

A good prognosis for progress in breast cancer

→ Mary Rice

Developments in adjuvant therapies, surgical techniques or genetic profiling are discussed in scores of forums throughout the year. But multidisciplinary requires a broader view of progress in the field – and that was the aim of the Milan Breast Cancer Observatory, held for the first time this summer.

At the 6th Milan Breast Cancer Conference held this June, distinguished specialists were asked to read the stars to divine what the coming year would hold in store for the world of breast cancer. In a session entitled the Milan Breast Cancer Observatory, scientists, clinicians, a representative from the advocacy group Europa Donna and a health reporter from the national press presented their predictions for their own fields of work over the 12 months ahead.

The Conference is an annual affair, organised by the European Institute of Oncology, and attended by leaders in surgery, radiotherapy, medical oncology, basic science, pathology, biostatistics and clinical trials, from all over the world.

This was the first year to feature an Observatory session on the agenda,

but it is intended to become an annual event.

The star-gazing exercise is designed to help conference participants to place their own work within the context of trends and developments in the wider field of breast cancer. This is becoming increasingly important as scientific progress is rapidly increasing our knowledge of the disease, particularly in the area of genetic profiling, with implications for pathology, diagnostics, therapeutic procedures and tailoring treatments. This rapid pace of progress, advised the Observatory's panel of experts, looks set to continue.

TARGETED TREATMENT

Gene expression profiles and proteomics were flagged up as the great white hope for the coming year. The expectation was that these would be

able to lead to tailored treatment based not just on genetic signatures but also on such factors as types of cancer and age. Early efforts will be made to bring microarrays and proteomic signatures into clinical practice in order to create appropriate treatments for individuals.

Tumour markers and genetic profiles have a number of other uses: they can help improve treatment selection for pre-operative chemotherapy, which will allow more women to preserve their breasts. They can also be used to identify sub-groups of patients at high risk of recurrence in order to modify treatment. This may help select patients with ductal carcinoma in situ (DCIS) for treatment by excision alone, thereby avoiding radiation.

The distinction between endocrine responsive and non-endocrine responsive disease is set to gain wider



recognition as a major tool for planning systemic therapies for breast cancer. Sequential endocrine adjuvant therapies are likely to be confirmed as a valuable therapeutic approach in women with endocrine responsive disease, though further studies to overcome resistance to endocrine therapies by sequential treatments are needed.

There will also be new opportunities for improving the use of therapies for patients with advanced breast cancer by using the new targeted treatments together with cytotoxic agents. These compounds will reach the stage of testing in the adjuvant setting very shortly.

Progress is also expected in the development of novel agents with one or a few biological targets, using advanced molecular and immunological technology to overcome mechanisms of malignant transformation, infiltration and metastasis which are still unclear.

HORMONE-SENSITIVE CANCERS

Aromatase inhibitors are set to become the standard adjuvant treat-

ment for women who have steroid-receptor-positive breast cancer, although warnings were raised of the need for special care in monitoring bone loss. Continuing refinements of adjuvant chemotherapy regimens are expected, paying particular attention to the selection of drugs and dosage, and to the treatment schedule.

In both developed and developing countries, clinical prediction for the appropriate use of tamoxifen in selected patients should become standard.

This strategy will be essential to offset increasing healthcare costs.

SENTINEL NODE BIOPSY

Sentinel node biopsy is set to become the universal standard of care for node-negative stage 1 and 2 breast cancer. The procedure will also be used more frequently after neoadjuvant therapy when the axilla is downstaged to node-negative after treatment.

OVERDIAGNOSIS

Diagnostic histopathologists will apply criteria to avoid overdiagnosis of DCIS and other conditions with

increased incidence rates. These increases have frequently been the result of including more minor changes, which, though similar, lack the intrinsic risk of local recurrence and evolution to the invasion of lesions that define the importance of DCIS. The level of threat to survival represented by different local and distant recurrences, including the time dependency of survival in high-grade, rapidly proliferating cancers, will be more precisely defined.

The increasing incidence of 'inflammatory carcinoma' will be significantly reduced by careful application of diagnostic criteria – an effort already begun by quantifying the degree of breast involvement by inflammatory changes. The importance of clustering in analysing standard data will become more widely recognised.

