PERGAMON

European Journal of Cancer 38 (2002) 1421–1425

European Journal of Cancer

www.ejconline.com

NEWS. . .NEWS. . .NEWS

ATAC: "Insufficient to change practice"

An expert panel at the 38th Annual Meeting of American Society of Clinical Oncology (ASCO, 18–21 May 2002, Orlando, FL, USA) concluded that the ATAC (Arimidex, Tamoxifen, Alone or in Combination) data, while promising, are insufficient to change current standard practice. The panel convened to assess whether use of aromatase inhibitors as adjuvant treatment for breast cancer should become routine.

A panel of 18 members, headed by Dr Eric P. Winer, was convened at the behest of the then ASCO chairman, Dr Larry Norton, and the Board of Directors. It followed the announcement from ATAC at the San Antonio Breast Cancer Symposium (December 2001). ATAC data suggested that adjuvant therapy with anastrozole (Arimidex) reduces risk of recurrence by relatively 17% among postmenopausal women with breast cancer, compared with the 'gold standard' tamoxifen.

The panel was instructed to conduct an evidence-based assessment to determine whether anastrozole (or any of the aromatase inhibitors) are appropriate for routine clinical use for breast cancer in the adjuvant setting. Their results are to be published in the Society's journal (*Journal of Clinical Oncology*) later this year.

The ATAC trial randomised women to receive either anastrozole, tamoxifen or both following completion of the primary therapy. Relapse-free survival and tolerability were examined (see *EJC* News, 2000, **38**(9)). In coming to its conclusions, the panel noted that the study had a median follow-up of 33 months and only one-third of patients had been followed for more than 3 years. They also pointed out that the differences in disease-free survival, although significant, were small. Furthermore, it can take 5 years to see the maximal benefit of tamoxifen treatment and it is not known whether this is also true for anastrozole, a factor that would obviously limit such early comparisons.

"MOST ATAC PATIENTS HAVE BEEN FOLLOWED LESS THAN 3 YEARS"

Potential toxicity is another issue. Although the short-term toxicity is generally similar for both drugs, there is currently no long-term data for anastrozole. Dr Winer said, "It took a decade to figure out the rare, but still serious, side-effects of tamoxifen." The panel's biggest concern with regard to the long-term effects is fractures, as these were more commonly seen following treatment with anastrozole. There is also a lack of confirmatory trials, although the results of some other trials should be announced within the next year or two. There is no reported survival advantage.

Speaking at a press conference at the ASCO 2002 conference, the panel was unanimous in its opinion, but is looking forward to seeing the updated data from ATAC. Nevertheless, they recommend that physicians discuss the available information with patients, and acknowledge that treatment approaches may change over time. It stated, "Individual healthcare providers and their patients will need to come to their own conclusions, with careful consideration of all the available data."

Emma Cannell, Scientific Editor, EJC attended the ASCO meeting and provided these reports.

"One at a time, please!"

Chemotherapy for early-stage breast cancer provides most benefit if given before tamoxifen starts, say US researchers. Dr Kathy Albain (Loyola University Medical Centre) presented results from the National Cancer Institute (NCI)'s Breast Intergroup Trial 0100 (*Proc Am Soc Clin Oncol* 2002, **21**, 143).

The study compared sequential and concurrent therapy with tamoxifen and chemotherapy (cyclophosphamide, doxorubicin and fluorouracil). It included 1477 postmenopausal women with early stage breast cancer that had spread to the lymph nodes but no further, and had tumours that were oestrogen or progesterone receptor positive.

After 8 years, 67% of women who received sequential therapy remained free of breast cancer, compared with 62% on concurrent therapy and 55% who received tamoxifen alone. This means that delaying tamoxifen until the completion of chemotherapy leads to an estimated 18% improvement in disease-free survival.

"Our results show that it is best to wait until chemotherapy is finished before starting tamoxifen to obtain optimal benefit from the chemotherapy," said Dr Albain.

