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Adjuvant Chemotherapy Using Cyclophosphamide, Methotrexate, and Fluorouracil for Breast Cancer: the Tuen Mun Hospital Experience

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ABSTRACT

Objective: *This report is of the experience with combination cyclophosphamide, methotrexate, and fluorouracil as adjuvant treatment for breast cancer at Tuen Mun Hospital.*

Patients and Methods: *Records of patients who received combination cyclophosphamide, methotrexate, and fluorouracil chemotherapy during 1990 to 2000 were reviewed. Chemotherapy consisted of oral cyclophosphamide 100 mg/m^2 on days 1 to 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. Treatment was repeated every 4 weeks for 6 planned cycles.*

Results: *406 patients were evaluable, of whom 352 (86.7%) completed 6 cycles of chemotherapy. The median duration of treatment was 24 weeks (range, 4 to 51 weeks). The median time from surgery to start of chemotherapy was 3.71 weeks (range, 1.3 to 36.7 weeks). Of the 406 patients, 34 (8.4%) were lost to follow up. At a median follow up of 4.75 years in June 2003, the status of the patients was as follows: 294 patients (72.4%) were alive and free of disease, 26 (6.4%) were alive with disease recurrence, while 83 (20.4%) died of breast cancer and 3 (0.7%) died of second malignancy. The 5- and 10-year relapse-free survival and overall survival were 72% and 64%, and 80% and 68%, respectively. The longest time interval between surgery and relapse was 9.41 years.*

Conclusion: *The use of the classical cyclophosphamide, methotrexate, and fluorouracil regimen as adjuvant chemotherapy for breast cancer patients in a community hospital has yielded early results comparable with those of the Milan Cancer Institute. With its favourable toxicity profile, cyclophosphamide, methotrexate, and fluorouracil could be offered to patients with early-stage breast cancer who cannot tolerate anthracycline-based chemotherapy due to other medical co-morbidities.*

Key Words: *Breast cancer, Chemotherapy, Cyclophosphamide, Fluorouracil, Methotrexate*

INTRODUCTION

Breast cancer has remained a substantial public health problem throughout the Western industrialised world. Until 30 years ago, treatment philosophy was dominated by the anatomical and mechanistic dogma of tumour cell spread, first by direct extension into contiguous tissue and then, by an orderly progression through the lymphatics, to the rest of the body. It was only towards the end of the 1960s that this Halstedian hypothesis was challenged, leading to the development of adjuvant chemotherapy in the 1970s.[1] The National Surgical Adjuvant Breast and Bowel Project (NSABP) utilised single-agent chemotherapy with melphalan delivered for 2 years,[2] while the Milan study employed a multiple-drug regimen known as CMF (cyclophosphamide, methotrexate, and fluorouracil) given in 12 monthly cycles.[3] Later, the Milan group confirmed that 6 cycles of adjuvant CMF were as effective as the same regimen delivered for a longer time. The positive effects of adjuvant chemotherapy in reducing the risk of disease relapse, which were mainly achieved during the first 3 years after surgery, were maintained throughout

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subsequent years. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) has shown in an overview that polychemotherapy as a single modality improved annual recurrence and survival rates by 24% and 15%, respectively.[4]

Breast cancer has remained the number one female cancer in Hong Kong since 1994.[5] In 2000, there were 1918 new cases with a crude incidence rate of 56.6 per 100,000. However, its ranking in cancer mortality dropped to the third position, having been overtaken by colon cancer since 1999. At the Tuen Mun Hospital, combination chemotherapy has been adopted since 1990 as adjuvant therapy for premenopausal women with node-positive disease or node-negative disease with poor prognostic features (e.g. large tumour size, grade 3 tumour), as well as postmenopausal women who were at higher risk of recurrence by virtue of node involvement or similar poor prognostic factors. This article is a report of the experience of using combination CMF as adjuvant treatment for breast cancer at the Tuen Mun Hospital.

PATIENTS AND METHODS

Records of patients who received combination CMF chemotherapy in the period from 1990 to 2000 in the Department of Clinical Oncology, Tuen Mun Hospital, were reviewed. To be included in this review, patients were required to have received definitive surgery for primary breast cancer with or without axillary lymphadenectomy, and no evidence of residual or metastatic disease on physical examination, chest X-ray, and liver function test.

