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Last minute bid to improve CT Directive

A meeting between academic researchers and representatives of the European Commission (EC) has raised hopes that, even at this late stage, improvements to the Clinical Trials Directive may be possible.

The meeting, which took place in Brussels in June, 2004, brought together the Director Generals of Research and of Enterprise, academic researchers and representatives from industry.

Dr. Patrick Therasse, Director of the EORTC Data Center said the meeting ''showed a willingness on both sides to try to find a possible solution to the problems raised by the Directive vis-à-vis academic research''.

Following the meeting, academic groups were each asked to submit, within days, a dossier outlining the problems of the Directive, and proposed short- and intermediate-term solutions. FECS has previously supplied such a dossier. The suggestions are to be used either to amend the Directive or – something which would be exceptional in the history of the EC – to draft a new Directive to correct shortcomings in the original.

The Directors-General were due to be replaced on July 1st, 2004, and Dr. Therasse said that they are ''exceptional people'' who are ''really determined'', if at all possible, to make last minute changes. However, Dr. Therasse acknowledged that their ability to alter the Directive at this stage is likely to be limited. ''The Commissioners were both apparently very willing to push things through, but the administrators are more reluctant to make changes,'' he said.

Changes could not be made immediately. But the Commission could be officially asked to consider points raised, and the process leading to change set in motion.

European collaboration 'required for children'

Collaboration between European countries for phase I/II clinical trials is essential for drug development in childhood cancers, say British and French researchers (*EJC* this issue). They describe the Innovative Therapies for Children with Cancer (ITCC) Project, a European, multidisciplinary pre-clinical and clinical research framework. It is devoted to the development of new anticancer drugs in children.

Lead author Dr. Sue Ablett (UK Childhood Cancer Study Group, UKCCSG, Leicester, UK) said that access to new drugs is a problem in paediatric oncology. For ethical reasons, new drugs must be tested in adults first, but she said, 'Most drugs studied in adults are never subsequently offered for investigation in children in Europe'.

The authors have long standing experience in international collaboration for early drug development. Their first collaboration was between the New Agents Group (NAG) of UKCCSG and the Pharmacology Group of the Société Française d'Oncologie Pédiatrique (SFOP). It aimed to provide a mechanism for investigation of new agents in children's tumours. From January 1994 to September 2002, the collaboration evaluated 10 different drugs within 17 studies; 13 of which are closed, three are ongoing and one is suspended.

However, Dr. Ablett says there are issues to be considered. Only four of the joint studies have been completed. 'It is not clear whether this is a reflection of a problem with the organisation, with drug availability, of patient numbers, with the pharmaceutical industry, or with a variable combination of these factors'.

In an accompanying editorial, Dr. Malcolm Smith and Dr. Barry Anderson (Cancer Therapy Evaluation Program, Bethesda, USA), state that Dr. Ablett and colleagues ''are to be commended'' for addressing the challenge of establishing an infrastructure for the timely and safe conduct of early phase clinical trials in children with cancer (*EJC*, this issue).

The other challenges are, they say: to gain timely access to new agents from pharmaceutical sponsors for preclinical evaluations and for phase I and II testing; and to prioritise agents for evaluation in children.

Positive opinion for pemetrexed

The European Committee for Medicinal Products for Human Use (CHMP) has issued a positive opinion for two cancer indications for pemetrexed. CHMP recommends that the European Commission approve pemetrexed as a single agent for patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy. It also recommends approval for pemetrexed in combination with cisplatin for unresectable malignant pleural mesothelioma in patients who have not received prior chemotherapy.

Pemetrexed is expected to be marketed throughout the European Union by Lilly under the brand name Alimta.

EJC News is compiled by:
Helen Saul
Tel: +44 (0)1865 843340
Fax: +44 (0)1865 843965
E-mail address: h.saul@elsevier.com

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Highlights from American Society of Clinical Oncology, June 5–8, 2004, New Orleans, Louisiana, USA

Change of standard therapy in prostate cancer

Men with advanced hormone-refractory prostate cancer should be considered candidates for first-line chemo-therapy, following the results of two major phase III trials, the meeting heard. Both showed that docetaxel (Taxotere)-based chemotherapy is associated with significant survival benefits.