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

PII: S0959-8049(02)00164-8

When—or whether—to PSA test

The screening interval for PSA tests in men with low initial readings could be reduced according to Dr ED Crawford (University of Colorado, Denver, CO, USA), speaking at a plenary session at ASCO. This is in light of an analysis of data from the US National Cancer Institute (NCI)'s nationwide Prostate, Lung, Colorectal and Ovarian (PLCO) trial, he said. However, Dr Steven N. Woolfe, (Commonwealth University Virginia) pointed out that it is still difficult to identify those cancers that are more indolent in their growth and development. It is also uncertain how PSA screening translates into effects on survival, and therefore the screening interval is not the most important question. (For discussion see *EJC* 2000, **36**, 1316–1321).

Rising levels of prostate-specific antigen (PSA) are considered a possible indicator of prostate cancer. The PLCO researchers examined PSA levels of 27 863 men aged 55–74 years who had an initial PSA of less than 4 ng/ml and at least one subsequent PSA test (*Proc Am Soc Clin Oncol* 2002, **21**(4). These men were divided into groups according to their baseline measure (<1, 1–1.9, 2–2.9 and 3–3.9 ng/ml) and followed annually for 5 years.

In men with a baseline PSA of less than 1 ng/ml, only 1.5% converted to levels higher than 4 ng/ml over the 5-year time period. Of those with a baseline PSA of 1–1.9 ng/ml, only 2.5% converted over 2 years. It has been assumed that screening should be carried out annually but, based on these results, the researchers recommended that those with initial PSAs of <1 ng/ml could be screened every 5 years and those with PSAs of 1–1.9 ng/ml every 2 years.

Dr Crawford stated that this would result in a 55% reduction in annual screens and save up to $1 billion a year. The authors did, however, recommend increased vigilance for those with higher initial PSA test readings (2–3.9 ng/ml) and suggested that these men may be candidates for chemoprevention trials.

In the discussion, Dr Woolfe said, "There is a continuing concern that we are still not able to tell which cancers are latent." He added that the "inadvertent harms of screening" should be considered as it is unclear what the health significance of converting is. Harm includes a reduced quality of life following treatment for localised prostate cancer and the detection of insignificant cancer. The question "should not be how often to screen, but whether to screen at all," he said. There is now a consensus among the American societies (American Urology Association, American Cancer Society, American College of Physicians, American Academy of Family Physicians) that decisions on screening should be shared. This leaves unanswered questions such as whether patients want to share in such decisions, and whether they can weigh the tradeoffs. For physicians, it may mean having to carry out such discussions in busy practices without the help of decision tools.

Mirroring this cautious interpretation, Dr Larry Norton (then Chairman of ASCO) said of the PLCO results, "While this research is exciting, these interim findings do not yet tell us if PSA screening itself improves survival."

"Two drugs are better than one in NSCLC"

Patients with advanced non-small cell lung cancer (NSCLC) treated with paclitaxel and carboplatin survived 2 months longer than those given paclitaxel alone, said Dr Rogerio Lilenbaum (The Mount Sinai Comprehensive Cancer Center, Miami Beach, US). "Two drugs are better than one," he said.

Combined treatment is considered by many to be the standard treatment for advanced NSCLC patients with a good performance status (PS) but, so far, no survival benefit has been observed compared with the single agent. A meta-analysis has shown a 2-fold increase in the response rate for combined therapy, but it is often associated with an increase in serious adverse events.

The researchers, in a Cancer and Leukemia Group B (CALGB) study (*Proc Am Soc Clin Oncol* 2002, **21**(2), randomised 584 stage IIIb/IV patients with NSCLC (of whom 158 were more than 70 years old) to receive either carboplatin and paclitaxel or the same dose of paclitaxel alone. Survival was their main endpoint, but cost-effectiveness and quality of life were also assessed, using the European Organization for Research and Treatment of Cancer Quality of Life (EORTC QLQ) instruments.

