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GEMCITABINE IN THE MANAGEMENT OF LOCALLY ADVANCED BREAST CANCER

How is the condition currently treated in the NHS?

Approximately 15% of patients still currently present with a large or locally advanced breast cancer. There are different opinions among clinicians as to the way in which locally advanced breast cancer should be treated. The following have been, and are currently, in practice:

1. Primary surgical treatment to the breast and axilla,

2. Primary hormonal therapy for patients with hormone receptor positive tumours, usually followed by surgery if the disease is rendered operable,

3. Primary (neoadjuvant) chemotherapy also followed by surgery if there is a reduction in the extent of disease loco-regionally,

4. Primary radiotherapy (less commonly).

Is there significant variation in clinical practice?

There is still a wide variation in the treatment that is given to patients with locally advanced breast cancer. This variation in treatment is not only present between clinicians within the NHS in the United Kingdom but also on an international basis.

There is, however, an increasing trend in the use of the primary or neoadjuvant chemotherapy and this does seem to be gaining a more widespread acceptance as the primary modality of treatment. The rationale for the use of the primary chemotherapy is two fold: firstly, to downstage the primary tumour and therefore facilitate breast conservation surgery to be carried out rather than mastectomy, and secondly, to eliminate or reduce micrometastatic disease with the intention of prolonging overall survival.

However, there are still substantial numbers of patients who proceed to primary surgery for this condition. The reason for this variation in treatment is the lack of evidence from good-quality randomised controlled trials as to what would be the most appropriate treatment. There are at least six trials where patients have been randomised to comparing adjuvant versus primary (neoadjuvant) chemotherapy in the management of patients with operable breast cancer. However, the trial designs, the types of patients included, the therapeutic regimens, and the endpoints of the studies have frequently been different. This has made interpretation of the results of these studies with respect to modifying clinical practice extremely difficult.

Are there differences in opinion between professionals as to what current practice should be?

As I've explained above there are currently differences in opinion between professionals as to what current best practice should be. The reason for this, clearly, is the lack of evidence from good-quality randomised controlled trials. Those randomised controlled trials that have been carried out in this area of predominantly focused on the use of chemotherapy given either as primary treatment or as treatment following surgical treatment in the adjuvant setting. Even then, as alluded to, these trials have not been able to provide a definitive answer. Therefore, practice has often been based on historical data and historical comparisons of different treatments with its obvious limitations.

Preliminary trials of gemcitabine have indicated that it has a significant antitumour activity in patients with breast cancer both in the advanced and metastatic disease settings:

- Up to 35% as first line treatment,
- Up to 30% after pre-treatment with anthracyclines/taxanes, and
- Up to 50% or higher when used in combination with other agents.

However, the effects on overall survival remain to be fully clarified in good quality randomised controlled trials.

Whilst there is an increasing acceptance that primary chemotherapy is appropriate for locally advanced breast cancer there is still a lack of evidence as to what is the most appropriate chemotherapeutic agent. Data from our studies in Aberdeen (J Clin Oncol 2002; 20: 1456-1466) and also from larger studies in the United States (J Clin Oncol 2006; 24: 2019-27) has indicated that a combination of a taxane and anthracycline will give the best results in terms of complete pathological response (up to 34%) and with major reductions in the clinical size of the tumour. However, although these were randomised controlled trials we are still lacking published trials to identify if the responses rates can be increased by the addition of gemcitabine.

Gemcitabine has also been evaluated in preliminary studies in the primary (neoadjuvant) treatment of breast cancer and of patients with locally advanced breast cancer. The response rates have been encouraging and comparable when used as a single agent and also vindicated high response rate when used in combination with other agents, eg vinorelbine, cisplatinin, docetaxel, paclitaxel, anthracyclines. These have been reviewed recently (Int J Oncol 2004; 24: 389-398, Seminol Oncol 2006; 33: S19-23) and have shown the promising results. The attached table summarises some of the key phase I and II trials that have been published.

Study ref	Patient number and disease stage	Agents used	Clinical Response	Pathological response (PR)
Anticancer drugs, 2005;16: 1023-8	50 with Stage T2-4	Gemcitabine and epirubicin		26% complete PR
Br J Cancer 2005;93: 406-11	42 with Stage II and IIIA	Gemcitabine, epirubicin, and taxol	Overall 98% Complete 26.8%	14.6% complete
Ann Oncol 2005;16:1624-31	44 with Stage II and III	Gemcitabine, doxorubicin and docetaxel	Overall 80% Complete 25%	17.5% complete
Oncology 2004:18:27-31	77 patients with primary breast cancer	Gemcitabine, docetaxel and doxorubicin		26% complete
Anticancer drugs, 2005;16: 21-29	19 with Stage I and II	Gemcitabine, docetaxel and doxorubicin	Overall 80%	11% complete
Eur J Cancer 2004;40:2432-8	77 with tumours greater than 2.1 cm or inflammatory	Gemcitabine, epirubicin and docetaxel	Overall 92%	26% complete
Seminol Oncol 2004;31:31-6	24 with Stage II and III	Gemcitabine, and docetaxel	Overall 79%	4% complete
Seminol Oncol 2001;28:57-61	39 with Stage IIIB	Gemcitabine and doxorubicin	Overall 95% Complete 18%	

Nevertheless, the evidence at present is that the most effective agents are taxanes and anthracyclines given in combination. More recent studies have also indicated that if these chemotherapeutic agents are used in combination with trastuzumab in patients with Her 2 positive disease, then pathological response rates of up to 50% can actually now be achieved. Again, the role of gemcitabine in such combinations of treatment is unknown.

In terms of side effects, the general overall toxicity profile seems comparable to many of the other chemotherapeutic agents in the current practice. In some of the randomised controlled trials of evaluating combinations of gem site been with tax savings and compared against other standard therapeutic regimens not haematological toxicity profiles have appeared to be less. However, well-designed, randomised controlled trials are necessary to understand fully the place of Gemcitabine in the clinical management of patients with locally advanced breast cancer.

Another area of contention is the role of primary endocrine treatment in patients with hormone receptor positive decease. There are many clinicians within the NHS who would treat patients with locally advanced breast cancer with primary endocrine therapy rather than primary chemotherapy if the hormone receptor status of the tumour were positive. The benefits of primary hormone therapy versus primary chemotherapy in patients with locally advanced breast cancer (hormone receptor positive) are again unknown due to the lack of randomised controlled trials.

What are the current alternatives?

As can be seen from the above, the current alternatives to the use of gemcitabine in the treatment of patients with locally advanced breast cancer are the other chemotherapeutic agents, primary endocrine therapy and with a small number of clinicians still undertaking primary surgical treatment.

In what setting should the technology be used?

The technology is a can of therapeutic agent and must be used under specialist supervision. It will be recommended by secondary care specialist clinics but chemotherapy at the present time is given in the primary care setting and I would expect that this agent would also be able to be given in the primary care setting. Given the framework that already exists in the community, in community care and with specialist nursing support for the provision of chemotherapy I do not think that if this technology were to be applied that significant changes would be required.

Is the technology used to within its licensed indications?

Gemcitabine is currently used in the treatment of patients with metastatic breast cancer within its licensed indications. It is not licensed for the treatment of patients with locally advanced breast cancer only and I am not aware of its use in this setting.

Additional sources of evidence

At the present time I do not think that there are additional sources of evidence. The most important consideration is the requirement for high quality randomised controlled trials to understand the place of gemcitabine in current treatment.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

I do not anticipate that the delivery of care for patients would be affected and NHS staff current training and education would be adequate. I also do not think that any extra facilities or equipment would be required.