As a result, the US Food and Drug Administration (FDA) recently approved the use of docetaxel injection, in combination with the steroid prednisone, for the treatment of patients with advanced metastatic prostate cancer.

The studies were presented at a Plenary Session. Discussant Dr. Bruce J. Roth (Vanderbilt-Ingram Cancer Center, USA) noted that only about half of those with hormone-independent prostate cancer are treated with chemotherapy at the point at which they might enjoy a survival benefit. The new findings mean that 'many more men may undergo timely chemotherapy as first-line treatment for this disease, with improved survival as a result,' he said.

The two trials should 'dispel the perception that men with advanced hormone-refractory prostate cancer are not candidates for first-line chemotherapy,' he said.

Dr. Mario A. Eisenberger (Sidney Kimmel Comprehensive Cancer Center) presented data on behalf of colleagues at 10 European and North American centres (*Proc Am Soc Clin Onc* 2004, 4). Patients with hormone-refractory prostate cancer received prednisolone plus either docetaxel or mitoxantrone.

Median follow up among 1006 randomised patients was 20.7 months. Those who received docetaxel had a median survival of 18.3 months, compared with 16.5 months among those who did not. The survival benefit with docetaxel was significant; pain response and PSA response were also improved. However, there was more grade 3 or 4 neutropenia.

Dr. Daniel P. Petrylak (Columbia University of Physicians and Surgeons, New York) presented data from SWOG 99-16, which compared docetaxel plus estramustine with mitoxantrone plus prednisolone (*Proc Am Soc Clin Onc* 2004, 3). The randomised phase III study included 770 men with progressive androgen-independent prostate cancer (AIPCA).

Median survival was 18 months in the group receiving docetaxel/estramustine, compared to 15 months among controls. Dr. Petrylak concluded that the study supports the use of docetaxel and estramustine as first line therapy for AIPCA. 'This is the first large randomised trial demonstrating a survival advantage in AIPCA,' he said.

Erlotinib in advanced NSCLC

The novel agent erlotinib prolonged survival in patients with advanced non small cell lung cancer (NSCLC), a Canadian study found (*Proc Am Soc Clin Onc* 2004, 7022). The patients received the epidermal growth factor receptor (EGFR) erlotinib (Tarceva) after failure of 1st or 2nd line chemotherapy.

The study was conducted by the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG). It included 731 patients with stage IIIB/IV NSCLC who were randomised to receive either erlotinib or placebo. Those who received the active compound had an overall survival of 6.7 months, compared to 4.7 months among those who received placebo. The study also showed statistically and clinically meaningful benefit for patients in terms of quality of life.

Study Chair Professor Frances A Shepherd (University of Toronto) said it was the first randomised trial to confirm that a Her1/EGFR inhibitor prolongs survival after 1st or 2nd line chemotherapy for NSCLC.

'These results represent an important medical advance in the treatment of advanced lung cancer patients,' she said.

Adjuvant chemotherapy in early NSCLC

Two studies presented at the meeting demonstrated that adjuvant chemotherapy improved survival in patients with completely resected NSCLC.

Dr. Timothy L. Winton (University of Alberta) presented data showing that 5 year survival of patients with stage IB and II NSCLC was 69% among those who received a combination of adjuvant vinorelbine and cisplatin. This compared with 54% among those who were followed expectantly after surgery (*Proc Am Soc Clin Onc*, 2004, 7019).

The National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) study included 482 patients and, Dr. Winton said, is the first randomised clinical trial to demonstrate that a 3rd generation platinum-based doublet prolongs both overall and recurrence-free survival after surgery in early stage NSCLC.

Dr. Gary M. Strauss (Brown University) gave a report from Cancer and Leukemia Group B (CALGB) protocol 9633. The study included 344 patients with resected stage IB NSCLC. They were randomised to observation or to receive paclitaxel and carboplatin (*Proc Am Soc Clin Onc* 2004, 7019).

The CALGB study recorded 4 year overall survival of 71% in the chemotherapy group, compared with 59% in the observation group. Lung cancer mortality was 15% in the chemotherapy group, compared with 26% among controls.

The reduction in both all-cause and lung cancer mortality was significant and Dr. Winton suggested that adjuvant chemotherapy could become the new standard of care for patients with early stage NSCLC. However, results of previous studies have been conflicting and the subject remains controversial.

