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Tamoxifen: 5 years and no more?

Updated results from a large US trial suggest that 5 years is the optimum duration of adjuvant treatment for breast cancer. The National Surgical Adjuvant Breast and Bowel Project (NSABP) found no additional benefit from tamoxifen administered for longer in women with node-negative breast cancer (*J Natl Cancer Inst* 2001, **93**, 684–690).

The original B-14 trial compared 5 years of tamoxifen with placebo in women with oestrogen receptor-positive breast cancer and negative axillary lymph nodes. Those who received the active drug and who were free of disease were then re-randomised to receive either placebo or continued treatment with tamoxifen. Results 4 years after re-randomisation suggested no further benefit from the prolonged tamoxifen therapy and, controversially, the trial was unblinded and stopped. Researchers led by Bernard Fisher (University of Pittsburgh, PA, USA) said the latest results, 3 years on, confirm the original finding.

When the trial was stopped, the advantage in both survival and disease-free survival among women receiving the placebo was almost statistically significant. The overall number of events and deaths is still greater in the tamoxifen group. This is not surprising, the researchers say, because the women had remained disease free for the first 5 years and had a good prognosis. Any small benefit of the drug would have to be weighed against the few serious adverse events, such as endometrial cancer, pulmonary embolism and stroke, associated with its use.

The researchers conceded that the duration of tamoxifen will not be finally determined for about 10 years when the findings from the UK trials aTTom (Adjuvant Tamoxifen Treatment, Offer More?) and ATLAS (Adjuvant Tamoxifen: Longer Against Shorter) become available. However, they said, "The current findings provide substantial justification for our prior conclusion that there is no additional advantage for continuing tamoxifen therapy for more than 5 years in patients with oestrogen receptor-positive tumours and negative axillary lymph nodes."

In an accompanying editorial (*J Natl Cancer Inst* 2001, **93**, 662–664), Dr Jeffrey Abrams (National Cancer Institute, Bethesda, MD, USA) agreed with the conclusion but added that larger trials in women at higher risk (lymph node-positive patients) could still show benefit from prolonged treatment. However, other therapies are becoming available. Third-generation aromatase inhibitors ''are challenging tamoxifen's supremacy in postmenopausal women'', and ovarian ablation ''may become a critical component of therapy'' for premenopausal women, he said.

Fish and prostate cancer

Eating fatty fish could decrease risk of prostate cancer, say Swedish researchers (*Lancet* 2001, **357**, 1764–1766). They found that those who ate no fish had two to three times the risk of prostate cancer, compared with those who ate high or moderate amounts.

The population-based prospective study followed 6272 men for 30 years. The men were all born between 1886 and 1925 and answered questionnaires in 1961 and 1967. They were followed until 1997 and diagnoses of prostate cancer or death were obtained from national registers.

The results were adjusted for other dietary and lifestyle factors and the researchers found that an increasing proportion of fish in the diet was associated with a decreasing frequency of prostate cancer. The link was strongest for men who died of the disease.

Sweden has a traditionally high consumption of fatty fish such as salmon, herring and mackerel, which contain high levels of omega-3 fatty acids. The researchers conclude that eating fatty fish may inhibit arachidonic acid-derived eicosanoid biosynthesis. "Our results confirm the hypothesis that fatty fish consumption lowers the risk of prostate cancer," they said.

Commenting on the work, Dr John Toy (Imperial Cancer Research Fund, London) said, "This is an interesting study that has surveyed an unusually large number of men and certainly adds to our knowledge."

Charities merger: talks go on

Plans for a merger between the Cancer Research Campaign and Imperial Cancer Research Fund are progressing. The councils of the two charities have agreed that the research programmes complement each other well and that there is potential for a merger "to bring real benefits to cancer research and to cancer patients".

Formal consultation and planning on merger proposals have been started and the process is expected to last several months.

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NICE advice on lung cancer drugs

The UK's National Institute for Clinical Excellence (NICE) has issued guidance on chemotherapy for advanced non-small cell lung cancer. It recommends that gemcitabine, paclitaxel and vinorelbine should each be considered part of first-line treatment for patients who are not suitable for potentially curative treatment. "The use of any one of these drugs in combination with a chemotherapy that is platinum-based, is likely to be the most effective form of treatment," it states.