BIostatisticians

How will all this be held together? Strengthening the collaborations between biostatistical scientists and clinical and laboratory scientists will be a critical part of achieving progress. Computation biology plays an increasingly important role in defining the molecular basis of disease and identifying targets for therapeutic intervention. Equally important for patient care will be the thoughtful application of current clinical trial methodologies to tailor trial design and analyse results separately for subpopulations of patients according to the steroid hormone receptor status of the primary tumour.

PATIENT PARTICIPATION

There will be a growing recognition of the contribution that patient advocates can make, particularly in the area of clinical trials. Patient groups will play a bigger role in

Aromatase inhibitors will become the standard adjuvant treatment for steroid-receptor-positive breast cancer

spreading information about ongoing trials, and we can also expect to see more patient advocates included in clinical trial committees, contributing their views and experiences to discussions and decisions about their design.

THE POLITICAL AGENDA

As of June 2003, Europe has been committed to a set of policies laid out in the Breast Cancer Resolution, which includes moving towards services provided through multidisciplinary teams in networks of specialist centres in line with the EUSOMA guidelines. Some progress can be expected on this front – faster in some countries than others. We can also hope to see progress in reaching the target set by the resolution of reducing breast cancer mortality by

25% and reducing disparities in five-year-survival across Europe from 16% to 5%.

THE MESSAGE

The health media will start to move away from the traditional emphasis on promoting breast awareness and breast checking – felt by most health commentators to be a ‘completed job’ – to translating and communicating to the public the ever-greater progress in breast cancer therapies. The partnership between health professionals and health media can be extremely productive for all concerned – not least the patient. In the long run, the informed patient will raise standards of care. Traditional barriers between the medical profession and the media are breaking down and specialists are increasingly

recognising the value of sharing their knowledge with the general public via the media.

GOOD FORTUNE AHEAD

Some bad omens were detected in some panelists’ planetary divinations. There were warnings that bureaucracy will continue to impose an unnecessary impediment and complication on academic clinical trials, and that industry was generally unsupportive of academic clinical research. Bureaucracy on the part of funding agencies was also seen as a threat, as was the level of public funding for research, which was seen to be decreasing.

But looked at overall, the constellations concerning breast cancer seem to augur well for the coming year, predicting continuing progress on multiple fronts, improved working together, learning from each other, and ensuring that more patients than ever have access to top-quality services.

The main points made by the panelists will be distributed widely in the breast cancer community to help both inform their work and give an overview of where research, treatment, and care is headed in the coming months. “Some of these developments may seem like small steps, but they combine to produce improvements in care for patients and hope for those who treat them,” said Alberto Costa, organiser of the Observatory. “It will be interesting to look back in five years time and see how things have changed.”

THE PANEL

- Monica Castiglione-Gertsch – SAKK/IBCSG (Swiss Group Clinical Cancer Research/International Breast Cancer Study Group), Bern
- Alberto Costa – The European School of Oncology, Milan
- Nancy Davidson – Sidney Kimmel Comprehensive Cancer Centre, The Johns Hopkins University, Baltimore
- Richard Gelber – Dana Farber Cancer Institute, Boston
- Aron Goldhirsch – European Institute of Oncology, Milan
- Stella Kyriakides – Europa Donna/The European Breast Cancer Coalition
- Virgil Craig Jordan – Robert H Lurie Cancer Center, Northwestern University Medical School, Chicago
- Monica Morrow – Northwestern Memorial Hospital, Chicago
- David L Page – The Vanderbilt-Ingram Cancer Center, Nashville
- Gordon F Schwartz – The Breast Health Institute (founder), and Jefferson Medical College, Philadelphia
- Isla Whitcroft – Health Journalist, London

Locoregional techniques: under-rated and under-researched

→ Rob Stepney

Attempts to control or cure cancers using localised therapies are still in their infancy. Studies have been patchy and sporadic, with little attempt to collaborate across centres or across specialties. So a number of pioneers in the field got together to try to map out the next steps.

