New approaches to breast cancer treatment

Diverse new approaches to the treatment of breast cancer were presented at the 2011 European Multidisciplinary Cancer Congress (Stockholm, Sweden; 23-27 September 2011). Possibly the simplest advance came from a large UK trial, which demonstrated that altering the schedule of established therapies could have a dramatic effect on local recurrence rates. At the other end of the spectrum, an innovative antibody-guided agent could become the first in a new class of cancer drugs.

The UK SECRAB (Sequencing of chemotherapy and radiotherapy in adjuvant breast cancer) study found that giving radiotherapy between or during chemotherapy cycles to women with early breast cancer — so-called synchronous chemoradiation — reduced the risk of local recurrence by 35% at a follow-up of 5 years. Synchronous treatment had minimal side-effects and was not linked to a detrimental effect on patients’ quality of life.

“It is amazing that we have been using chemotherapy and radiotherapy for 30 years and this is the first study that has shown a way of optimising it,” said lead researcher, Indrajit Fernando (University of Birmingham, UK), adding that the study has implications for health economics: “There is no cost to this. It’s not like a drug that is going to cost £3000 a course; these are changes that are not going to increase the cost of therapy.”

SECRAB was set up in 1998, with funding from the Cancer Research Campaign (which became Cancer Research UK). Its aim was to manipulate the sequencing of therapy (chemotherapy is normally completed before radiotherapy is given) to try reduce the risk of local recurrence. Previous work had suggested that reversing the normal sequence and giving radiotherapy ahead of chemotherapy could have a detrimental impact on survival. So Fernando’s group did not delay the chemotherapy, but instead, brought forward the radiotherapy and either sandwiched it between chemotherapy cycles, or, where longer courses of radiotherapy were used, gave the treatments concomitantly.

The Phase III trial included 2,296 women who had undergone breast conserving surgery or mastectomy. They were randomised to receive the normal sequential chemoradiation, or synchronous treatment. Five year follow-up found local recurrence rates of 2.8% and 5.1% in the synchronous and sequential groups, respectively. The difference was statistically significant (EJC 2011. 47: Suppl 2; LBA#2).

There was an increase in moderate and severe skin reactions with synchronous treatment: 24% compared to 15% in the sequential group. However, in the vast majority (96%), skin reaction had settled within 4-6 weeks of completing treatment. Fernando: “It was really a modest increase in acute skin toxicity. We should also note that this trial ran from 1998 to 2004, and..."
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since then we have been using far more modern ways of delivering radiotherapy, which significantly reduce acute skin reaction.”

Longer term, there is a suggestion that synchronous treatment could impact on survival. “What we didn’t know when we set up the study was that, in addition to the terrible shock and morbidity of developing a local recurrence, we can also potentially have an impact on survival,” said Fernando. “According to the Early Breast Cancer Trialists’ Collaborative Group (2005), one breast cancer death can be avoided for every 4 local recurrences prevented. Therefore, even a 2.3% reduction in local recurrence rates will have an impact worldwide when we consider that this is a very common cancer.” To date, there have been too few events in the SECRAB group to establish this.

Nevertheless, Fernando says that the benefits – including a strong patient preference for shorter overall treatment times – has convinced him to adopt synchronous treatment schedules with CMF-based chemotherapy, and he believes others should follow suit: “Clinical practice needs to be reviewed for patients who are being treated with a CMF or an anthracycline/CMF chemotherapy schedule. The data will be forwarded to the National Institute of Clinical Excellence in the UK but the results have implications worldwide,” he said.

Another innovation presented at the Stockholm meeting came in the form of an innovative “magic” molecule, T-DM1, which appears to be a significant advance in the quest to target HER2-positive breast cancer cells. T-DM1 combines trastuzumab with the highly toxic chemotherapy, maytansine, by means of a stable linker protein. The idea is that trastuzumab attaches to HER2-positive receptors on the cancer cell, the whole molecule is internalised in the cancer cell, and only then do proteolytic enzymes in the cell cut the linker protein, and release the chemotherapy which in turn kills the cancer cell.

Presenting phase II data, Sara Hurvitz (University of California, Los Angeles, USA) said, “The magic of this molecule is in the linker, which is stable and does not release the chemotherapy until T-DM1 has been internalised in the cell. Furthermore, this molecule retains the anti-tumour activity of trastuzumab.”

The open-label, phase II trial included 137 patients with locally advanced or metastatic HER2-positive breast cancer, who had never received chemotherapy or HER2-targeted therapy. They were randomised to receive either T-DM1 or standard therapy (trastuzumab plus docetaxel). Progression-free survival was 14.2 months for women in the T-DM1 arm, and 9.2 months in the standard therapy arm. In the T-DM1 arm, 7.2% women discontinued treatment due to side-effects, compared to 28.8% in the control arm. Patients on T-DM1 were treated for an average of 10 months, compared to 5.5 months for those in the control arm (EJC 2011. 47: Suppl 1 #5001).

Hurvitz said this was probably due to reduced toxicity: “Patients had moderate to severe toxicity with trastuzumab and docetaxel 89% of the time, compared to half of that with T-DM1. This is
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underscoring that targeted delivery of chemotherapy in this combined molecule leads to less toxic therapy.