Postmenopausal patients were defined as women whose last menstrual period occurred more than 12 months before chemotherapy was started. Women who had had a hysterectomy for other disease or whose menstrual history was not recorded were classified as postmenopausal if they were aged 50 years or more at presentation.

Treatment

Chemotherapy consisted of the 'classical' Bonadonna regimen: oral cyclophosphamide 100 mg/m^2 on days 1 to 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. Treatment was repeated every 4 weeks for 6 planned cycles. In cases of poor marrow recovery, the dose was reduced or treatment was suspended at the discretion of the attending oncologist. Adjuvant radiotherapy to the chest wall (or remaining breast tissue after lumpectomy) using pairs of glancing fields and to the ipsilateral axillary/supraclavicular nodal basin using direct photon beam was also given if indicated. Since 1998, all patients who had hormone-positive tumours were also prescribed tamoxifen for 5 years after chemotherapy.

Dose Calculation

The exact amount of drug that could have been received in 6 cycles regardless of dose reduction for toxicity or other reasons was calculated. The exact amount of drug that was actually received was then calculated, with consideration for dose reduction for toxicity or other reasons. The total amount of drug actually received was then divided by the amount of drug planned for 6 cycles. The dose intensity is given by the mean value of this ratio of all 3 drugs. The relapse-free survival (RFS) and overall survival (OS) were then related to various dose levels. Three dose levels were selected according to Bonadonna and Valagussa (level I, ≥85%; level II, 65% to 84%; and level III, <65%) as the basis for the dose-response findings of this report.[2]

Follow Up

Patients had regular follow up at the clinic after completion of chemotherapy. Patients who did not return for the last scheduled appointment were traced by telephone or by the electronic public health information system established by the Hong Kong Hospital Authority. They were considered to be lost to follow up if they could not be contacted despite these efforts.

Statistical Analysis

For statistical analysis, the outcome variables were RFS and OS. RFS was calculated from the date of surgery to the date of disease recurrence. A recurrence was defined as local recurrence, regional recurrence, or distant metastasis. A new cancer developing in the contralateral breast was considered to be a second primary cancer and not a disease recurrence. A local recurrence was defined as a tumour lesion in the chest wall (or in the remaining breast tissue in cases of breast conservation surgery). A regional recurrence was defined as relapse in an ipsilateral node in the axillary area. Multiple site recurrence was defined as 2 or more tumour sites discovered within 1 month. Disease recurrence was diagnosed by biopsy and/or the appearance of typical abnormalities on a radiographic or scintigraphic study. Patients without a recurrence were included at the last date they were known to be disease-free. OS was calculated from the date of surgery to

the date of death. Those who were still alive were included at the last date they were known to be still alive. Survival distribution was estimated by the Kaplan-Meier product-limit method and compared 2 or more distributions using the log-rank test.[6,7]

Cox proportional hazards regression was carried out by resorting to a backward procedure to model the relationship of RFS and OS with clinical variables.[8] These variables included age, menstrual status, the number of positive nodes, tumour size, overall stage, tumour grade, hormonal receptor status, tamoxifen therapy, duration of chemotherapy, dose intensity, type of surgery performed, and local and regional radiotherapy. Statistical analysis was performed with the Statistical Package for the Social Sciences software version 11.0.

RESULTS

Treatment

The records of 406 patients were evaluated. All patients received curative surgery for breast cancer, either in the form of mastectomy (n = 385; 94.8%) or breast conservation surgery (n = 21; 5.2%). The age at presentation ranged from 25 to 68 years (median, 43 years). 357 patients were premenopausal and 49 were postmenopausal. Tumour characteristics are summarised in Table 1. Of the 406 evaluable patients, 352 (86.7%) completed 6 cycles of chemotherapy. The median duration of treatment was 24 weeks (range, 4 to 51 weeks). The median time from surgery to start of chemotherapy was 3.71 weeks (range, 1.30 to 36.70 weeks). Delay of referral from the surgeon was the primary reason for the late initiation of chemotherapy. Adjuvant radiotherapy to the chest wall (or remaining breast) was given to 325 patients (80.0%), while 202 patients (49.8%) received radiotherapy to regional nodes. Hormonal therapy, either in the form of oral tamoxifen 20 mg for 5 years or ovarian ablation, was given to 93 patients (22.9%) and 10 patients (2.5%), respectively (Table 2). Four patients who had received ovarian ablation were also given tamoxifen. Maximal effort in tracing the menstrual history of the premenopausal women revealed that 62 patients were still having normal menstrual cycles approximately 6 months after completion of chemotherapy, while 110 patients reported interruption of menstruation. However, at least 14 of the 110 women had regained normal menstrual cycles.