Discussant Dr. Katherine Pisters (Anderson Cancer Center) noted that patients in the two studies presented had earlier stage disease than in earlier work, they had uniform disease and the studies enrolled more women. Both involved drug regimens that are not toxic and included a 3rd generation agent.

EUROFILE

Wanted: 500,000 extra researchers in Europe

The actual and projected shortage of scientists in Europe has been the cause of debate in Brussels over the past few years, but until now little concrete action has been proposed to deal with the situation. So it was good to hear members of a European High Level Group (HLG) on Human Resources for Science and Technology call for 'a little less conversation and a little more action' when presenting their report at a conference in Brussels recently.

The group, chaired by José Mariano Gago, a former Portuguese science minister, was set up by the European Commission to look at the human resources implications of reaching the Lisbon and Barcelona targets for growth in high-tech. They found that Europe was likely to fall well short of the additional 500,000 researchers estimated to be essential to achieve these targets.

In 2001, the number of researchers per 1000 of the workforce was 5.7 for the EU-15 and 3.5 for the new member states. For most countries, employment in R&D had grown at a faster rate than total employment in the period 1995–2002, but large differences between countries remained. These figures may look relatively healthy, but should be compared with the 9.14 researchers per 1000 of the workforce for Japan and 8.08 for the USA, says the report.

There was worse to come. ''If you look at the differences between Europe and the US in terms of investment available per researcher in the public sector, European researchers get about half the amount that US researchers do'' said Gago at the conference. ''The difference is minimal for the private sector but it is huge for the public sector, and this has profound political consequences. Either you reduce the number of researchers in the public sector, or you are not giving them good working conditions''. Poor career prospects required the full spotlight of national and European policies, said Gago, and well paid, attractive careers in the public sector needed both to be set up and properly marketed to future generations.

The group called for significant portions of both national and European Commission budgets to be committed to solving the shortage of personnel in science, engineering and technology. The shortage should be addressed as part of wider EU policies, for example fiscal and foreign policy, they said, and pay and career structures in the public sector needed a dramatic improvement.

'COMMON EUROPEAN FISCAL POLICIES ARE REQUIRED'

''Until now no one has decided on common fiscal policies at European level, but if there's one area where that is required, it's in human resources'', said Gago. ''You can't get 500,000 extra researchers just by goodwill. Science policy requires more than just science policy to solve its problems''.

A huge increase in the number of women entering science was also recommended by the group, with childcare facilities being available to all. Women remain severely underrepresented in many areas of scientific research in many countries, the report says. ''In many countries they are still not reaching the upper echelons of the research hierarchies. However, they remain the most obvious source for increasing human resources for science and technology in Europe''.

'WOMEN REMAIN THE MOST OBVIOUS SOURCE OF PERSONNEL'

Conference participants were largely agreed on what needed to be done. ''Training people for R&D only makes sense if governments are willing to create an economy that wants to and is able to support R&D-led growth'', said Luciano Maiani from the University of Rome. ''Good salaries are essential to attract intellectual capacity from other countries''.

''Europe needs to create world class universities that act as a beacon for students around the world who want to study with the best and be taught by those at the forefront of the field,'' said Andrew Wyckoff from the Organisation for Economic Co-operation and Development (OECD). ''Europe must draw in the best and keep the best''.

The group were critical of this view. The report says that popularising science is essential to encourage people into careers in research, and that this should begin at primary school. ''Certain economists doubt that actions to promote science popularisation and even science teaching at primary and secondary levels are really helpful in increasing recruitment into science careers'', says the report. ''They believe that the most important point on which efforts should be concentrated n Europe, is at university level. We do not agree with these views which, in our opinion, disregard the social and cultural context of scientific development in democratic societies''.

Lowering school drop out rates in many European countries could be a key objective for broadening the qualification pool for R&D professions, say the authors. ''Relying on importing suitably qualified workers from outside the EU is not a sustainable, long-term solution, given the global nature of the market and the dynamics at play''.

The Commission has said that it will consider an awareness-raising campaign to address the problems, but whether this will lead to any concrete improvements in a potentially catastrophic situation for the economy and health of Europe remains to be seen.

