Experience of neoadjuvant chemotherapy for breast cancer at a public hospital: retrospective study

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Objective. To review local experience of neoadjuvant chemotherapy in breast cancer.
Design. Retrospective study.
Setting. Public hospital, Hong Kong.
Patients. Seventeen patients who presented from August 1988 through April 1997 with locally advanced breast cancer, which was treated with neoadjuvant chemotherapy.
Results. The clinical response rate was 71% and two of the 12 patients who responded to chemotherapy achieved complete remission. Three patients had their tumours downstaged sufficiently to allow them to undergo breast conservation surgery after neoadjuvant chemotherapy. None of these three patients has so far had a local recurrence of disease.
Conclusion. Neoadjuvant chemotherapy can achieve a high objective response rate in patients with locally advanced breast cancer and thus enables breast conservation surgery to be performed on patients who are initially not suitable for this procedure.

HKMJ 2000;6:265-8

Key words: Antineoplastic agents, combined; Breast neoplasms/surgery; Neoadjuvant therapy; Neoplasm recurrence, local; Neoplasm staging

Introduction

The value of adjuvant chemotherapy in treating breast cancer is well documented.[1] The idea of neoadjuvant chemotherapy has been recently applied to breast cancer treatment and studies have shown the efficacy of neoadjuvant chemotherapy in downstaging the primary tumour.[2] The use of neoadjuvant chemotherapy thus allows breast conservation surgery to be performed instead of mastectomy. This study reviews the experience of neoadjuvant chemotherapy at the Breast Centre of the Department of Surgery at the Kwong Wah Hospital.

Materials and methods

Seventeen patients who presented to the Kwong Wah Hospital from August 1988 through April 1997 with locally advanced breast cancer were included in this study. Breast cancer was diagnosed by fine-needle aspiration cytology and confirmed by needle biopsy examination. Locally advanced breast cancer was defined as either T3 or T4, according to the tumour-node-metastasis (TNM) classification. Investigations that were performed to detect systemic metastasis included chest X-ray, liver ultrasonography, and bone scanning. Patients with evidence of systemic metastasis were excluded from this review.

Treatment with neoadjuvant chemotherapy consisted of the classical cyclophosphamide, methotrexate, and 5-flurouracil (CMF) regimen—that is, oral cyclophosphamide 100 mg/m^2 from day 1 to day 14, intravenous methotrexate 40 mg/m^2 on days 1 and 8, and intravenous 5-fluorouracil 600 mg/m^2 on days 1 and 8, all repeated every 28 days. In addition, tamoxifen 20 mg/d was given to postmenopausal patients whose tumour was positive for the oestrogen receptor, as tested by immunohistochemistry. Clinical responses were assessed by comparing bidimensional measurements of the tumour size before and after chemotherapy. Serial mammography and ultrasonography were also used for six patients. Clinical responses were categorised by using the classification system of the World Health Organization (WHO).[3] The two largest perpendicular diameters of the primary tumour were measured and their products were calculated before and after the

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administration of chemotherapy. Patients were categorised as being in complete remission if there was no clinical evidence of tumour remaining in the breast. A partial response was defined as a reduction in the diameter product of more than 50%. If there was an increase of more than 25% in the diameter product, the patient was considered to have progressive disease. Patients whose tumour response did not meet the definitions of complete remission, partial response, or progressive disease were considered to have stable disease.

Patients were evaluated after three cycles of CMF chemotherapy had been given. Tumours that responded to treatment were given three more cycles of chemotherapy before surgery. Otherwise, surgery was performed after only three cycles of chemotherapy. Patients were advised to undergo breast conservation surgery if the tumour diameter decreased to 2 cm or less. Otherwise, modified radical mastectomy was performed. Specimens were sent to the pathology department for detailed assessment.

After receiving postoperative radiotherapy, patients who had had three cycles of primary chemotherapy were given three more cycles of CMF chemotherapy. Patients with an oestrogen-receptor positive tumour were also given tamoxifen. All patients were followed up to detect any local or systemic recurrences. Physical examination was performed during the follow-up visits. Imaging studies such as chest X-ray and bone scanning were not performed routinely if patients were asymptomatic.

Results

The mean patient age was 48 years (range, 36-70 years). The mean tumour diameter was 7.4 cm. The tumour staging for each patient before chemotherapy was given is shown in Table 1. Thirteen of the 17 patients received CMF chemotherapy only, whereas four patients received chemotherapy and tamoxifen. Twelve (71%) of the 17 patients responded to neoadjuvant chemotherapy, and clinically complete responses were achieved in two of these patients. Ten patients had partial responses and five had stable disease (Table 2). None of the patients had progressive disease during chemotherapy, and chemotherapy was generally well tolerated. The toxicity gradings of each patient, according to the WHO toxicity grading system,[3] are shown in Table 1. Leukopenia developed in two patients, one of whom had grade 2 toxicity, which required a reduction in the chemotherapy dose. There were no cases of infection during the treatment period. Other side effects such as nausea and vomiting were considered to be minor (grade 1 toxicity). Alopecia occurred in all patients and three of them had complete alopecia (grade 3 toxicity).