Table 1. Tumour characteristics.

	Number of patients	Percent of patients
Histology		
Infiltrative ductal carcinoma	392	96.6
Infiltrative lobular carcinoma	7	1.7
Unknown/other	7	1.7
Grade		
1	36	8.9
2	136	33.5
3	198	48.8
Unknown	36	8.9
Hormonal receptor		
Negative	108	26.6
Positive	143	35.2
Unknown	155	38.2
c-cerb2 Overexpression		
No	22	5.4
Yes	23	5.7
Unknown	361	88.9
Margin		
Clear	255	62.8
Close	76	18.7
Involved	14	3.4
Unknown	61	15.0
Lymphovascular permeation		
Negative	96	23.6
Positive	98	24.1
Unknown	212	52.2
T stage		
T1	99	24.4
T2	244	60.1
T3	54	13.3
T4	9	2.2
Tumour size		
≤2 cm	105	25.9
2-5 cm	248	61.0
>5 cm	53	13.1
Number of nodes		
0	122	30.0
1-3	177	43.6
4-10	79	19.5
>10	28	6.9
Stage		
UICC 1987		
I	32	7.9
IIA	142	35.0
IIB	184	45.3
IIIA	40	9.9
IIIB	8	2.0
AJCC 2003		
I	32	7.9
IIA	125	30.8
IIB	119	29.3
IIIA	91	22.4
IIIB	6	1.5
IIIC	33	8.1

Abbreviations: AJCC = American Joint Committee on Cancer; UICC = International Union Against Cancer.

Outcome and Prognostic Factors

Of the 406 patients, 34 (8.4%) were lost to follow up. At a median follow up of 4.75 years in June 2003, the status of the patients was as follows: 294 patients (72.4%) were alive and free of disease, 26 (6.4%) were alive with disease recurrence, while 83 (20.4%) died of breast cancer and 3 (0.7%) died of second malignancy.

Table 2. Number of patients receiving hormonal therapy.

	Tamoxifen	Ovarian ablation
Hormone receptor-negative (n = 108)	6	3
Hormone receptor-positive (n = 143)	76	4
Hormone receptor status unknown (n = 155)	11	3

Table 3. Pattern of treatment failures.

	Number of treatment failures	Failure at first relapse
Local	18	11
Regional	2	2
Distant	108	102
Bone	61	43
Distant lymph node	35	33
Lung	32	22
Liver	27	16
Brain	13	8
Others	7	6

The 5- and 10-year RFS and OS were 72% and 64%, and 80% and 68%, respectively. The longest time interval between surgery and relapse was 9.41 years.

The sites of recurrent disease and their frequency are shown in Table 3. Most patients who developed distant metastases had no evidence of local or regional recurrence. Bone was the most common site and often the first site of distant metastasis, followed by lymph nodes (including supraclavicular and cervical nodes).

Eighteen patients developed local recurrence in the chest wall, 11 of whom had local recurrence as the first event. All but one of them had received local radiotherapy to the chest wall after surgery.

The RFS for different stages (International Union Against Cancer 1987) of breast cancer are shown in Figure 1. There is significant separation of the curves for stages I to IIIA ($p < 0.0001$). The RFS at 5 years were as follows: stage I, 89.4%; stage IIA, 79.5%; stage IIB, 73.6%; stage IIIA, 34.6%; and stage IIIB, 40%. However, a Will-Roger phenomenon[9] could be observed using the American Joint Committee on Cancer 2003 staging system (Figure 2). The RFS at 5 years for stage IIA was 82.6%; stage IIB was 83.2%; stage IIIA was 56.6%; stage IIIB was 66.7%; and stage IIIC was 26.1%.