Mary Rice
Brussels

Genetics and early cancer in Koreans

Young Korean breast cancer patients showed a high prevalence of *BRCA* mutations in a genetic analysis, researchers say (*JCO* 2004, **22,** 1638–45). However, most of the mutation carriers had no previous family history of breast or ovarian cancer (low penetrance).

Lead investigator Dr. Doo Ho Choi (Soonchunhyang University, Seoul, Korea) said, ''These data suggest that there may be different genetic and aetiological factors affecting [the] transmission and penetrance of the *BRCA* genes in Korean patients with breast cancer diagnosed at a young age''.

Breast cancer in Korean women is observed approximately 15 years earlier than in white US women and a higher proportion (around a quarter) of invasive breast cancer cases occur in patients aged less than 40 years.

Dr. Choi's group investigated the prevalence of mutations in two genes, *BRCA1* and *BRCA2*, which have been associated with early onset breast cancer. They also recorded the family history of breast and ovarian cancer in 60 hospital-based breast cancer patients aged 40 years or under. They completed, for the first time, a complete sequencing of both genes in Korean population.

Nine patients had 11 deleterious mutations (6 *BRCA1*, 5 *BRCA2*) – two patients had deleterious mutations in both.

'MOST MUTATION CARRIERS HAD NO FAMILY HISTORY'

The median age of onset of cancer was similar in these nine cases to the patients without mutations. Missense mutations of unknown significance were identified in seven patients. Several mutations were novel (6/11 deleterious mutations; 4/7 missense mutations).

Most of the patients with deleterious mutations (7/9) had no history of breast or ovarian cancer in their first- or second-degree relatives. This was true for three patients with more than one mutation.

This mutation rate is comparable or higher than other studies, according to Dr. Choi. ''This is particularly notable given that the incidence of breast cancer in Korean women is amongst the lowest in the world, and these patients were selected not by family history, but only by having breast cancer diagnosed at a young age''.

Unlike other populations with high prevalences, no recurrent founder mutations were observed in the Korean patients. These differences may be attributable to genetic or environmental modifying effects – such as the Asian diet.

'THE INCIDENCE IN KOREA IS EXCEPTIONALLY LOW'

''Dr. Choi called for large population-based screening studies to establish the frequency, penetrance and significance of *BRCA* gene variations. ''Only then will it be possible to oer reliable results and meaningful counselling to Korean women with breast cancer who choose to have such testing'', he concluded.

Emma Cannell

ASCO continued

Novel agent improves survival in glioma patients

Novel agent temozolomide (TMZ) has improved the outlook for patients with glioblastoma multiforme (GBM). An EORTC study found it significantly increased both progression-free and overall survival (*Proc Am Soc Clin Onc* 2004, 2).

The phase III trial, conducted by EORTC Brain and Radiotherapy (RT) Groups and the National Cancer Institute of Cancer (NCIC), included 573 patients from 85 centres across Europe and Canada. Patients were aged between 18 and 70 years and had histologically proven newly diagnosed GBM. They were randomised to receive standard RT, with or without concomitant and adjuvant TMZ.

Patients receiving combined treatment had a median survival of 15 months, compared to 12 months among those receiving RT alone. Progression-free survival was 7.2 months, compared to 5.0 months in the RT group; and 2-year survival was 26%, compared with 8%.

Presenting the results, Dr. Roger Stupp (University Hospital, Lausanne, Switzerland), said that patients in the study continue to be followed to evaluate long term effects of treatment. He concluded that concomitant and adjuvant TMZ 'significantly improves' progression-free and overall survival in GBM. The treatment is safe and well-tolerated, he said.

MA 17 Final

The final analysis of the MA 17 trial demonstrated a 39% increase in overall survival for postmenopausal women with early stage, node-positive breast cancer in the extended adjuvant setting (*Proc Am Soc Clin Onc* 2004, 847).

The MA 17 study evaluated extended adjuvant treatment with letrozole versus placebo in 5187 postmenopausal women with early breast cancer. It was designed to offer women ''life lines'' beyond tamoxifen, which is not considered suitable after 5 years since it can function as an agonist, stimulating cancer cells to grow.

The women all received adjuvant tamoxifen for 5 years and were then randomised to receive either letrozole (Femara) or placebo. After an average of 2.5 years in this extended adjuvant setting, those receiving the active drug also had a 40% reduction in risk of distant metastases, regardless of nodal status.