Where the problem caused by a tumour is primarily local, it would be logical to consider a local approach to treatment. Yet typically, locoregional approaches have been considered only as palliative treatments of last resort. When their use earlier in the course of disease has been advocated, there has often been more enthusiasm than effective evaluation. The numbers of patients studied has generally been small, collaboration limited, and results highly dependent on the expertise of the individual operator.

Nonetheless, there is a growing body of evidence regarding a variety of techniques used in different settings to show that, when used appropriately, locoregional techniques can have a significant impact not only on quality of life, but also survival. Experiences

in advanced breast cancer, melanoma confined to a limb, soft tissue sarcoma, and isolated liver metastases from colorectal cancer have all shown that local tumour responses can be obtained with relatively low toxicity. The use of intra-arterial administration of chemotherapy may even open up treatment possibilities to patients who are too frail to tolerate systemic therapy. And this route could prove a highly cost-effective approach. Another big advantage is the possibility that patients with regionally advanced tumours of the limbs may be able to avoid amputation.

Despite this body of evidence, many of today's cancer patients are missing out because too many treatment centres remain unaware of the possibilities offered by current techniques, and too few studies are being done to improve locoregional treatments. So

earlier this year, the European School of Oncology (ESO) brought together experts who have pioneered locoregional techniques in various cancers. They were asked to piece together an overview of the current state of knowledge and experience in this field, for dissemination among cancer clinicians, and with the aim of stimulating interest in carrying out trials.

A notable feature of the group was that both medical and surgical oncologists were well represented (see box overleaf for participants). This is important because the key to the successful use of locoregional techniques often lies with the way they are integrated within the wider therapeutic approach – with each other, with the best of systemic treatments, and with surgery – which requires collaboration between a variety of specialisms.

OPTIONS AND EVIDENCE

The range of locoregional approaches (chemotherapeutic, biological and physical) is constantly expanding. The main ones can be listed as:

- Chemotherapy infused through the hepatic or internal mammary arteries
- Isolated limb perfusion with combinations of conventional cytotoxic agents and cytokines
- Chemoembolisation
- Embolisation utilising yttrium-labelled microspheres, which both mechanically obstruct the tumour vasculature and irradiate local malignant tissue
- Radiofrequency, laser and cryoablation
- Photodynamic therapy
- Hyperthermia

Though all of these have been used in various settings, only a few have so far been studied in randomised controlled trials. Maurizio Cantore reported a recent randomised, multi-centre study into the effectiveness of intra-arterial administration of FLEC (5-FU, leucovorin, epirubicin and carboplatin) in patients with unresectable pancreatic cancer. The results showed that this locoregional therapy improved survival by an average of two months compared with patients treated with systemic gemcitabine.

Similarly encouraging results have come out of a randomised trial in colon cancer metastatic to the liver, which showed better survival when systemic chemotherapy was preceded by hepatic artery infusion than when systemic treatment was given alone. And, following promising phase II results, including a median 15 month survival, the European Organisation for Research and Treatment of Cancer (EORTC) has just accepted the protocol for a study of intra-arterial versus systemic fote-mustine in ocular melanoma.

PRIMARY AND SECONDARIES

Both locally advanced disease and metastases can be amenable to local therapy.

When surgery is not an option for hepatic metastases from colorectal cancer (CRC), lesions can still be treated – by cryosurgery, radiofrequency or laser ablation, or hepatic arterial infusion of chemotherapy. Phase I/II studies of intra-arterial irinotecan and oxaliplatin have achieved partial response rates of up to 40%. So it seems that newer drugs with good systemic efficacy are also active when locally administered, and their controlled evaluation is a clear priority.

Giammaria Fiorentini described how patients with unresectable chemotherapy-resistant CRC metastases can also be treated by hepatic artery administration of yttrium-90 labelled microspheres. This treatment has the potential to downstage disease to the point of resectability, as has been demonstrated by Andrew Kennedy and colleagues in the US. The beta-emitting isotope, carried by either resin or glass beads, irradiates malignant cells within a few millimetres of the site of embolisation, while delivering little radiation to normal liver.