Univariate analyses of RFS and OS according to patient variables and treatment factors are shown in

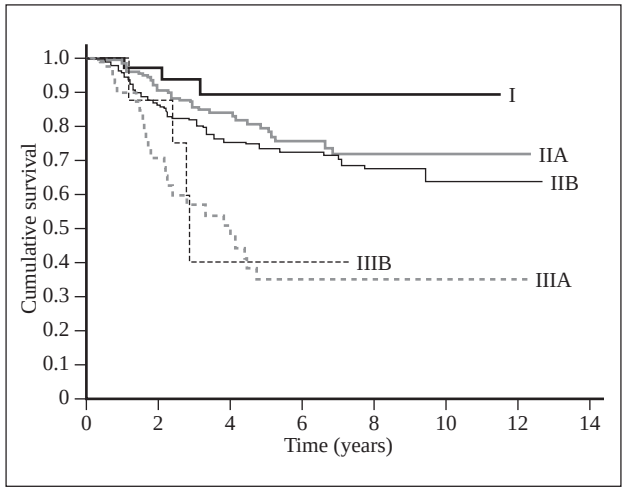

Figure 1. Relapse-free survival by International Union Against Cancer 1987 staging.

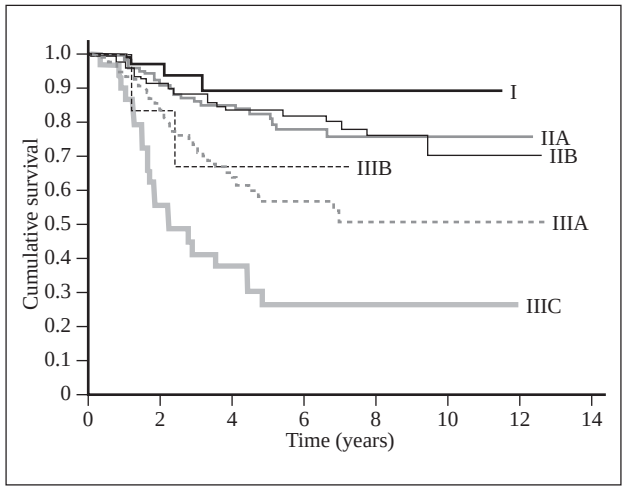

Figure 2. Relapse-free survival by American Joint Commmittee on Cancer 2003 staging.

Table 4. The most important prognostic factor is the presence of metastatic disease in the axillary nodes and the number of positive nodes (Table 5). The 5-year RFS was 89% for node-negative patients compared with 65.3% for node-positive patients ($p < 0.00001$). Figure 3 illustrates the RFS on the basis of number of involved nodes. For the 28 patients with more than 10 positive nodes at the time of mastectomy, 17 relapsed, 12 of whom relapsed within the first 2 years after surgery, giving a median RFS of only 1.7 years.

Figure 4 shows that the RFS at 5 years was dependent on the dose level of chemotherapy received. Within each dose level, the results were related to the number of axillary lymph nodes and, within each patient subgroup with a certain number of nodes, the 5-year RFS was also dose-related. It is important to emphasise that there was no statistically significant difference by the chi-squared

Table 4. Univariate analysis of relapse-free survival and overall survival.

Prognostic factors	Number of patients	Relapse [n (%)]	p Value	Death [n (%)]	p Value
Age (years)					
20-39	130	33 (25.4)	0.62	27 (21.0)	0.57
40-49	215	62 (28.8)		46 (21.4)	
≥50	61	16 (26.2)		13 (21.3)	
Menopausal status					
Premenopausal	357	98 (27.5)	0.50	74 (20.7)	0.10
Postmenopausal	49	13 (26.5)		12 (24.5)	
Hormonal receptor status ± tamoxifen					
Negative, no tamoxifen	102	25 (24.5)	0.02	24 (23.5)	0.0005
Negative, tamoxifen	6	3 (50.0)		3 (50.0)	
Positive, no tamoxifen	67	20 (29.9)		13 (19.4)	
Positive, tamoxifen	76	10 (13.2)		2 (2.6)	
Unknown, no tamoxifen	144	47 (32.6)		39 (27.0)	
Unknown, tamoxifen	11	6 (54.5)		5 (45.5)	
Grade					
1	36	10 (27.8)	0.99*	7 (19.4)	0.9*
2	136	38 (27.9)		28 (20.6)	
3	198	53 (26.8)		44 (22.2)	
Unknown	36	10 (27.8)		7 (19.4)	
Duration of chemotherapy >24 weeks					
No	354	95 (26.8)	0.39	73 (20.6)	0.41
Yes	52	16 (30.8)		13 (4.0)	
Local Surgery					
Mastectomy	385	107	0.72	85	0.23
Lumpectomy	21	4		1	
Local radiotherapy					
Yes	325	96	0.37	76	0.32
No	81	15		10	
Regional radiotherapy					
Yes	202	77	0.0001	58	0.0076
No	204	34		28	
Stage International Union Against Cancer 1987					
I	32	3 (9.4)	<0.0001	2 (6.3)	<0.0001
IIA	142	30 (21.1)		20 (14.1)	
IIB	184	51 (27.7)		42 (22.8)	
IIIA	40	23 (57.5)		18 (45.0)	
IIIB	8	4 (50.0)		4 (50.0)	
Tumour size					
≤2 cm	105	25 (23.8)	<0.0001	15 (14.3)	<0.0001
2-5 cm	248	59 (23.8)		47 (20.0)	
>5 cm	53	27 (50.9)		24 (45.3)	
Number of positive nodes					
0	122	15 (12.3)	<0.0001	14 (11.5)	<0.0001
1-3	177	45 (25.4)		30 (16.9)	
4-10	79	34 (43.0)		28 (35.4)	
>10	28	17 (60.7)		14 (50.0)	
Dose intensity					
≤64%	38	15 (39.5)	<0.003	11 (28.9)	0.051
65-84%	16	4 (25.0)		3 (18.8)	
≥85%	352	92 (26.1)		72 (20.5)	

