Neoadjuvant studies offer mixed messages

Emma Mason

Three recent papers have failed to confirm any clear benefit of neoadjuvant treatment on overall survival. But its value in minimising the extent of surgery and its potential for greater survival effect using newer drugs may yet repay the faith many oncologists have in this approach to treatment.

Neoadjuvant therapy – the administering of any treatment such as chemo-, radio- or hormone therapy before the main local or locoregional treatment for a cancer – has an enthusiastic following amongst oncologists for several types of cancer. A growing body of literature points towards benefits in treatment, organ preservation and survival, but the benefits are not always clear-cut.

Survival

In a brief communication published last November (*JNCI* 2004; vol. 96, no. 22) Pier Luigi Zorat and his colleagues from the radiotherapy department, Ospedale Ca' Foncello, Treviso, Italy, reported results from a 10-year follow-up of a randomised phase III trial of neoadjuvant chemotherapy in head and neck cancer.

Their multicentre trial, started in 1986, enrolled 237 patients with non-metastatic stage III or IV head and neck squamous cell carcinoma (HNSCC). The patients were randomly assigned to receive either four cycles of neoadjuvant chemotherapy (cisplatin and 5-fluorouracil) followed by locoregional treatment (surgery and radiotherapy, or radiotherapy alone), or to receive locoregional treatment alone.

However, after 10 years it became clear that for patients with operable cancer, there was no statistically significant difference in overall survival between the two groups (22.7% for neoadjuvant treatment versus 14.2% for locoregional treatment alone). In contrast, there was a statistically significant survival difference for patients with inoperable cancer (16% versus 6%).

The authors conclude that: "Four cycles of neoadjuvant chemotherapy is a promising approach for treating patients with inoperable advanced head and neck cancer, but not for treating patients with operable disease."

Zorat and his co-authors say that neoadjuvant chemotherapy continues to be a common clinical practice for HNSCC in many centres, even though there is no evidence it does any good: "Current data do not support the use of neoadjuvant chemotherapy in HNSCC." They agree with the authors of previous studies, however, that it can play a positive role in minimising surgery to allow preservation of organs such as the voice box.

The authors accept that their study could be limited by the fact that, as it was started in 1986, there were older drugs in use and radiotherapy alone was the standard treatment for inoperable HNSCC. "Trials initiated after this study have demonstrated the superiority of concomitant chemotherapy and radiotherapy in locally advanced disease over radiotherapy alone."

They point out that research has yet to be done to establish the value of adding neoadjuvant chemotherapy before concomitant chemotherapy and radiotherapy for patients with inoperable HNSCC. "Our results provide a strong rationale for studies investigating this issue. The advent of new active drugs, such as taxanes, makes questions about the utility of neoadju-

Pier Luigi Zorat: Neoadjuvant chemotherapy is promising in treating inoperable advanced head and neck cancer, but not for patients with operable disease

Jacques Bernier: Neoadjuvant therapy may be more effective in head and neck cancers using some of the newer and more active drugs, including non-cytotoxics

vant chemotherapy more interesting."
Zorat adds that it would be worthwhile limiting such studies with new drugs and new schedules to patients with inoperable HNSCC only.
"The benefits might be an increase in disease-free survival, while the disadvantages might be an increase in toxicity."
Jacques Bernier, director of the department of radio-oncology at the Oncology Institute of Southern Switzerland, Bellinzona, agrees. "The advent of 'new' drugs like taxanes – more recent, at least, than cisplatin and 5-fluorouracil – enables us to revisit the role of NACT [neoadjuvant cancer therapy] in head and neck oncology, both for unresectable disease and in patients to whom an organ preservation programme is applied. It is clear that we have now got more active drugs and that this observation paves the way for more investigation in the framework of NACT, and also with non-cytotoxic compounds such as anti-EGFR [epidermal growth factor receptor] and anti-VEGF [vascular endothelial growth factor]."
Bernier, who was the principal investigator of the European Organisation for Research and Treatment of Cancer (EORTC) study on the administration of concurrent cisplatin and radiotherapy in people with advanced head and neck cancer after surgery, believes that it is too early to be certain of the benefits of neoadjuvant therapy in head and neck cancers, even though it is being used more often now.
"It should not be considered a standard approach yet. For the time being, we have to test if NACT can be considered a safe approach in the framework of organ preservation programmes and can increase the disease-free survival and local control rates in unresectable disease. This needs confirmation."