A series of 243 patients treated this way have shown a median survival of 12.8 months. There were no deaths or cases of radiation hepatitis resulting from the treatment, and levels of pain, fever and gastrointestinal toxicity were considered 'reasonable'. Trials involving delivery of radioactive microspheres in combination with current chemotherapy are underway. In locally advanced or recurrent breast cancer, good long-term local control is essential for quality of life, and taking a locoregional approach makes sense because of the strong correlation between dose and response seen with most cytotoxics. In Cantore's experience, the internal mammary artery is simple to cannulate. In locally advanced disease, infusion of FEM (5-FU, epirubicin and mitomycin) chemotherapy has achieved good rates of partial response, with the majority of tumours becoming operable, at the cost of mild systemic toxicity. But the intra-arterial approach is less effective with recurrent tumours.

Haematological toxicity was mild – with only one case of a grade 3 anaemia among 83 patients. Local erythema and hemialopecia were relatively common side effects

TASK FORCE MEMBERS

The Task Force on Locoregional Techniques met in Bentivoglio, Italy, and was hosted by the Ramazzini Foundation. The participating experts were, pictured from left to right (*opposite*):

- Maurizio Cantore, Carrara, Italy – medical oncologist
- Martin Highley, Dundee, Scotland – medical oncologist
- Beniamino Palmieri, Scientific Co-ordinator of the Task Force, University of Modena and Reggio Emilia, Italy – surgeon
- Ferdy Lejeune, Lausanne, Switzerland – surgeon
- Giammaria Fiorentini, Empoli, Italy – medical oncologist
- Cornelis van de Velde, Leiden, the Netherlands – surgeon (*not shown*)
- Hans-Joachim Schmoll, Halle, Germany – medical oncologist (*not shown*)
- Morando Soffriti, Ramazzini Foundation – experimental oncologist (*not shown*)



The Task Force

and there were two cases of carotid spasm.

Whether used in locally advanced breast cancer or recurrent tumours, this locoregional technique, advises Cantore, should be undertaken only as part of an integrated strategy including systemic and surgical approaches.

SYNERGIES

Martin Highley described how a temporary alteration in cell physiology caused by one drug may facilitate the uptake and cytotoxicity of another. For example, in isolated limb perfusion, combining tumour necrosis factor (TNF) with melphalan potentiates vascular changes, increases leakage of melphalan and leads to a six-fold higher concentration of the cytotoxic in tumour tissue. Combining agents that target the endothelial cell with agents that target the tumour cell may enhance the efficacy of treatment.

Combretastatin inhibits tubulin polymerisation in the endothelial cell, leading to destruction of neovascula-

ture and necrosis in the tumour core. But combretastatin given alone leaves a viable rim, suggesting a role for chemotherapy. The optimal sequencing of vascular targeting agents and chemotherapy is not clear, but there is at least the potential for using the former to trap cytotoxic agents in the tumour.

Ferdy Lejeune and his Lausanne group have striking experience of how biological and cytotoxic agents can be combined within a locoregional approach. In patients with locally advanced melanoma of the limbs, isolated limb perfusion with melphalan achieves a 50–60% rate of complete response. Adding TNF and interferon gamma to the perfusion (accompanied by hyperthermia) raises the complete response rate to 80–90%, and disease can be confined to the limb for long periods. The superiority of intensive biochemotherapy over melphalan alone is supported by interim analysis of a phase III trial in the US.

The European TNF Core Group investigating this approach also has

evidence of efficacy in 250 patients with inoperable soft tissue sarcomas. Isolated limb perfusion combining the three agents enabled amputation to be avoided in 80% of cases. Such perfusion exposes tumour to drug concentrations ten times greater than can be achieved with systemic administration. A corollary is that leakage into the systemic circulation must be kept below 10%, and continuously monitored.

One of the most intriguing examples of integrating locoregional approaches is hepatic arterial chemo-occlusion combining mitomycin and interferon alpha with microspheres. Both the microspheres and interferon are anti-angiogenic. This is an approach suited to the 30% of patients with metastatic CRC whose disease is confined to the liver for relatively long periods.

Hans-Joachim Schmoll and colleagues from Halle, Germany, have been treating patients with highly refractory disease with a three-weekly schedule. This is associated with low toxicity, requires a hospital stay of 2–3 days, and has induced disease stabilisation or better in 90% of cases.