* Test on known value only.

test in the major prognostic variables (age, menopausal status, number of positive lymph nodes, and tumour size) among the 3 dose levels. Test for interaction between tumour size and number of positive nodes was done using a scatter plot and there was no significant relationship between these 2 important covariates.

After multivariate analysis, RFS was found to be significantly influenced by the extent of nodal involvement, tumour size, dose intensity, and tamoxifen therapy (Table 6). The presence of metastatic disease in axillary lymph nodes remained the strongest poor prognostic factor for RFS. For the node-positive patients, it was the increasing number of involved nodes that adversely affected RFS, followed by a large tumour size >4 cm. Furthermore, there was also a clear dose-response effect for RFS, indicating that CMF was useful only when given in a full or nearly full dose (≥85% of the

Table 5. Comparison of 5-year relapse-free survival (RFS) according to number of positive nodes.

Nodal status	5-year RFS at Tuen Mun Hospital (%)	95% Confidence interval	5-year RFS by Bonadonna and Valagussa[2] (%)
Node-negative	89.30	83.49-95.17	Not available
Node-positive	65.33	59.21-71.45	64.00
1-3 nodes	75.54	68.60-82.48	70.00
4-10 nodes	55.01	42.97-67.05	Not available
>10 nodes	29.31	10.69-47.93	Not available

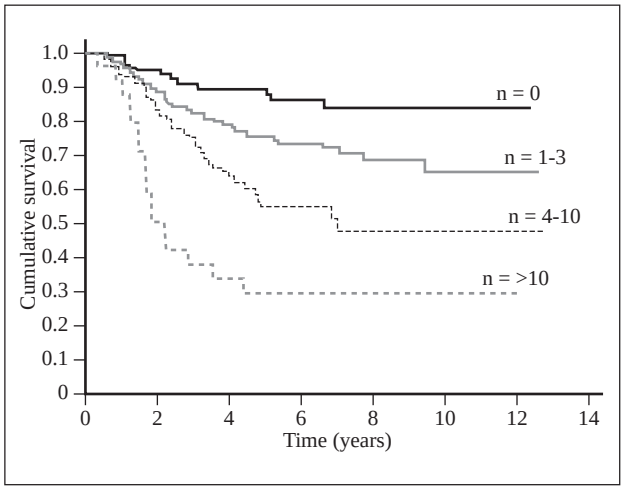

Figure 3. Relapse-free survival by number of positive nodes.

