating the safety of a wide resection followed by radiotherapy spared countless women from mastectomy and its consequences.

In further research into the quality of life for breast cancer patients, he developed axillary-sparing sentinal

Professor Axel Ullrich

node dissection to prevent lymphoedema. Recently he has been developing the use of intraoperative radiotherapy, which reduces the time needed for multi-modality therapy.

Professor Veronesi has had a long and distinguished career, in which he has fostered multi-disciplinary research. His leadership in this regard has been recognised in his election as President of many societies, including the Federation of European Cancer Societies (FECS), European Organization for the Research and Treatment of Cancer (EORTC), International Union Against Cancer (UICC). His commitment both to treatment and to training led him to found the European School of Oncology, which celebrated its 20th anniversary in 2002.

The King Faisal International Prize for Medicine has been awarded for the past 25 years. A total of 43 scholars from 11 different countries have been recipients. The topic for the 2004 prize is Invasive Cardiology.

Prediction of benefit from treatment

DNA markers may predict benefit from adjuvant treatment in patients with colon cancer, say UK researchers. They found that retention of heterozygosity at one or more 17p or 18q sites was associated with the ability to benefit from adjuvant fluorouracil. Their results support the principle of developing molecular markers as predictive factors in treatment decisions (*Lancet* 2002; 360: 1381–91).

They obtained normal and tumour tissue samples from 393 patients with colon cancer. The patients were already participating in a trial (the UK AXIS trial) of postoperative portal vein infusion fluorouracil versus control. Those selected for inclusion were randomised in 1994 or before to ensure more than 5 years' follow-up. They had curatively resectable Dukes' B or C tumours, and only primary colon, not rectal cancer, because of previous evidence that adjuvant chemotherapy is more effective in colon than rectal cancer.

'PREDICTION IS A RELEVANT AND USEFUL EXERCISE'

Four loci were considered: *P53* (17p13), *D18S61* (18q22.3), *D18S851* (18q21.1), *DP1* (5q21).The researchers found that retention of heterozygosity at loci on chromosomes 17p and 18q predicted benefit from adjuvant fluorouracil. Only *D18S61* was significantly predictive as a single marker, but combining data from all three 17p and 18q sites gave significant predictive value applicable to 80% of patients.

Loss of heterozygosity (LOH) at *D18S61* was a good prognostic marker in untreated patients but associated with a significantly poorer benefit from chemotherapy. Similarly, those with LOH at *P53* benefited little from fluorouracil.

"Prediction of benefit from adjuvant treatment is a relevant and useful exercise, which could form an important element of the cost-benefit balance in clinical decision-making," the researchers say.

PODIUM

Cancer drugs: The next 10 years

Dr George Blackledge is Medical Director of AstraZeneca Pharmaceuticals. He trained in medical oncology and previously led the academic oncology unit at University of Birmingham, UK. His current role involves setting the strategy for the development of new agents and the prioritisation of these agents.

Dr George Blackledge

How bright is the outlook for anti-cancer drugs?
The outlook is bright. We now have enough information to suggest that the new approach, based on specific molecular targeting, is working. It is not always working as well as we would like but it is working and we have to study further issues related to identifying appropriate patient subsets for different treatments.

Five or ten years ago, it was thought that once a target had been identified, we would be able to down-regulate it and demonstrate striking clinical effect. Drugs would come quickly into practice. This now seems a bit unrealistic. Even in a cell as abnormal as a cancer cell, there are so many other controlling factors, that, apart from in small subsets of patients who have specific genetic mutations, the situation remains complex. We are going to have to work hard to show a difference in most malignancies.

How good are we at identifying subsets of patients?
We are not very far down that line. Breast cancer patients aren't treated with hormonal therapy if they are ER−ve; they don't receive trastuzumab (Herceptin) unless they are HER+ve. But there aren't many such examples.

Why is this so difficult?
There are over 2000 receptors on a normal cell surface. If we target only the receptors linked to growth, there are 575. That's a vast number of signalling pathways to understand, especially since many interact with each other. You can target one enzyme or one receptor very easily, but the question is: what does it mean? We can get a beautiful demonstration of anticancer activity in a mouse xenograft, but it may bear no relationship to the situation in a human tumour. Or only in a small subset of patients.

There was a lot of noise about the human genome project, but we do not live by DNA alone; we are dependent on its products. Proteins and the interaction between proteins is probably more important for uncontrolled cell growth. That's not to say DNA is not important, but it is only part of the puzzle.

It's been said that we need a whole new way of testing new drugs. Do you agree?
I have some sympathy with the view. We want to know whether patients live better and live longer and the question is: how do you discover this? It is different from the old mechanism. We don't do phase I dose escalation trials to maximum tolerated dose any more; it's translational science and biomarkers. We want to know whether anything is happening at the target, and downstream of it, and whether this relates to clinical effect. These are new kinds of trials, which nobody has done before and we are often working with endpoints that have not been validated in patients. It is complicated.

However, the available technologies have changed beyond recognition, even in the last 4 years. There is a whole series of phosphorylated antibodies, better understanding of the fundamental biology, and of validation techniques such as biomarkers. If an antioestrogen binds to an oestrogen receptor, you really want to know whether it has an effect on whether a cell divides. And you measure that using antibodies to Ki67.

Even given this, there have been disappointments such as with Iressa.

We know already that Iressa makes a major difference for certain groups of patients with lung cancer. We learnt from the combination trials—albeit rather expensively—how not to use it. Which is necessary knowledge. But EGFR inhibitors can be directed at other targets on specific growth pathways, and there is further evidence of subsets of head and neck cancers which may be susceptible.

Is there any chance of cancer becoming a chronic disease, rather than a killer, over the next few years?
In some cancers, we have achieved that. In breast and prostate cancers, 5 year survival is 86% and 97% respectively, and that is due to improved treatment: local treatment with surgery or radiotherapy, targeted systemic treatment and hormonal therapies. If we could achieve as much with other cancers, nobody would be complaining.

Where do you think we will see progress over the next 5–10 years?
We will see further treatments for lung cancer, probably also for head and neck cancer and colorectal cancers. In both breast and prostate cancer, we will learn how to add new treatments to existing therapies.

Overall, the future looks good and I am optimistic. If you look back over a few decades we have made tremendous progress. Developments in molecular biology may mean we are on the verge of something new, but we will have to manage expectations and the knowledge itself. Progress won't be as much as is expected or as fast as is hoped.