

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.