Docetaxel alone should be considered in locally advanced and metastatic cancer where patients have relapsed after receiving chemotherapy with other agents, the guidance states.

Mr Andrew Dillon, Chief Executive of NICE, said, "The appropriate use of these drugs offers those patients who benefit from them additional months of life."

Dr Mike Leahy (Imperial Cancer Research Fund Unit, Leeds University, UK) welcomed the recognition given to the newer agents, as well as the more established drugs such as cisplatin. "Treatment such as this is toxic and is not suitable for all patients but in the hands of experienced oncologists these drugs are useful tools in the management of this common disease," he said.

Adolescents are 'neglected'

Young people with cancer are "a manifestly neglected population", according to an author in this issue of *EJC* (*Eur J Cancer* 2001, **37**, 1523–1527). Professor Ronald Barr (McMaster University, Hamilton, Ontario, Canada) said, ''Much remains to be done to meet the needs of adolescents with cancer.''

The incidence rate of cancer among adolescents in the US increased by 30% between 1973 and 1995, while that in childhood rose by only 10%. At the same time, the fall in the cancer-related mortality rate in adolescents was less striking, so that adolescents are now less likely to be cured than are children.

Adolescents face a series of maturational tasks and the added burden of cancer often leads to problems such as a loss of self-esteem, perturbation of body image and a fear of peer rejection. "It is small wonder that many adolescents with cancer travel a difficult path in seeking a return to normality, some bearing permanent scars (both physical and emotional) from their journey," writes Professor Barr.

The challenges to the healthcare system "may appear to be legion," he said. "Perhaps the most intransigent difficulty is posed by the paediatric-to-adult transition. While there is reasonable agreement that this is necessary and desirable, for most adolescents with cancer, it does not occur in a planned orderly fashion." This has resulted in low accrual rates of adolescents in therapeutic clinical trials and a lack of long-term follow-up.

Adult data show that treatment at a regional specialist oncology centre and according to a recognised protocol are both associated with significantly higher survival rates. The accompanying editorial (*Eur J Cancer* 2001, **37**, 1527–1530) extrapolates from this to suggest, ''Specialist adolescent services may provide a survival advantage''.

However, it concludes, "Regardless of the arguments for and against dedicated teenage cancer units, many young people will continue to be cared for in either paediatric or adult services. Therefore, it is the responsibility of all services caring for young people to improve these services to meet the specific needs of adolescents."

Professor Mike Richards, UK National Cancer Director, told *EJC*: ''I do believe that teenagers with cancers have particular needs, for example psychosocial and educational, and have recently spoken at two conferences—one for professionals and one for teenage patients—organised by the Teenage Cancer Trust on this issue. The National Institute for Clinical Excellence (NICE) will commission a comprehensive package of guidance on cancer services covering all cancers, including those affecting children and adolescents, over the next 3 years which all health authorities will be expected to implement.''

Importance of HPV status ''may be overestimated''

HPV status is likely to be of limited benefit in screening for cervical cancer, say UK researchers (*Lancet* 2001, **357**, 1831–1836). They found that most infections are episodic, that prolonged exposure to HPV is not necessary for progression to high-grade CIN, and that little lead-time is gained by detection of HPV.

The study included 1075 women who had a normal smear and were HPV negative. They were aged 15–19 years and were recruited between 1988 and 1992. Cervical and serum samples were taken every 6 months, and a risk-factor profile completed.

During the study, 246 women had an abnormal smear. However, 98 tested negative for HPV up to and including the visit when the first abnormal smear was reported. Infections were episodic and apparently lasted only a short period of time but the researchers found that prolonged HPV exposure was not necessary for progression to take place. "High-grade CIN might be a surprisingly early manifestation of HPV infection," they said.