Better local control

The results of a study of neoadjuvant treatment for rectal cancer, published last October, also failed to show any difference in overall survival. Rolf Sauer, from the department of radiation therapy, University of Erlangen, Germany, and colleagues compared preoperative versus postoperative chemoradiotherapy for patients with locally advanced rectal cancer (*NEJM* 2004; 351:1731-40).
Patients with clinical stage T3 or T4 or node-positive disease were enrolled in the trial between February 1995 and September 2002; 421 were randomly assigned to receive neoadjuvant chemoradiotherapy (radiotherapy and fluorouracil) and 402 to receive postoperative chemoradiotherapy (using the same doses as for the preoperative chemoradiotherapy

"Current data do not support the use of adjuvant chemo in head and neck squamous cell cancer"

Rolf Sauer: Neoadjuvant chemoradiotherapy in rectal cancer gives better local control, less toxicity, and more sphincter preservation in patients with low-lying tumours

Lars Påhlman: The local recurrence problem has been solved with good surgery after neoadjuvant radiotherapy. Up-front chemo may help reduce distant metastases

with an additional boost of 540 cGy). The five-year survival rates were almost identical between the two groups – 76% and 74% respectively. However, there were other significant differences. The local recurrence rate in the neoadjuvant therapy group was just 6% – less than half that in the postoperative chemoradiotherapy group (13%). Grade 3 and 4 acute toxic effects occurred in 27% of the first group, compared with 40% of the second group, and rates of long-term toxic effects were 14% and 24% respectively. A statistically significant increase in sphincter preservation was achieved in patients from the neoadjuvant group whose tumours required abdominoperineal excision.

Neoadjuvant therapy also had an important effect on tumour stage. The authors report that "After preoperative chemoradiotherapy, there was a significant shift toward earlier TNM stages: 8% of the patients in this group had a complete response, according to histopathological examination of the tumour specimen, and only 25% (as compared with 40% in the postoperative treatment group) had positive lymph nodes (TNM stage III)."

But they also highlight the fallibility of tumour staging. "Eighteen percent of the patients in the postoperative treatment group had TNM stage I disease on histopathological examination of their resected specimen; all 18% had previously been found to have stage T3, T4 or node-positive disease on endorectal ultrasonography."

This could lead to early-stage tumours being over-treated in patients receiving neoadjuvant therapy, but the authors believe that innovative techniques such as three-dimensional endosonography and magnetic resonance imaging could improve the accuracy of staging.

They conclude: "Although no survival benefit was achieved with preoperative as compared with postoperative chemoradiotherapy, we suggest that preoperative chemoradiotherapy is the preferred treatment for patients with locally advanced rectal cancer, given that it is associated with a superior overall compliance rate, and improved rate of local control, reduced toxicity, and an increased rate of sphincter preservation in patients with low-lying tumours."

Commenting on the study, Lars Påhlman, of the department of surgery (colorectal unit) at Uppsala University Hospital, Sweden, says "The treatment of locally advanced rectal cancer has already changed to neoadjuvant chemoradiotherapy; this study makes an important contribution with regard to low local recurrence rates."

He believes that improved chemoradiotherapy has the potential to

"Up-front chemo followed by radiotherapy and then surgery may be the next step in rectal cancer"

John Ioannidis: Some sort of breast conserving surgery is warranted regardless of whether neoadjuvant or adjuvant treatment is adopted

Monica Morrow: Neoadjuvant breast cancer treatment should be reserved for women who need it in order to be able to have a lumpectomy

Nicholas Pavlidis: Further research and longer follow-up results from the ongoing studies using taxanes or trastuzumab combinations are urgently needed

improve not only rates of distant recurrences, but also survival rates. "The local recurrence problem has been solved with good surgery after neoadjuvant radiotherapy. The next step is to concentrate on distant metastases. Therefore, I do believe that up-front chemotherapy for some months, followed by radiotherapy and finally surgery will be the next step."

Surgery remains key

The importance of surgery and of not relying exclusively on neoadjuvant therapy is underlined in a third paper, 'Neoadjuvant versus adjuvant systemic treatment in breast cancer, a meta-analysis' by Davide Mauri, Nicholas Pavlidis and John Ioannidis, which was published this February (*JNCI* 2005; vol. 97, no. 3).

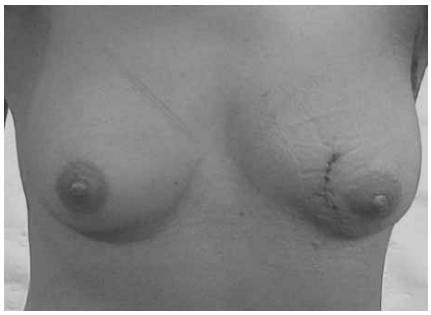
They evaluated nine randomised studies of breast cancer patients treated either with neoadjuvant therapy (chemotherapy or hormone therapy) or with adjuvant therapy, between 1983 and 1999. The meta-analysis included 3,946 women, regardless of whether they had been treated with additional surgery or radiotherapy or both.