On-going phase III trials EMILIA (comparing T-DM1 to lapatinib and capecitabine in trastuzumab-resistant HER2-positive metastatic breast cancer) and MARIANNE (T-DM1 combined with pertuzumab versus trastuzumab plus taxane in first-line treatment of patients of HER2-positive metastatic breast cancer) are expected to report in the spring of 2012. Referring to the phase II study, Hurvitz said: “I find this data incredibly promising and exciting but we’ll have to wait for the phase III data and I think it’s going to be out very shortly,” she said.

The idea of the antibody-drug link is more than a decade old, Hurvitz said, but T-DM1 is the first successful application. Jean-Charles Soria (Institut Gustave Roussy, Villejuif, France) said that the pharmaceutical company Genentech “is so excited by this approach that they have more than 12 antibodies that are ready or already in phase I trials. They are antibody-drug conjugates using exactly the same technology. A stable link which is only released once the molecule is internalised is completely new.”

However, he also applauded Fernando’s work on treatment schedules, which will place less strain on health budgets: “There are two ways of improving the management of breast cancer. One is with the extremely innovative but most likely costly molecularly-targeted agents like T-DM1. The other is at no cost, optimising the way we use the therapies that have been established now for over a century and which can also potentially bring survival benefits – just optimising chemoradiotherapy.

‘We can use innovative but costly targeted agents. Or, at no cost, we can optimise therapies that have been established for over a century’ – Jean-Charles Soria

“People need to realise that multidisciplinarity can bring real improvements. It’s not just something to talk about; it can have profound implications.”

Other, unexpected, results presented at the meeting will prompt further research. The AZURE trial examined the effect of the bisphosphonate, zoledronic acid, in patients with stage II/III breast cancer. The drug is mainly used to treat osteoporosis, but is given to cancer patients to protect against the effects of secondary bone cancer. Laboratory studies have suggested direct anti-tumour effects, and AZURE was set up to investigate.

The multicentre study, which included 3,360 women recruited from 174 centres, had a pragmatic design. Women all received standard adjuvant treatment – whether hormonal, radio- or chemotherapy – and were then randomized to receive either 5 years' zoledronic acid, or no additional treatment.
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In the group as a whole, there was no difference in disease-free survival (EJC 2011. 47: Suppl 1 #5019 and NEJM 2011 doi:10.1056/nejmoa1105195). "It looks at first sight to be a disappointing study," Robert Coleman (Weston Park Hospital, Sheffield, UK) told delegates.

However, a preplanned subgroup analysis found a clear benefit to the treatment among postmenopausal women. A 25% reduction in recurrence has already translated into a 25% reduction in the risk of dying.

"This is a strange result. Zoledronic acid is meant to affect bone," Coleman said. "It does reduce bone recurrence a little bit but not significantly, and that is unaffected by age. The most remarkable result of the study is what happens outside bone. In older women there is a marked reduction in spread to other organs or back to the breast, whereas in younger patients there appears to be an adverse effect of this treatment approach."

The mechanism of action isn't known, but Coleman said that breast cancer can lie dormant in the body for years, with cells surviving in the bone marrow, supported by normal nutrients and the stem cells there. "By disrupting the bone turnover and the molecules that come from bone with an agent like zoledronic acid, you're changing the fuel supply to these cancer cells and they are presumably less able to survive and go off to other parts of the body."

The results should not be seen in isolation; an Austrian study also found a survival advantage among women pushed into the menopause, and other data due to be presented at San Antonio later in 2011 "will give essentially the same answer. Like most developments in adjuvant therapy for breast cancer, we don't change practice on the basis of one study, but I think the amalgamation of evidence will in time help us understand these data," Coleman said.

Finally, a Swedish study underlined the importance of taking repeated biopsies through the course of breast cancer. Researchers found that one in three patients have altered oestrogen (ER) or progesterone receptor (PR) status, and 15% altered human epidermal growth factor receptor2 or HER2 status, as the disease progresses.

Presenting the data, Linda Lindström (Karolinska Institute, Stockholm) said: "Until now, we thought that these predictive markers remained stable during the course of the cancer. But it is now apparent that these breast tumour markers, which are used to decide the best treatment for the patient, change as the tumour progresses and this significantly affects the way patients respond to particular therapies."

The study included patients in the Stockholm healthcare region who had who had a recurrence of breast cancer between 1997 and 2007. Among 119 patients, 36.1% were stable ER positive, 30.3% were stable ER negative, but the rest had changes in status according to the site of relapse (local, loco-regional and metastases). 16% changed from ER positive to negative, 12.6% changed from negative to positive, and 5% altered back and forth throughout tumour progression. In the PR group, most changes were from positive to negative.
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The researchers now intend to carry out a prospective study in which they will examine clinical markers in breast cancer patients throughout tumour progression. “We believe that tumour instability may be due to many different factors, for instance the choice of therapy and other host characteristics, and that some inherent tumour behaviour may well be shared by different tumour types,” Lindström said.