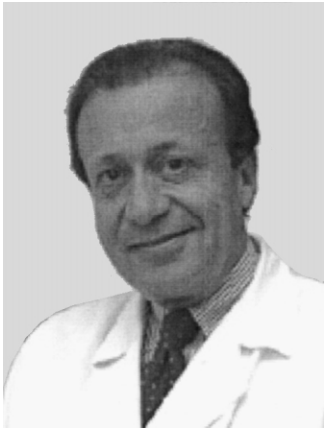
They said that only limited inferences could be drawn from HPV status at a single point in time and urged caution on the move to incorporate HPV status into the cervical cancer screening programme. "There is a risk ... of compounding our imperfect understanding of the disease process with an even less perfect understanding of the natural history of the HPV infection, thus causing more women unnecessary anxiety and presenting the clinician with yet another set of management dilemmas."

In an editorial, (*Lancet* 2001, **357**, 1816) Dr Anthony Miller (Deutsches Krebsforschungszentrum, Heidelberg, Germany) said ''A test is needed that indicates the virus will exert its oncogenic potential in that woman—which probably means that attention should be transferred from the agent to the host.''

AWARDS AND APPOINTMENTS

Italian breast cancer centre reports

A new breast cancer centre in Pavia, a University city just south of Milan, Italy, has published its first annual report. The centre, which was set up in 2000, is sponsored by the European Institute of Oncology (EIO),



Dr Alberto Costa

and is headed by Dr Alberto Costa, breast surgeon and Director of the European School of Oncology (ESO) since 1982.

The centre, which was formed at the initiative of Professor Umberto Veronesi, was based on previously existing departments of radiotherapy, medical oncology and rehabilitation at the Maugeri Foundation, a major Italian private non-profit healthcare organisation. In addition, two dedicated operating theatres and a new pathology department were opened last year.

Dr Costa left EIO in May 2000 to open the new centre, which in its first year carried out 700 surgical operations, half of which were for primary cancer; 150 sentinel node biopsies with radioguided probe; and over 100 plastic surgery procedures for breast reconstruction and cosmetic modelling. The centre is a member of the EORTC breast cancer group and has started randomising patients into various clinical trials. Its main original studies include a randomised trial on radiotherapy versus no treatment after breast conserving therapy in patients over the age of 60. It is also conducting a pilot study on pre-operative Herceptin in cerbB2-positive patients.

Along with his clinical commitment in Pavia, Dr Costa will remain as director of ESO, and will also continue to contribute to the development of European organisations such as FECS, EUSOMA, SENDO and *EJC*.

Move to industry

Professor Karol Sikora, formerly Clinical Director of cancer services at Hammersmith Hospital, London, has taken a post with AstraZeneca, UK,

Professor Karol Sikora

managing research into innovative cancer treatments. ''I look forward to working with such a visionary team,'' he said. Professor Sikora said he will continue his links with academia through his position on the editorial boards of several scientific journals and continued involvement with the National Cancer Forum in the UK.

New EORTC Fellowship Scheme

A new fellowship scheme, aimed at promoting translational research, has been launched by EORTC in collaboration with AstraZeneca. The 2-year fellowship is open to qualified medical practitioners or scientists who intend to follow a career in oncology. Translational research will be carried out at EORTC affiliated institutions alongside ongoing or planned EORTC clinical or laboratory studies.

The scheme was announced at the 1st EORTC translational research meeting, Belgium, in June 2001. It is intended to recognise the growing importance of linking laboratory investigations to clinical outcomes and translating advances in molecular and cellular pathology into patient benefit.

Professor Herbie Newell, Chairman of EORTC laboratory research, said, ''Translational research represents one of the most powerful routes to further clinical progress in cancer treatment, providing us with a pathway to utilising laboratory and clinical research to increase both patient's survival and quality of life. The EORTC—AstraZeneca Translational Research Fellowship will spearhead further translational research and encourage interest in this important area, which will achieve our ultimate goal of improving the standard of cancer treatment in Europe''.

Further details can be found on the EORTC website (http://www.eortc.be).

Professor Herbie Newell

Activating EORTC studies

"The work at the EORTC Data Center gives me an opportunity to combine theory with practice," said Dr Liliana Baila, a medical fellow at the EORTC's Breast Group in Brussels. She received her MD from the University of Tirgu-Mures, Romania, and specialised in paediatrics at the University Hospital there. Last year, she received a Masters degree in medical and pharmaceutical research from Vrije Universiteit, Brussels.