In three patients (one patient with a complete response and two with a partial response), the tumour was downstaged sufficiently to allow them to undergo breast conservation surgery. This procedure involved a wide local excision and axillary dissection, followed by radiotherapy to the residual breast. Thirteen patients underwent mastectomy, and two of them required

Table 1. Response of patients with breast cancer to treatment and surgery

Patient	Tumour size before chemotherapy (cm)	Tumour stage before chemotherapy	Clinical response*	Alopecia grade	Type of surgery	Recurrence
1	6.0	T4b	PR†	2‖	Mastectomy	Local
2	7.2	T3	PR	2	Mastectomy	-
3	10.0	T4b	PR	3	Mastectomy	Local, systemic
4	6.0	T4b	SD‡	2	Mastectomy	Local, systemic
5	6.0	T3	SD	2**	Mastectomy	-
6	8.0	T3	SD	2	Mastectomy	-
7	6.0	T3	PR	2	Breast-conserving	-
8	5.9	T3	PR	3	Mastectomy	-
9	5.7	T3	CR§¶	3	Breast-conserving	-
10	6.7	T3	CR	2	Mastectomy	Systemic
11	8.4	T3	PR	2	Mastectomy	Local
12	5.0	T4a	PR	2	Refused	-
13	6.4	T3	SD	2	Mastectomy	-
14	15.0	T4b	SD	2	Mastectomy	-
15	6.5	T4b	PR	2	Mastectomy	Local, systemic
16	5.2	T3	PR	2	Breast-conserving	-
17	12.5	T3	PR	2	Mastectomy	Local, systemic

* All patients experienced nausea and vomiting
† PR partial response
‡ SD stable disease
§ CR complete response
¶ Pathologically complete response
‖ Patient 1 also had leukopenia grade 1
** Patient 4 also had leukopenia grade 2

Table 2. Patient outcome and response to chemotherapy

Clinical response	Patient status at last follow-up		
	Disease-free	Local or systemic recurrence	Total
Complete response	1	1	2
Partial response	5	5	10
Stable disease	4	1	5
Total	10	7	17

myocutaneous flap coverage. All 13 patients who underwent mastectomy received radiotherapy to the chest wall. One patient who showed a partial response to chemotherapy refused to undergo surgery; she received radiotherapy only and remained well 10 years after treatment (last follow-up visit, August 1998).

A pathologically complete response was found in the patient who had shown a complete response after chemotherapy and who subsequently underwent breast conservation surgery. Of the 16 patients who underwent surgery after the neoadjuvant chemotherapy, the lymph nodes were found to be involved in 13 patients, and the oestrogen receptor status was positive in eight patients. Twelve patients had a grade 3 tumour, according to the Bloom and Richardson classification,[4] whereas the remaining four had grade 2 tumours.

The median follow-up period was 37 months (range, 16 months to 10 years). Two patients experienced isolated local recurrence, whereas four patients had both local and systemic recurrences. These six patients had originally undergone mastectomies. Systemic metastasis occurred in one patient, who died 2 years after treatment. None of the three patients who underwent breast conservation surgery has so far had a local recurrence of disease.

Discussion

The use of neoadjuvant chemotherapy to treat breast cancers has been shown to be efficacious.[2] In the National Surgical Adjuvant Breast and Bowel Project B-18,[2] an objective response was seen in 80% of 747 patients after they received neoadjuvant chemotherapy of doxorubicin and cyclophosphamide. Furthermore, there was an overall 12% increase in the incidence of lumpectomy in this group, and in women with tumours larger than 5 cm in diameter, there was a 175% increase in the lumpectomy rate.

The overall response rate in this study was 71%, which is similar to the figure reported in other studies.[5-8] By using neoadjuvant chemotherapy, we achieved tumour downstaging in 12 (71%) of the 17 patients and breast conservation in four (24%) patients, three of whom underwent breast conservation surgery. Breast conservation would have otherwise been impossible for their locally advanced tumours.

Neoadjuvant chemotherapy has the theoretical advantage of providing early treatment of micrometastasis, thereby leading to an increased survival rate. Mauriac et al[9] have shown that the use of neoadjuvant chemotherapy increases the overall survival rate compared with when conventional treatment is used, but there is no difference in the relapse-free survival rate. Other studies have not shown any survival benefit from using neoadjuvant chemotherapy.[10,11]

Patients who have a complete response to chemotherapy have a better outcome than patients who show no response to chemotherapy.[11] Although this study attempted to investigate the outcome of patients with their pathological response to neoadjuvant chemotherapy (Table 2), no conclusion could be made because of the small number of patients in our series.

Assessing residual disease after the administration of chemotherapy is important in helping to select patients for breast conservation surgery. Apart from measuring the tumour diameter directly, imaging techniques such as mammography and ultrasonography may provide further information about the tumour size after chemotherapy, although the agreement of the results with the pathological size is generally not satisfactory.[12] Powles et al[7] have attributed the poor correlation of mammography results to the difficulty in defining accurately the tumour size from studying the mammogram and the persistence of architectural distortion after chemotherapy. Whether magnetic resonance imaging (MRI) can provide a better correlation with the pathological size remains uncertain, but early results appear promising.[13] Cross et al[14] have shown that the reduction in tumour enhancement on an MRI scan correlates with the extent of the disease as seen at the pathological examination. We have started a prospective study to see if MRI can provide an accurate assessment of the tumour size after chemotherapy and to compare MRI with clinical assessment, mammography, and ultrasonography.

In conclusion, neoadjuvant chemotherapy can achieve a high objective response rate (71%) in patients with locally advanced breast cancer. The regimen thus enables breast conservation surgery to be performed on patients who are initially not suitable for this procedure.

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