The overall response rate was 17% versus 29% in favour of the combination arm, a statistically significant difference. Nevertheless, haematological toxicity was also significantly more common in the combination arm, although febrile neutropenia was similar. Failure-free survival was 2.5 months versus 4.6 months, median survival time was 6.7 months versus 8.8 months and the confidence intervals did not overlap for these parameters. One-year survival was not significantly different (33% versus 37%) reflecting the coming together of the survival curves as often occurs over time.

The elderly patients showed similar trends to the overall population. Median survival among those with a PS of 2 was 3 months, compared with 8.8 months for those with a PS of 1 or less. "The benefit for the PS2 patients remains to be confirmed," the researchers concluded. There were no differences in QoL or costs between the two arms.

Two other randomised studies reported at ASCO confirmed the benefit of two drugs compared with one (*Proc Am Soc Clin Oncol* 2001, **21**, 1162; *Proc Am Soc Clin Oncol* 2002, **21**, 1163). They also showed an approximate 2-month benefit for the combined arms versus single agent treatment. All three trials showed an approximate 5% longer 1-year survival in the combined arms.

Dr Paul A. Bunn (University of Colorado Cancer Center), the new Chairman of ASCO, discussing this data, said, "We have a long way to go, but can see the top; please help us reach the summit."

Future therapies "will target and control"

Data on targeted therapy took centre stage at ASCO. In the opening ceremony, Dr Andrew von Eschenbach, newly-appointed Director of the National Cancer Institute, said that we are moving from a "seek and destroy" strategy to one of "target and control". It is like moving from "weapons of destruction to interventions for control and prevention," he said.

The success of STI-571 (Imatinib mesylate, Glivec) provides the "proof of principle" that targeted strategies can work, he said. It demonstrates the complexity of cancer systems and reenforces the idea that there is no magic bullet to destroy cancer. The attack on cancer will involve a combination and integration of therapies that will allow oncologists to intervene through multiple pathways, he said.

STI-571 "has lasting effects in GIST"

STI-571 has lasting effects in over 60% of patients 1 year after beginning treatment for gastrointestinal stromal tumours (GIST), scientists say. The effects are specific to GISTs and not other soft-tissue sarcoma (STS) subtypes (*Proc Am Soc Clin Oncol* 2002, **21**, 1608; *Proc Am Soc Clin Oncol* 2002, **21**, 1609).

STI-571, one of the first targeted drugs to be developed for clinical use, works as a tyrosine kinase inhibitor of the KIT protein and platelet-derived growth factor receptor (PDGFR). The former is frequently mutated and constitutively expressed in GISTs, whilst PDGFR is often expressed in other STS. GISTs are rare, advanced stomach cancers with a poor survival following standard cytotoxic drug treatment.

Dr Margaret von Mehren (Fox Chase Cancer Center, Philadelphia) reported the results of 147 patients with GIST treated with either 400 or 600 mg/day of the drug. A response was seen in 93 patients (63%). After a median follow-up of 15 months, 73% remain in the study and the median survival has not yet been reached. There were no differences in response between the two doses.

Some 18% of patients (17/93) progressed after initially responding and in these patients the pharmacokinetic and KIT status was reassessed. There was a possible loss of KIT in 1 patient, but further studies are underway to assess all the mechanisms of possible resistance. Dr von Mehren said, "As long as the patient benefits, I would recommend a continuation of treatment."

In a similar EORTC study, also presented at the meeting, an overall response rate of 71% was seen in GIST patients. There were no objective responses in other STS subtypes examined, although 29% of these patients experienced stable disease. The median time to response was fairly slow, at approximately 4 months.

The treatment was generally well tolerated in these studies and the main toxicities observed were fatigue, oedema, rash, nausea and some haematological toxicity. Some side-effects became less severe with prolonged treatment, as was also seen in the IDEAL 2 trial (see over) in which ZD1839 (Iressa) was used to treat advanced NSCLC.