Dr Liliana Baila

She is involved in the activation process of two EORTC studies. The first is a randomised phase II–III trial in first line hormonal treatment for metastatic breast cancer. It is testing Exemestane or Tamoxifen in postmenopausal patients, and will include 768 patients. "This trial is a priority for us taking into account the new recently FDA approved drugs for this indication," says Dr Baila. They include Femara (Letrozole, January 2001) and Arimidex (Anastrazole, September 2000).

The second is the Perioperative Endocrine Adjuvant Trial (PEAT), a double-blind phase III clinical trial comparing a single pre-operative dose of Faslodex™ (long acting ICI 182.780) with placebo on tumour recurrence in pre- and postmenopausal women treated for operable first primary breast cancer. This is an Intergroup trial in collaboration with the BIG group and will include 3500 patients. The trial will also test the possible influence of menstrual cycle phase at the time of surgery. ''Perioperative treatment with one single injection of Faslodex™, in this setting, is a very small burden to the patient and also very simple in practice. The supposed beneficial effect of this treatment could be added to the results of conventional or experimental postoperative adjuvant treatment. It is an interesting study,'' said Dr Baila.

Before working at the EORTC Data Center, she had never been involved in clinical trials. "Being involved in clinical trial research gives physicians the opportunity to actively participate in the development and implementation of new treatment modalities. It also gives them new responsibilities and challenges which will offer patients a better quality of life and better treatments," she said.

Dr Baila misses working with patients, but finds her work at the EORTC satisfying. ''Instead of having direct contact with patients, I have indirect contact with a much greater number of patients than in a hospital,'' she said.

Samantha Christey
EORTC Communications Officer

Administrative director for UK Cancer Institute

The UK's recently formed National Cancer Research Institute (NCRI) has appointed its first Administrative Director. Dr Liam O'Toole, currently Programme Manager of molecular and cellular medicine at the Medical Research Council (MRC) is due to take up his post in July 2001.

The NCRI was formed in April 2001 to take a strategic overview of cancer research and bring together all UK funders. Its role is to identify gaps in existing research, take advantage of new opportunities and ensure effective planning and co-ordination of research to optimise current work. It covers basic science and research into cancer prevention and treatments.

The NCRI incorporates the recently developed National Cancer Research Network (NCRN) to co-ordinate phase III trials in the UK, and the National Translational Cancer Research Institute (NTCRI). NCRN Director Dr Peter Selby and NTCRI Director Professor David Kerr will report directly to the NCRI Board. The Board is comprised of representatives from cancer charities, the National Health Service and regional health authorities, and from industry. Dr O'Toole's role is to run the secretariat to the Board.

Dr Liam O'Toole

Dr O'Toole, who contributed to the development of the Cancer Research Funders Forum and its transition into the NCRI, is due to take up his new post in July, 2001. He said the NCRI is an 'incredibly exciting' development. 'It makes you ask why it hasn't been done before. What is so exciting is that all the big funders—the NHS, MRC, ICRF and CRC—are 100% behind it and want to co-ordinate. It's a refreshing approach to research funding, rather than separate organisations each doing their own thing.'

"THE NCRI IS A GOLDEN OPPORTUNITY"

"The NCRI is a golden opportunity for the key funders in cancer research to work in partnership. I hope we can ensure the UK's cancer research programme remains at the forefront internationally and that the benefits are passed on to people living with the disease. I'm looking forward to leading the NCRI to achieve that objective."

An early NCRI is to establish and maintain a national tumour bank.

INTERVIEW

Professor Paul Kleihues is Director of the International Agency for Research on Cancer in Lyon, France. His research has focused on brain tumours and in 2001, he was awarded the FECS' Clinical Research Award and the French Cancer League's Gold Medal. He was elected to the German Academy of Sciences Leopoldina in 1999 and, recently, to the Swiss Academy of Medical Sciences. He is on the editorial board of numerous cancer and neuropathology journals and is an editorial consultant for EJC.