Interim results from MA-17 (*NEJM 2003* **349**(19), 1793–1802) showed that taking letrozole in the extended adjuvant setting produced a 43% reduction in likelihood of relapse and a 46% reduction in cancer arising in the other breast, compared to patients given placebo. These results were published in an expedited review after the independent data monitoring committee stopped the study after 2.4 years. There was widespread criticism that this had not allowed sucient time to show survival advantages. The latest results, which include all outstanding data, should allow such criticisms to be laid to rest. Principal investigator Dr. Paul Goss (Princess Margaret Hospital, Toronto) said, ''Had we waited we would have shown a survival advantage upfront''.

Dr. Martine Piccart (Institut Jules Bordet, Brussels, Belgium), said she believes that with time, the same benefits will be seen for node negative women. ''The results are really good news for all breast cancer patients,'' she said.

PODIUM

Back to the Future

EJC was founded 40 years ago, in June 1964, when our current editor-in-chief, Professor John Smyth, was an undergraduate at Cambridge University, UK. Professor of Medical Oncology at Edinburgh University since 1979, he is a former President of ESMO and President-Elect of FECS. To mark EJC's 40th Anniversary, Professor Smyth chose key papers from the early issues and asked today's experts for an update. Old and new papers are published together in a Special Issue later this month.

John Smyth as an undergraduate

What has changed in 40 years?

Technology. Research in the 1960s and 1970s was limited by the experimental techniques available. Interestingly we're still asking many of the same questions. Our forebears 40 years ago showed remarkable prescience in wanting to examine the role of viruses, chromosome damage and DNA, given the technology they were working with.

Where has most progress been made?

Back in the 1960s, the importance of DNA in abnormal cellular growth was known and one paper described cytophotometric measurements of DNA content in tumours. The updated paper by John Ansell discusses our very much more specific understanding. They suspected the Philadelphia chromosome's role in chronic myeloid leukaemia (CML); it has now been dissected down to the level of the genes. That is real progress.

Where else is this apparent?

An early paper by SR Humphreys describes the value of studying spontaneous rather than transplantable tumours in mice. Now, mice can be genetically engineered to carry genes for early, intermediate or late cancer. This allows us to ask whether the genes truly have the proposed effect. Modelling is of a different order.

You mentioned the role of viruses?

Forty years ago, researchers knew that viruses could cause cancer in animals and, they postulated, also in humans. They simply did not have the technology to pick up small quantities of human viruses. In the update, Dorothy Crawford suggests that one-fifth of human cancers could have a viral aetiology. It is these cancers that could be preventable, or eradicated, with the use of vaccines.

Did you come across dead-ends?

Plenty of ideas have been tried and found wanting. 40 years ago people were trying to induce cancer in a mouse by scratching a carcinogen on its skin. Compare that with the genetic techniques in common use today.

You seem to be saying that our basic ideas have not moved on?

I do not want to sound negative because 40 years in the history of original thought is nothing. It is just that our main achievement has been the development of the technology to address long-standing questions. If many of the questions have remained unchanged, it could be that we are thinking along the right lines!

What about changes in cancer care?

Cancer chemotherapy hardly existed in the 1960s. Procarbazine, one of the very few drugs around cured. Hodgkin's Disease in the 1960s, but was so toxic that it also induced second cancers and was dropped.

Transplantation of bone marrow cells, to protect the bone marrow during radiation and chemotherapy was discussed then. Use of bone marrow stem cells was only a dream yet now, de Vries is discussing the 'happy destiny' of frozen haematopoietic stem cells, which may be able to repopulate organs other than bone marrow.

Concepts such as holistic care and quality of life had not arisen 40 years ago because we had not got past first base on cancer treatments. Now they, and not just survival, are of prime importance.

How does looking back inform future progress?

It allows us to pinpoint key areas in which we should invest time and energy. In drug development, random screening to look for active chemicals may be a waste of time when scientists are increasingly identifying new targets for therapeutic attack. But it is reassuring that refining ideas, unravelling differences between normal and malignant growth, and continuing to apply them, does pay dividends. We now have the tools to test ideas quickly. And information exchange is now so rapid we don't have to wait a year to see the results of someone's work.

The EJC Special Issue 'Back to the Future' (EJC 2004 ***40,*** *13) will be published in July 2004.*