

What is the place of the technology in current practice?

Breast cancer is the commonest cancer in women in the UK. The majority of women present with early breast cancer and are increasingly successfully treated with a combination of local and systemic therapies. However, 10% of women presenting with breast cancer have metastatic disease at diagnosis and a further 30-40% of women with early breast cancer eventually relapse. Current therapies cannot cure metastatic breast cancer (MBC) and the aims of treatment are to palliate symptoms, improve quality of life and prolong survival by a modest amount. Many treatment strategies are used in this disease setting. This is largely due to the heterogeneity of the metastatic breast cancer which necessitate different approaches for different patients. Treatments used to treat MBC include: chemotherapy, endocrine therapies, trastuzumab, bisphosphonates and radiotherapy.

Factors leading to the heterogeneity of breast cancer include those related to the patient (age, menopausal status, comorbidity, performance status and patient choice) and those that are related to the tumour (stage, sites of metastases, hormone receptor status, HER2 status, previous response to therapy and time since initial therapy). Prognosis is different depending on the individual circumstances. Factors associated with a good outcome include older age, hormone receptor positive, bone metastases, good performance status and previous response to endocrine therapies. Such patients are often at least initially treated with endocrine manipulations including tamoxifen and aromatase inhibitors, with chemotherapy reserved for patients who have failed these therapies. A worse outcome can be expected for younger patients with visceral metastases and hormone receptor negative disease. Such patients are usually treated with chemotherapy.

Various chemotherapy schedules are used for the treatment of MBC. These include anthracyclines, taxanes, capecitabine and vinorelbine. Anthracyclines and increasingly taxanes are used in the adjuvant setting for the treatment of early breast cancer. There is currently a need for new combinations of chemotherapy agents that improve outcomes without the excess toxicity that would impair quality of life. Previously NICE has approved the use of taxanes (docetaxel and paclitaxel), capecitabine and vinorelbine (including the combination of docetaxel and capecitabine) for the treatment of MBC. Variations are to be found in the order in which these agents are used and also in whether taxanes are used. The reasons why these variations exist in practice are not well described. The current limitations of NICE guidance in MBC relate to the docetaxel/capecitabine combination which is infrequently used despite higher response rates and longer survival because of the increased toxicity of this schedule and the lack of guidance on use of chemotherapy beyond third line therapy (ie after multiple relapses). In the latter situation chemotherapy agents are used outside NICE guidance as worthwhile benefits can still be achieved for individual selected patients.

Gemcitabine is a chemotherapy agent that is widely used in oncology across different disease sites particularly non-small cell lung cancer and pancreatic cancer. It is relatively easy to administer and well tolerated. It is often used in combination with other agents. One such combination is gemcitabine and paclitaxel which is frequently used in lung cancer. In MBC the combination of gemcitabine and paclitaxel has been shown to be superior to paclitaxel alone in a well-conducted randomised trial (Albain KS et al 2004). The combination of gemcitabine and docetaxel has been shown to have similar efficacy but with improved toxicity profile compared to docetaxel and capecitabine (Chan S et al 2005).

Currently the paclitaxel/gemcitabine combination is not widely used despite its proven efficacy because of the lack of funding in the absence of NICE guidance. I believe that the Albain trial demonstrated clear superiority of the combination over paclitaxel alone (which is NICE approved) with acceptable toxicity. However, in the UK docetaxel rather than paclitaxel is more widely used because of the shorter duration and the higher response rates. In my view the combination of gemcitabine/paclitaxel would be used for patients in whom a high response is required such as patients with visceral metastases where in the absence of response disease progression may preclude any other chemotherapy to be used. These are patients for whom the combination of docetaxel/capecitabine (which is NICE approved) is considered but maybe rejected due to the toxicity of this schedule. The gemcitabine/paclitaxel combination has a better toxicity profile. This is based on cross-trial comparisons and extrapolations from the Chan trial of docetaxel/capecitabine vs paclitaxel/gemcitabine.

I strongly believe that NICE approval for the gemcitabine/paclitaxel combination as first-line therapy for women with MBC (who have previously received anthracyclines) will increase the options of chemotherapy for them.

References

Albain KS et al. Global phase III study of gemcitabine plus paclitaxel (GT) vs paclitaxel (T) as frontline therapy for metastatic breast cancer (MBC): First report of overall survival. *Journal of Clinical Oncology*, 2004 ASCO Annual Meeting Proceedings (Post-Meeting Edition), vol 22, no 14S (July 15 supplement): 510.

Chan S et al. Gemcitabine plus docetaxel (GD) versus capecitabine plus docetaxel (CD) for anthracycline-pretreated metastatic breast cancer (MBC) patients (pts): Results of a European Phase III study.

The advantages and disadvantages of the technology

Advantages

Improved outcomes over existing therapy

Good toxicity profile

Considerable experience in NHS chemotherapy units because of its use in other cancer sites

Disadvantages

Extra chemotherapy visits (for each 3-week cycle there is an additional day 8 injection)

Increased cost compared to paclitaxel alone but similar cost to docetaxel/capecitabine combination

Any additional sources of evidence?

Phase II evidence for activity of gemcitabine alone or in combination with other agents, for example carboplatin for the treatment of MBC. No large randomised trials.

Implementation issues

There is already considerable experience within the NHS in the use of gemcitabine, including the combination with paclitaxel, as it is used in non-small cell lung cancer. No extra training is required. No additional facilities or equipment would be required. It would be possible to implement this technology across the NHS in a timely manner.