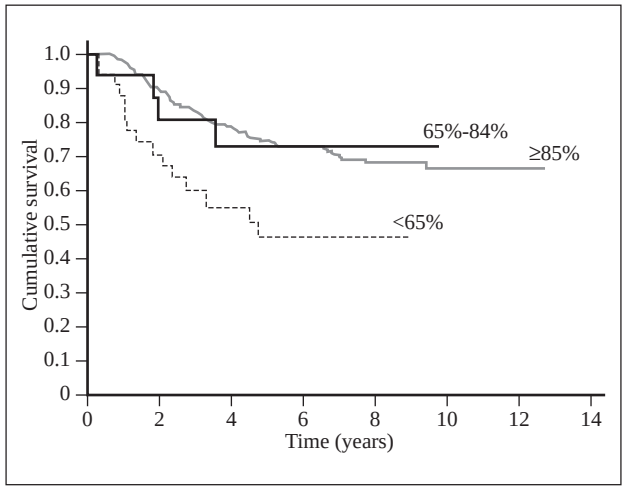

Figure 4. Relapse-free survival by dose intensity.

planned dose). Those patients who received less than 85% of the planned dose were more likely to have disease relapse. Patients with tumours positive for hormone receptors also had a better RFS if they were given tamoxifen therapy, but those with negative or unknown receptor status did not obtain the same benefit.

Patients who had received adjuvant radiotherapy to the regional lymph nodes were found to have a higher chance of disease relapse and death by univariate analysis. However, they may represent patients who had more positive nodes and larger tumours, since such adverse prognostic factors are considered to be indications for adjuvant regional radiotherapy. After multivariate analysis, the impact of adjuvant radiotherapy on RFS and OS was found to be statistically insignificant.

Table 7 shows that after CMF chemotherapy, there was no statistically significant difference in OS between

Table 6. Multivariate analysis of prognostic factors for relapse-free survival.

Prognostic factors	Hazard ratio	Confidence interval	p Value
Number of positive nodes			
0	1		
1-3	2.3	1.3-4.1	0.006
4-10	3.7	2.0-6.7	<0.0001
>10	7.1	3.5-14.4	<0.0001
Tumour size			
≤4 cm	1		
>4 cm	2.0	1.3-2.9	0.0006
Dose intensity			
≥85%	1		
<85%	1.9	1.1-3.1	0.015
Hormonal therapy			
Receptor negative without tamoxifen	1		
Receptor negative/unknown with tamoxifen	1.18	0.53-2.66	0.68
Receptor positive/unknown without tamoxifen	0.78	0.48-1.24	0.29
Receptor positive with tamoxifen	0.39	0.18-0.83	0.01

Table 7. Multivariate analysis of prognostic factors for overall survival.

Prognostic factors	Hazard ratio	Confidence interval	p Value
Number of positive nodes			
0	1		
1-3	1.7	0.9-3.3	0.09
4-10	3.7	1.9-7.0	0.0001
>10	5.3	2.5-11.3	<0.0001
Tumour size			
≤4 cm	1		
>4 cm	1.9	1.3-3.0	0.003
Hormonal therapy			
Receptor negative without tamoxifen	1		
Receptor negative/unknown with tamoxifen	1.37	0.61-3.08	0.45
Receptor positive/unknown without tamoxifen	0.54	0.33-0.89	0.02
Receptor positive with tamoxifen	0.10	0.02-0.43	0.002

Table 8. Acute toxicities by Common Toxicity Criteria version 3.0.

	Grade 1-2 (%)	Grade 3-4 (%)
Anaemia	50.5	0.2
Leukopenia	65.8	13.5
Thrombocytopenia	40.6	1.5
Emesis	37.2	2.7
Alopecia	1.5	Not applicable

patients with zero and 1 to 3 positive nodes (p = 0.187). However, those with 4 or more positive nodes or a larger tumour size >4 cm still had a higher risk of dying from the disease. Patients who had hormone receptor-positive tumours and were given tamoxifen also had a better OS.

Toxicity

The frequency of chemotherapy-induced myelosuppression, emesis, and alopecia is shown in Table 8. Toxicities were graded by Common Toxicity Criteria version 3.0.[10] The incidence of grade 3 to 4 toxicity was 0.2% for anaemia, 13.5% for leukopenia, 1.5% for thrombocytopenia, and 1 patient developed febrile neutropenia but recovered uneventfully. Only 2.7% of patients reported grade 3 or above alopecia. One patient who was a hepatitis B surface antigen carrier developed reactivation of viral hepatitis but she fully recovered after lamivudine therapy. No patient died of acute complications of chemotherapy.