In the discussion, Dr R.S. Benjamin (University of Texas, M.D. Anderson Cancer Center) said targeted therapy moves us from an "age of dinosaurs" to a "wave of the future", although he felt the final word "was not yet in". He also said we need to reassess how responses to these treatments are classified. The current RECIST criteria, which measure the longest diameter can often give a false impression of the size of the tumour. The presentations stated that tumours often become less dense with STI-571 treatment and that measurements should take this into account.

STI-571 in early CML

Patients with newly-diagnosed chronic myeloid leukaemia (CML) may benefit from STI-571, scientists say. Those with advanced CML have previously been shown to have a good response to the drug, but this is the first evidence of benefit in earlier stages of the disease. Patients on STI-571 had a significantly longer time to progression, compared with those given interferon (*Proc Am Soc Clin Oncol* 2002, **21** (1).

In the study presented at ASCO, 1106 patients with newly diagnosed CML were randomised to receive either interferon plus cytarabine or STI-571 alone (either 400 or escalation to 600 mg/day). Six months after therapy, 8 patients on STI-571 (1.4%) had worsening leukaemia; compared with 57 (10.3%) on interferon; this was significant. At 1 year, these figures were 24 (4%) for those on STI-571; and 103 (19%) for those on interferon.

After a median follow-up of approximately 14 months, 90% of the STI-571 patients were still on the therapy compared with 30% in the interferon arm. Moreover, 39% of the interferon patients crossed over to the STI-571 arm. In the STI-571 arm, 83% showed a major cytogenetic response compared with 20% on the interferon. For a complete cytogenetic response, these numbers were 68% versus 7%, respectively. STI-571 was generally well tolerated with oedema, nausea, muscle cramps and rashes being the most common non-haematological toxicities.

Presenting the data, Dr. Brian Druker, on behalf of the International Randomised Interferon vs. STI-571 (IRIS) study group, said survival still needs to be examined, as does the optimal dose of the drug and whether it should be used in combination therapies. The drug costs approximately $25 000 per year but this should be weighed against the economic benefits of treatment as patients on the drug will often be able to work. "Although the long-term results of STI-571 remain unknown, it should now be considered standard therapy for newly-diagnosed CML patients," he said.

In the following discussion, Dr Steven MacKinnon (University College, London) compared STI-571 treatment with transplantation. He said that it is now unusual not to be able to find a donor, but that between 20 and 35% of patients die from transplant-related problems. All patients should be offered STI-571, he said, and should remain on therapy if in complete response. Patients who fail to respond should be offered a transplant, he said.

Novel treatments for advanced NSCLC

A novel treatment is showing encouraging results in the treatment of advanced non-small cell lung cancer NSCLC, scientists reported at ASCO. Two phase 2 trials showed response rates of between 10 and 20% among heavily pretreated patients who were given ZD 1839 (Iressa), the low molecular weight inhibitor of the epidermal growth factor receptor (EGFR). (IDEAL 1 and 2, *Proc Am Soc Clin Oncol* 2002, **21**, 1188; *Proc Am Soc Clin Oncol* 2002, **21**, 1166).

EGFR is frequently overexpressed on the surface of lung cancer cells and is thought to be important in the development and progression of disease. The median survival for patients with advanced NSCLC treated with platinum-based chemotherapy is 8 months; 1-year survival is 35%. Docetaxel is the most common second-line treatment, with a response rate of 7% and median survival of 6 months. Clearly, new treatments are needed.

Dr Fukuoka (Kinki University School of Medicine, Osaka, Japan) presented the results of IDEAL 1, a double-blind study in which 210 patients were given either 250 or 500 mg/day of ZD1839 as second- or third-line treatments. Both groups were closely matched for age, gender and performance status. Most patients were male and had adenocarcinoma. Response rates of approximately 20% were observed for both doses, but the low dose was associated with less toxicity and resulted in fewer withdrawals, dose reductions and interruptions. Rash and diarrhoea were the most common symptoms. A median duration of response of more than 3 months was observed for both doses and the disease control rates were 54.4% (250 mg) and 51.4% (500 mg). There was no difference in response between those who had received one or two previous regimens.