On the basis of these promising results, there is a need for studies into the possible benefits of chemo-occlusion therapy in other cancers such as breast cancer, melanoma, leiomyosarcoma and neuroendocrine tumours, where the high vessel density in tumours such as carcinoid may justify intra-arterial treatment with anti-angiogenic agents like bevacizumab.

Other combinations of techniques discussed by the Task Force include the use of regional hyperthermia with neoadjuvant chemotherapy in the treatment of soft tissue sarcoma, for which promising results (49% five-

year survival) have been reported by Rolf Issels and colleagues. One possibility is that higher temperatures increase influx of cytotoxics into tumour cells.

Also mentioned were investigations being carried out in Slovenia, France and Sweden into the combination of chemotherapy (iv bleomycin and platinum) with the administration of electric shock to damage the tumour cell membrane – the technique of electrochemoporation.

AND NOT FORGETTING SURGERY

Recognising the potential of the technologies considered above does not diminish the central role of surgery in locoregional disease control, and the importance of debate about how radical this should be. This is a particularly live issue in gastric cancer, where some practitioners favour extended lymph node dissection, while others argue for a more limited procedure.

Cornelis van de Velde presented the data of the Dutch Gastric Cancer Group, which had looked at comparative survival rates between patients treated using the conservative approach (D1) and those treated with the more radical approach (D2). At twelve years' follow-up there is still no survival advantage for patients randomised to the more extensive 'Japanese style' surgery. One reason is the greater mortality associated with radical surgery, arising mainly from postoperative complications following splenectomy and pancreatectomy. However, advances in surgical techniques mean that today this can largely be avoided. The outcome of any comparison between D1 and D2 procedures using current techniques might, therefore, be somewhat different.

Indeed, if mortality from postopera-

tive complications is excluded from consideration, patients with more than three positive nodes appear to have experienced better survival when treated more radically. At ten years, the survival rate in the D2 group was 26%, while it was 0% among D1 patients. Among gastric cancer patients with only one positive node, there was no significant survival difference. A study comparing good, extensive surgery with locoregional control versus US-style postoperative chemoradiotherapy is now planned.

THE NEXT STEPS

The meeting of the Task Force revealed that a wide range of techniques are being tried out in many settings either to avoid the toxicity of systemic therapies or to add to their impact. Side-effects generally appear to be less unpleasant and dangerous than with many systemic treatments, though care is needed to ensure that where high concentrations of toxic drugs are used, they do not leak out into the general circulation.

The problem remains a shortage of randomised controlled trials that can provide the level of evidence needed to demonstrate which techniques or combinations of techniques give the best results in which settings. Currently, there are not even any

agreed criteria for evaluating the effects of such treatments.

The Task Force agreed a number of priorities to speed up progress in this area:

- Establish evaluation criteria for trials of locoregional therapy
- Encourage collaboration within and across disciplines. The Italian co-operative group SITILO (Societa Italiana di Terapie Integrate Locoregionali in Oncologia) may serve as a model
- Examine whether cytotoxics such as irinotecan and oxaliplatin show efficacy when given intra-arterially
- Explore multimodality approaches.

In several tumours, chemoradiotherapy has become the norm. Techniques should be tried in combination – optimal systemic chemotherapy with optimal local chemotherapy, or systemic chemotherapy with radiofrequency approaches or hyperthermia, for example

- Evaluate new ways of quickly establishing whether treatment is having an effect. Functional Positron Emission Tomography (PET), nuclear magnetic resonance (NMR), ultrasound and tumour markers may all usefully complement conventional evaluation of effect.

An ESO course on Locoregional Control of Advanced Cancer is scheduled for 12-13 September 2005, in Orta, Italy.

ESO TASK FORCES

Since 1993 ESO has been bringing together small groups of experts to address important issues in oncology. These Task Forces have covered topics ranging from gene therapy to nutrition in the cancer patient. The meetings' conclusions are generally published in the ESO series of *Task Force Reviews* and may appear as position papers, usually in the *European Journal of Cancer*. Where appropriate, Task Forces lay the groundwork for ESO's educational activities.