Professor Paul Kleihues

Where did you train?
I took my medical degree at the University of Münster, Germany and then went to the Max-Planck Institute for Brain Research in Cologne, Germany for 12 years. I also had two sabbaticals in London.

Who inspired you?
Peter Magee at the Middlesex Hospital, London, in the early 1970s, pioneered research into N-nitroso compounds, which are powerful carcinogens in animals. We may have overestimated their role in humans but we learnt a lot about organ specificity and the early stages of carcinogenesis. Also, I was strongly influenced by Hermann Druckrey in Freiburg, Germany, who was the first to establish the mathematical basis of dose–response in carcinogenesis, a remarkable achievement in the late 1950s.

Why did you choose to work in the field of cancer?
I intended to be a neurologist and worked on cerebrovascular diseases at the Max-Planck Institute but experimental research into brain tumours was at an exciting stage at the time.

Did any other branch of medicine appeal?
Internal medicine would have been my second choice, but I was attracted to research after getting some interesting early results.

Might you have done something else altogether?
I was, and still am, a great fan of Georg Friedrich Handel and for a couple of terms, while studying medicine, I also studied the history of music, though I never saw it as a serious career path. You have to find the right balance between what you like to do and where your talents lie. Mine lie in law and politics, perhaps more so than in basic research, but however well my various administrative roles have gone, none have matched the pleasure and professional satisfaction I get from producing a good original paper.

What has been the highlight of your career to date?
I was Dean of the medical faculty of the University of Zurich between 1990 and 1992, the first Dean of German nationality for 60 years. Being from a country that brought death and destruction to many people, I considered this an expression of trust and confidence.

. . . and your greatest regret?
Career-wise, I have been very fortunate and really do not have a major regret.

If you could complete only one more task before you retire, what would it be?
I will be retiring from the Agency in Lyon at the end of 2003 and my main goal is to finish editing 10 volumes of the new World Health Organization classification of tumours by then. Identifying tumours on the basis of histopathology alone is no longer appropriate. In the new edition, morphology and genetic typing are combined to produce a practical and biologically meaningful classification, which is also predictive of outcome and response to therapy. This may not sound exciting but in malignant lymphomas, for example, disagreement over classification has made it almost impossible to compare therapeutic trials on an international basis.

What is your greatest fear?
The recent rise of xenophobia and nationalism in several European countries. Somehow, the lessons we learned in two world wars appear to be slipping into the background. Political stability is often a fragile thing and we need to protect it proactively. In biomedical research, we have had 50 wonderful years of unparalleled collaboration and exchange of data. We must do everything to maintain this spirit of international collaboration.

What impact has the Internet had on your working life?
The decision in the US to make *Medline/PubMed* freely available on the Internet has had a major influence. If I publish something on brain tumour genetics, anyone worldwide with a PC can read the abstract within a few weeks or even faster. Putting scientific results into the public domain is very appropriate, since most biomedical research is produced using taxpayers' money.

How do you relax?
I play the piano and like to swim. I have an apartment in Nice where I go for long weekends. There I can swim in the Mediterranean from early May well into November.

Who is your favourite author?
My all-time favourite is a well-known, fascinating, persuasive personality of the 18th Century. Born in Venice, he travelled Europe extensively and wrote the history of his life in French on Castle Dux in what is now the Czech Republic: Giacomo Casanova. Recently, I enjoyed novels by the Dutch author Maarten t'Hart. Some of his fascinating work reflects on resistance and collaboration during the war. References to classical music are abundant and some volumes come with a companion CD of the music quoted.

What piece of advice would you give someone starting out now?
Choose the laboratory for your Ph.D. and post-doctoral period with great care. Good scientists usually come from good labs. You get the best out of yourself if you are working with those who are better than you are.

What is your greatest vice?
First, I have a tendency to oversimplify and things often turn out to be more complicated than I portray them. Second, I am basically somewhat lazy and only work hard because I take on so many assignments. Finally—and this may be the worst—I am becoming increasingly impatient. As I get older, it often takes me longer to get things done, but at the same time, nobody seems to be fast enough for me.