Second Malignancy

Thirteen patients developed contralateral breast cancer. Another 9 patients who did not have relapse of breast cancer developed a second cancer. The median time from surgery to occurrence of non-breast second malignancy was 2.6 years. Eight of these patients developed a solid malignancy, including carcinoma of the lung, stomach, colon, ovary, uterine corpus, and thyroid. One patient who had received 1 cycle of CMF and then further chemotherapy in another regional hospital due to geographical reasons developed acute promyelocytic leukaemia 3 years after chemotherapy. Since the usual latent period of alkylating agent-related leukaemia is approximately 5 to 10 years and this patient was not known to have pre-existing myelodysplasia, the event was not regarded as CMF-induced leukaemia.[11]

DISCUSSION

It has been well established that breast cancer is a systemic disease and that recurrence of this disease could be reduced by the administration of adjuvant chemotherapy after surgery. The results of this retrospective study indicate a positive CMF dose-response relationship for the treatment of breast cancer. Such findings agree with the results of Bonadonna and Valagussa,[2] who reported a 5-year RFS of 64% in 449 node-positive patients given CMF as a 12-cycle regimen. Although these results showed that treatment with an adequate dose (level I) of CMF for 12 cycles was superior to the same dose for 6 cycles, the practical issue of dose reduction in subsequent cycles due to marrow intolerance could defeat the purpose of holding the remaining tumour cells in check during cycles 7 to 12.

The role of tamoxifen for hormone-responsive tumours has been well documented by the EBCTCG in their meta-analysis in 1998.[12] We also tried to evaluate our local experience of tamoxifen therapy in this retrospective review. Seventeen patients with negative or unknown hormone receptor status received tamoxifen in the earlier part of the study period, although they did not derive the same benefit as those patients with hormone receptor-positive tumours. On the other hand, tamoxifen as adjuvant therapy did confer a survival benefit for patients with hormone receptor-positive tumours, with a reduction in relapse and death of

61% and 90%, respectively. Of the 211 patients with unknown or positive hormonal receptor status who were not given immediate tamoxifen, 67 relapsed. Forty patients were given tamoxifen as salvage therapy, thus reducing their risk of death.

There are 2 prospective randomised studies comparing the use of CMF chemotherapy with temporary medical castration using gonadotrophin releasing hormone analogue. The Zoladex Early Breast Cancer Research Association Study by Jonat et al showed equivalent disease-free survival (DFS) in oestrogen receptor-positive breast cancer patients treated either with CMF or goserelin for 2 years,[13] while Jakesz et al compared combination CMF (cyclophosphamide 600 mg/m^2 intravenously on day 1, methotrexate 40 mg/m^2 intravenously on day 1, and 5-fluorouracil 600 mg/m^2 intravenously on days 1 and 8 every 4 weeks for 6 cycles) against subcutaneous goserelin 3.6 mg every 28 days for 3 years, followed by 5 years of tamoxifen 20 mg once daily for pre- and perimenopausal breast cancer patients with positive nodes.[14] At a median follow up of 5 years, these researchers reported a significant improvement of RFS and local recurrence-free survival in the group treated with endocrine therapy. However, their chemotherapy group did not include 'standard' CMF as used in our study. In addition, distant recurrences were equally frequent in that trial's endocrine and chemotherapy groups. Therefore, the superiority of endocrine therapy over chemotherapy remains doubtful, inasmuch as breast cancer can disseminate early.

Although there are many different adjuvant chemotherapy regimens, 6 cycles of CMF, 6 cycles of FAC (5-fluorouracil, doxorubicin [adriamycin], cyclophosphamide) and 4 cycles of AC (doxorubicin, cyclophosphamide) are the most commonly used regimens in Hong Kong. The NSABP B-15 is a 3-group study comparing 4 cycles of AC with or without reinduction chemotherapy with parenteral CMF against 6 cycles of oral CMF alone in node-positive tamoxifen non-responsive early breast cancer.[15] The outcome indicators (DFS, distant DFS, and survival) for AC and CMF were almost identical. AC seems preferable since, following total mastectomy, AC was completed on day 63 versus day 154 for conventional CMF and patients visited health professionals 3 times as often for conventional CMF as for AC. The meta-analysis by the EBCTCG has reported a slightly superior result in favour of anthracycline-based regimens.[4] The absolute difference was approximately 3%.

There has also been recent interest in the role of adriamycin for tumours over-expressing HER-2 oncogene.[16,17] We have therefore adopted AC combination chemotherapy as one of the adjuvant regimens for early stage breast cancer in recent years. Among the 23 patients who had breast cancer over-expressing HER-2 (c-erb2) oncogenes, only 3 patients relapsed after developing distant failure and the rest survived for 2.7 to 8.3 years.