Fabrice André (Institut Gustave Roussy, Villejuif, France) said the study “further underlines the importance of taking regular biopsies in patients who relapse so that they can be sure of getting the most appropriate treatment, and of running trials looking at the relationship between the profiles of metastatic lesions and new agents specifically targeted at them.”

Helen Saul

EUROFILE

Negotiations begin on new European research programme

The EU's next multi-billion research programme, starting in 2014, is expected to allocate in excess of 370 million Euros to cancer activities. With political negotiations over the content and funding due to start in December 2011, Europe's cancer organisations have put forward essential areas for funding as well as the reform of current EU funding practices.

The European Commission’s consultation on the next EU research programme received 775 position papers before its deadline of 20 May 2011. A month later, the Commission changed the name of the programme from Framework 8 to Horizon 2020. In December 2011, it will be asking member state governments for more than 80 million Euros to fund it for a seven year period from 2014 to 2020. This represents an increase of 57 percent from the 50.6 billion Euros allocated to the current Framework 7 programme which started in 2007, and in which cancer activities will account for approximately 370 million Euros by the end of the programme in 2013.

Health research related to Europe's ageing population is one key area Horizon 2020 will aim to address. There is a growing consensus among cancer organisations that funding should be directed to fields where there is sparse research activity, with prevention topping the list for many of Europe's cancer centres, such as the Karolinska in Sweden.

"No one is currently engaged in this research although we know that with prevention strategies we can reduce the incidence of cancer. The size of cancer prevention studies makes them expensive to conduct for any one institution or country. They need to be conducted at EU level precisely because they tend to involve large cohorts followed over a number of decades," says Håkan Mellstedt, professor of oncologic biotherapy at the Karolinska Institute, and director of the Karolinska cancer centre, Stockholm.

Breast and prostate cancers should be first in line for prevention research funding, according to Jaak Janssens, president of the European Cancer Prevention Organisation and Interventional
Oncology Society. "We need to establish the molecular biology for both breast and prostate cancers then further delineate which cancers are going to proceed as real killer cancers. It is urgent work. A lot of conditions lay idle for a number of years not causing harm. At the moment, we can't say which."

However, Janssens is sceptical that prevention studies will make it onto the next European research agenda. "You need a lot of lobbying to get prevention research on the agenda and this lobbying needs a lot of money to be put forward. Only industry is able to do that. However, industry thinks there is no commercial gain in doing prevention studies, and the consequence is low interest."

Transferring any EU funding earmarked for cardiovascular disease research would be a viable way of funding it at a European level says Janssens. "Cancer prevention needs at least the same budget as cardiovascular disease research. Addressing prevention issues is more important than work on cardiovascular diseases and the added value at European level could be much higher than for cardiovascular diseases. The work on cardiovascular diseases could be supported by the industry because they are commercial beneficiaries," he says.

The Academy of Cancer Sciences tells the European Commission the public funding of cancer prevention research is a "major problem" in its response to the consultation on EU research. "The EU must adopt an infrastructure that leverages all available other sources of funding," it writes. Cancer organisations also want to see the development of enabling technologies at the forefront of an EU research agenda. "The development of enabling technologies in the medical research sector also plays a critical role in the preparation of new therapeutics. Information communication technology, together with biomarkers and other technologies which allow therapeutics to be appropriately targeted for patient benefit, should be a key focus," writes Cancer UK in its position paper.

Cancer UK also flags up research infrastructure funding issues. "We are concerned that projects involving the creation and development of databases are in danger of falling down the gaps of research grants," it writes.

The European Society of Radiology and the European Institute for Biomedical Imaging Radiologists go further by proposing new co-ordinated EU funding structures to support the development of pan-European research infrastructures, and sustain their operation over the long term.
These funding structures are supported by Pancare, the pan-European network of care for sufferers and survivors of childhood and adolescent cancer. A common European platform or infrastructure to support small and large-scale transnational collaborations is needed because of the rarity of childhood cancers explains Pancare chair, Lars Hjorth, in his position paper. “The knowledge for how to make this work over time exists within the community of paediatric oncology in Europe; what is needed is the necessary funds and means for it to happen,” he writes.

Cancer organisations are unanimous in asking the Commission to streamline time-consuming research funding application procedures and remove the legislative hurdles in conducting academic clinical trials in Europe, before the start of Horizon 2020. The European Cancer Organisation, ECCO believes the development of research infrastructures would entice industry to conduct more clinical trials in Europe. ECCO advocates the use of EU structural funds for regional infrastructures, EU participation in member-state run infrastructure initiatives, and public-private partnerships with industry, as possible sources of financing in its recommendations to the Commission. "In the cancer area it will be important to fund infrastructures for independent clinical research that will enhance academic independence while, at the same time, attract the pharmaceutical industry, since an interesting partnership would be promoted and would presumably prevent the industry from the temptation of seeking opportunities in Asia as a preferred clinical trial arena," it writes.

ECCO also proposes a new mechanism to support top researchers through "dream teams" which would allow industry to contribute cash and provide new drugs for study.

The negotiation process with national governments will kick off when the Commission submits its draft of Horizon 2020 to the EU Council of Ministers on 6 Dec 2011.

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