The results showed no difference in overall survival, disease progression or distant metastases between the neoadjuvant and adjuvant treatment arms.

However, neoadjuvant therapy was associated with a statistically significant 22% increased relative risk of locoregional recurrences, especially in trials where radiotherapy without surgery was more common in the neoadjuvant arms than in the adjuvant arms.

"Consequently, we recommend avoiding the use of radiotherapy without any surgical treatment, even in the

"Neoadjuvant breast cancer treatment is no better than adjuvant in terms of hard clinical outcomes"



Neoadjuvant therapy can play a role in minimising surgery and thus preserving organs. In breast cancer, neoadjuvant chemotherapy can be used to shrink a tumour that would otherwise be too large for a lumpectomy. This will allow more women to save their breasts, though there will be a slightly increased risk for local recurrence

presence of an apparently good clinical response to neoadjuvant chemotherapy," say the authors. "Some sort of breast-conserving surgical intervention is likely to be warranted, regardless of whether neoadjuvant or adjuvant treatment is adopted and regardless of the patient's initial clinical response."

Monica Morrow, the G. Willing Pepper Professor of Cancer Research and chairperson of the department of surgical oncology at the Fox Chase Cancer Center, Philadelphia, USA, argues that the results of the meta-analysis do not mean that neoadjuvant therapy should be abandoned for breast cancer patients – just that surgery should always be included as well.

"Everyone needs surgery after neoadjuvant treatment. There is no reliable way to tell if all the cancer is dead, and in most cases it is not, so surgery facilitates local control."

The authors agree. Ioannidis, chairman of the department of hygiene and epidemiology at the University of Ioannina School of Medicine, Greece, says: "What the meta-analysis shows is that neoadjuvant treatment is not better than adjuvant treatment in terms of hard clinical outcomes; it is worse for local recurrences if surgery is not performed. This is not an issue when surgery is performed as well."

Morrow says another interesting finding from the study was that neoadjuvant therapy did not necessarily mean that more breast cancer patients were spared mastectomies and could have breast-conserving treatment (BCT) instead.

This was partly because many of them were already candidates for breast conservation. She says the increased risk of local recurrence in women receiving the neoadjuvant treatment might also be due to the fact that, although the therapy may shrink the tumour, it is still difficult for surgeons to be sure whether or not the tissue around the margins of the tumour is disease-free.

However, says Morrow: "BCT should not be avoided in women getting neoadjuvant treatment, but neoadjuvant treatment (outside of a trial) should be reserved for women who need it in order to be able to have a lumpectomy.

"Right now, some women get neoadjuvant therapy who could undergo an initial lumpectomy, because it seems like a good idea. This overview shows no hint of a survival benefit with this approach, but some downside with regard to the surgery. On the other hand, if the tumour is too big to do a lumpectomy without neoadjuvant treatment, the small increase in local recurrence is worth it because it will still result in more women saving their breasts."

Pavlidis, professor of medical oncology at the University of Ioannina School of Medicine, points out that all the studies in the meta-analysis used older, second-generation anticancer drugs, including mainly anthracycline-based chemotherapy, and that therefore it is not safe to extrapolate the results to newer drugs with different modes of action. "Further research and longer follow-up results from the ongoing studies using taxanes or trastuzumab [Herceptin] combinations are urgently needed," he says.

But would newer drugs produce any difference in survival between neoadjuvant and adjuvant therapy? Ioannidis says: "One might speculate that with more potent chemotherapeutical regimens, survival might improve, but this might be equally so either with neoadjuvant or with adjuvant chemotherapy; neoadjuvant use may not have necessarily an extra benefit."

Try it and see

As with the two previous studies mentioned here, the meta-analysis raises a number of further questions. For instance, could neoadjuvant therapy serve to identify early on how well patients respond to a particular treatment, so that if they respond well, a shorter course could be given, while a poor response could enable doctors to switch to a different therapy?

"Right now, patients are given a fixed number of cycles of neoadjuvant treatment whether or not they respond", says Morrow. "It would be interesting to do a study of switching to a different therapy after one or two cycles of treatment if there is no response, to see if that provides a better outcome. Markers that predict response are desperately needed, and will only be found from neoadjuvant trials," she said.