Differences between the Japanese and non-Japanese groups in the study could have been a reflection of imbalances in baseline characteristics, Dr Fukuoka said. The data suggests that ZD1839 represents "an important novel treatment option for patients with pretreated advanced NSCLC," he said.

These results were mirrored in IDEAL 2. In this trial, approximately two-thirds of patients had had three or more prior chemotherapy regimens. 216 patients were enrolled (90% with stage IV NSCLC) and response rates of 12 and 9% were obtained for the low (250 mg/day) and high (500 mg/day) doses groups, respectively. There was a median time to symptom improvement of 2 weeks and symptom improvement was observed in 43 and 35% of the patients, respectively.

Another novel treatment, the monoclonal antibody against HER2, trastuzumab (Herceptin), showed disappointing results. Immunohistochemistry has demonstrated HER2 overexpression in 20–25% of NSCLC patients. However, a randomised phase II study comparing gemcitabine and cisplatin alone, with the same drugs in combination with trastuzumab, gave little cause for optimism.

Presenting the data, Dr Gatzemeier (Hospital Grosshansdorf, Grosshansdorf, Germany) said he does not believe that trastuzumab has a role in lung cancer. Dr Lawrence Einhorn (Indiana University Medical Center) agreed with Dr Gatzemeier. The study was "definitive" and showed that trastuzumab has no place in the treatment of lung cancer, he said.

In his discussion of all three studies, Dr Einhorn also cautioned that the data from both IDEAL trials lacks sufficient follow-up to measure a survival benefit. However, he said, "This is missing the point." These trials have given hope to a heavily pretreated patient population, and approximately 40% experienced symptom improvement, he said. Other questions remain to be answered such as whether the level of EGFR expression is important and whether patients with hepatic or CNS metastases will also respond.

The Data Monitoring Committee said that results from the phase III trials using ZD1839 are not mature enough yet to be presented, but they are likely to be available at next year's meeting and will be eagerly awaited.

Surgery for BRCA women

Women who have mutations in *BRCA1* and *BRCA2* genes can reduce their risk of breast and ovarian cancer by having surgery, researchers say. Removal of the ovaries and fallopian tubes reduced the risk of these subsequent cancers by 75%, compared with intensive ovarian screening, they say (*Proc Am Soc Clin Oncol* 2002, **21** (3)).

The study was conducted at Memorial Sloan-Kettering Cancer Center, New York, and included 173 women whose genetic tests revealed mutations in the *BRCA1* and *BRCA2* genes. Within this group, 101 women chose preventive salpingo-oophorectomy. The other 72 opted for intensive ovarian screening with transvaginal ultrasound and a CA-125 blood test twice a year.

After a 2-year follow-up, three breast and one peritoneal cancers were diagnosed in women who had preventive surgery. Among those who opted for screening, eight breast cancers, four ovarian cancers and one peritoneal cancer were diagnosed.

In addition to reducing the risk of ovarian cancer, removing the ovaries is believed to reduce breast cancer risk by decreasing oestrogen, thereby halting or slowing the development of breast cancers that may depend on this hormone to spur their growth. However, researchers say this is the first time that it has been demonstrated that surgery can reduce risks.

"We now have prospective evidence to present to patients so that they can make informed decisions about their care," said lead investigator Dr Kenneth Offit.

The women in the study will be followed-up over the longer term to evaluate the long-term effects of preventive surgery on cancer rates, other health risks and on overall survival.

In the following discussion, Dr Olufunmilayo Olopade (University of Chicago) suggested that surgery could be delayed until after women have had families. Ovarian cancer risk increases sharply in these women beyond the age of 40, when it becomes much higher than in the general population. "There is a lot of hope and optimism that the surgery will decrease mortality," she said.