While the patients who had 1 to 3 positive nodes had a 5-year RFS of 75.5%, the 5-year RFS of 55% for patients with 4 to 10 positive nodes remained far from satisfactory. The outcome of patients with 10 or more involved axillary nodes was also dismal. Less than 30% of such patients survived more than 5 years. New regimens that can improve the outcome of such poor risk patients are eagerly awaited. In fact, use of sequential chemotherapy with doxorubicin followed by CMF (doxorubicin 75 mg/m^2 every 3 weeks for 4 cycles then cyclophosphamide 600 mg/m^2 intravenously on day 1, methotrexate 40 mg/m^2 intravenously on day 1, and 5-fluorouracil 600 mg/m^2 intravenously on day 1 every 3 weeks for 8 cycles) for women with extensive nodal involvement had yielded a 10-year RFS and total survival of 42% and 58%, respectively, in another Milan series.[18]

Levine et al have shown the superiority of 6 monthly cycles of CEF (cyclophosphamide 75 mg/m^2 orally on days 1 to 14, epirubicin 60 mg/m^2 intravenously on days 1 and 8, and 5-fluorouracil 500 mg/m^2 intravenously on days 1 and 8) over monthly CMF (cyclophosphamide 100 mg/m^2 orally on days 1 to 14, methotrexate 40 mg/m^2 intravenously on days 1 and 8, 5-fluorouracil 600 mg/m^2 intravenously on days 1 and 8) in terms of both DFS and OS in premenopausal women with axillary node-positive breast cancer.[19] The French Adjuvant Study Group has reported a 5-year DFS and OS of 66.3% and 77.4%, respectively, with a high-dose epirubicin regimen (FEC100).[20] The advantage of using FEC100 (5-fluorouracil 500 mg/m^2 intravenously on day 1, epirubicin 100 mg/m^2 intravenously on day 1, and cyclophosphamide 500 mg/m^2 intravenously on day 1 every 3 weeks) over FEC50 (5-fluorouracil 500 mg/m^2 intravenously on day 1, epirubicin 50 mg/m^2 intravenously on day 1, and cyclophosphamide 500 mg/m^2 intravenously on day 1 every 3 weeks) was shown only in patients with more than 3 positive nodes. The place of anthracyclines in adjuvant therapy for patients with poor risk factors is therefore well established.

The role of taxanes as adjuvant therapy for breast cancer continues to evolve. The Breast Cancer International Research Group 001 study has established docetaxel in combination with doxorubicin and cyclophosphamide to have major clinical value in the adjuvant treatment of women with early-stage node-positive breast cancer.[21] The Cancer and Leukaemia Group B (CALGB) 9344 study and NSABP-B28 study have also tested the efficacy of 4 cycles of doxorubicin and cyclophosphamide followed by 4 cycles of paclitaxel (AC x 4 + T) and both studies have demonstrated a DFS advantage for the taxane-containing regimen for node-positive breast cancer.[22] However, the optimal agent, duration, and schedule (sequential or combination), as well as interaction with hormonal receptor status remain unanswered. The CALGB 9741 trial is a 2 x 2 factorial design study testing the novel concepts based on mathematical models of tumour cell growth kinetics but it was not powered for individual comparisons of the 4 treatment groups. The reported data should still be viewed as immature.[23,24] Breast cancer may have the most heterogeneous natural history of all human cancers. Late recurrence is not uncommon.[25] A true picture of outcomes for breast cancer and its treatment requires information well beyond 10 years from diagnosis. Longer follow up is therefore necessary.

In this report, we have also shown that the recent change in the breast cancer staging system witnesses the Will-Rogers effect: implementing the 2003 American Joint Committee on Cancer staging for breast cancer improved the stage-specific RFS for stages IIA to IIIB disease. As the cohort of each stage with poor outcome was allocated to a higher stage, the RFS for any one stage was improved. Careful attention should therefore be devoted to this effect before we can draw any conclusion regarding the efficacy of new treatments.

In conclusion, the use of the classical CMF regimen as adjuvant chemotherapy for breast cancer patients in a community hospital has yielded early results comparable with those of the Milan Cancer Institute. With its favourable toxicity profile, CMF could be offered to patients with early-stage breast cancer who cannot tolerate anthracycline-based chemotherapy due to other medical co-morbidities.

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