INTERVIEW

Professor Bin Kroon is head of surgery at the Netherlands Cancer Institute, Amsterdam. Past positions include President of ESSO, Member of FECS Council, Member of Accreditation Council of Oncology in Europe (ACOE) and Treasurer of World Federation of Surgical Oncology Societies. His special interests include melanoma, sarcoma and isolated limb perfusion.

Professor Bin Kroon

Where did you train?
Initially at the University of Groningen, the Netherlands, then I did an internship in Curaçao, became interested in tropical medicine and stayed there quite some time! I also worked in Nigeria for 3 years, but eventually returned and completed my surgical training in Rotterdam.

Who inspired you?
My father, who died when I was 12. He wanted to be a doctor, but he was from a family in the Netherlands with no academic tradition and it was impossible. He became a factory manager, and staff who worked with him have told me he was excellent at his job, but also that he had the capacity and capability to have been a perfect doctor.

Why did you choose to work in the field of cancer?
I enjoy the fight. Cancer is the enemy and you have to destroy it with the most gentle and subtle surgical techniques. Every patient is complicated and you frequently have to deal with things you have never seen before. The particular injustice of cancer, which is itself part of life, right down to the DNA, inspires me to work with these patients.

Did any other branch of medicine appeal?
I loved tropical medicine, and would have continued except that we wanted our children educated in the Netherlands. I worked in Nigeria after the Biafran war, in which millions of people died of famine. We built and organised a hospital with money from the Netherlands government. When I got back, I flirted with psychiatry, but after a few months found I missed somatic medicine too much and trained in surgery.

Might you have done something else altogether?
No. My wife is in the medical field, and so are my 4 children. I never considered anything else.

What has been the highlight of your career to date?
We were frontrunners in the use of the sentinel node biopsy at the Netherlands Cancer Institute. I remember the morning I went to work, knowing that I would not do another elective axillary dissection.

A year ago I was asked to become an honorary member of the Dutch Society of Surgical Oncology. Surgical oncologists need to know and trust each other and to do operations together and that now is the situation in the Netherlands, thanks to this Society.

. . . and your greatest regret?
Not being able to get funds for our work on sentinel node biopsy 10 years ago. We knew how important it is to reduce the mutilation of surgery but could not convince the people holding the purse strings. Perhaps it wasn't complicated enough to be interesting. But in the end the hospital authorities supported us.

If you could complete only one more task before you retire, what would it be?
To find a method—perhaps genetic profiling with microarrays—which will determine which patients will benefit from adjuvant treatments. At present 70–80% of patients receiving these drugs do not benefit from them.

What is your greatest fear?
The devaluation of the medical profession, and its transformation into an 8 to 5 job, regulated to death by the government and decision-makers. I fear that doctors will no longer lead hospitals and will lose the respect of their patients.

What impact has the Internet had on your working life?
Not much. My children are teaching me, and I can send emails and search the literature, but I still spend most of my time in the operating theatre or in clinics. It's had more impact on my secretary.

How do you relax?
I love ice skating. In the Netherlands the canals freeze in winter, and you can skate long distances; I've done a 200 km route twice. I also like sailing, traveling, classical music, and soccer. I used to play for Heerenveen, now in the Premier League, but couldn't continue when I went to medical school.

Who is your favourite author?
The late Durlacher, a Dutch Jewish writer. He described the return of Jewish survivors of concentration camps to their homes in the Netherlands, and the ignorance and hypocrisy they faced from their old friends and neighbours.

What do you wish you had known before you embarked on your career?
Nothing. I followed my intuition and am completely satisfied.

What piece of advice would you give someone starting out now?
In surgical oncology, you need to specialise on an organ or organs, but also keep an overview of surgical oncology and of the disease. Remember that you are working for the benefit of the patient, and be ready to ask help of other specialists, especially oncologists and radiotherapists.

What is your greatest vice?
I am a perfectionist. But I'm learning. It is not always necessary to get 8 or 9 out of 10. Frequently 6 is enough. I was also inclined to dwell on the past but I can now look ahead and let bygones be bygones.