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CHEMOTHERAPY IN ADVANCED BREAST CARCINOMA

Comparison between doxorubicin-cyclophosphamide and cyclophosphamide-methotrexate-5-fluorouracil-vincristine-prednisone

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Abstract

Two chemotherapeutic regimens were compared in 102 patients with metastatic breast carcinoma, randomized to either doxorubicin-cyclophosphamide (DC) or cyclophosphamide-methotrexate- 5 -fluorouracil-vincristine-prednisone (CMFVP). The objective response rates were 32 per cent in the former and 35 per cent in the latter group, the complete response rates 6.4 and 21.8 per cent, and mean duration of the remission 7.7 and 11.2 months, respectively. Most responders had multiple metastases and had received previous hormonal treatment. The DC regimen was found to be slightly more toxic than CMFVP.

Response rates of metastatic breast carcinoma to chemotherapy have increased markedly during recent years (5). While complete remissions are rare, meaningful palliation and prolonged survival can be provided for most patients (8). GREENSPAN (4) was the first to combine several drugs in the treatment of advanced breast malignancy, and COOPER (2) reported an 88 per cent response rate by combining cyclophosphamide, methotrexate, 5-fluorouracil, vincristine and prednisone (CMFVP). Although others have not reached this response rate, CMFVP has been frequently used in the treatment of advanced breast cancer. A response rate of 56 per cent has later been reported, and this was independent of prednisone and vincristine in the regimen (1).

Enhanced response rates of up to 80 per cent have been observed in patients with metastatic breast cancer if doxorubicin is included in the regimen (6, 13). Therefore, several comparisons have been reported regarding COOPER's (2) CMFVP regimen and combinations containing doxorubicin (3, 6, 11). In general, patients under 50 years of age are more likely to respond to non-doxorubicin combinations. Doxorubicin combinations, in their turn, seem to be more effective in patients with soft tissue or bone metastases, or both, but not in patients with visceral spreading of the disease. Doxorubicin combinations generally induce more gastrointestinal side effects and alopecia, and a recent report (8) indicates that CMFVP does not markedly differ in efficiency from doxorubicin-containing regimens.

The purpose of the present analysis was to identify some pretreatment characteristics in patients with metastatic breast cancer, related to the response to chemotherapy, and to compare response rates and toxicity of doxorubicin-cyclophosphamide (DC) with CMFVP as first-line chemotherapy in this disease.

Material and Methods

During 1977 through 1982, 102 patients with metastatic breast carcinoma and the characteristics listed in Table 1 were randomized according to their dates of birth: 47 patients with even dates received DC and 55 patients with odd dates CMFVP (Table 2).

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Most patients had, after initial mastectomy, received postoperative irradiation with 6 MV roentgen rays (30–40 Gy) against parasternal, supraclavicular and axillary lymph node regions and the operation field. At the time of randomization, the patients had metastases as summarized in Table 3.

Before the beginning of each cycle of chemotherapy, physical examination, electrocardiography, and chest radiography were performed. Total blood cell count, creatinine clearance and routine liver function tests were monitored before, and weekly during the cycle. The response was evaluated according to the recommendations of UICC, WHO and NCI (1979). The toxicity was evaluated using the scale recommended by the Southwest Oncology Group (13). Student's t-test was used for the statistical analyses.

Table 1

Patient characteristics

	Total	DC regimen	CMFVP regimen
Mean age (years)	53	52	54
Premenopausal	37	17	20
Menopausal	22	15	7
Postmenopausal	43	15	28
Mean disease free interval (months)	28	25	30
No previous hormonal or chemotherapy	26	13	13
Previous hormonal therapy	66	32	34
Previous hormonal and chemotherapy	10	2	8

Table 2

The chemotherapy regimens

DC regimen	
Doxorubicin	40 mg/m^2 intravenously on day 1
Cyclophosphamide	200 mg/m^2 orally on days 3, 4, 5 and 6
Duration of cycle 21 days. Maximum cumulative dose of doxorubicin 450 mg/m^2 if heart area previously irradiated, otherwise 550 mg/m^2 (7)	
CMFVP regimen	
Cyclophosphamide	50 mg × 3 orally on days 1 to 14
Methotrexate	50 mg/m^2 intravenously on days 1 and 8
5-fluorouracil	700 mg/m^2 intravenously on days 1 and 8
Vincristine	1 mg intravenously on days 1 and 8
Prednisone	60 mg per day orally on days 1 to 14
Duration of cycle 28 days (2)	

Results

The response rates in both groups appear in Table 3. The rate was 32 per cent in the DC group and lasted on average for 7.7 months; the corresponding values in the CMFVP group were 35 per cent and 11.2 months. The differences were not statistically significant. The complete response rates were 6.4 and 21.8 per cent, respectively. One patient in the CMFVP group showed a response that has lasted for 57 months, and is still continuing the treatment. This patient had liver metastases documented by ultrasound and coeliac arteriography. Another patient with metastases in the lung, bones and soft tissue recieved CMFVP regimens for 2 years. This patient is still without evidence of the disease 4 years and 8 months after the first cycle of chemotherapy. Most responders in both groups had multiple metastases (60% in the DC and 68% in the CMFVP group, Table 3).

In 14 patients the maximum cumulative dose of doxorubicin (450 mg/m^2 or 550 mg/m^2) was reached before progression of the disease. In these cases, the treatment was usually changed to CMFVP.

Toxicity. The observations regarding toxicity appear in Table 4. Haematologic toxicity was similar in the two groups. However, some cases of severe (degrees 3 and 4) leukopenia were seen in the DC group. Gastrointestinal toxicity, joint pain, fatigue and chin pain were seen more often in the DC group, and all patients in this group developed alopecia. Stomatitis, psychotic disorders, Cushing's disease, eye disorders, vertigo, diabetic complications, and vincristine-related mild neuropathy were observed more frequently in the CMFVP group. One patient in this group developed severe psychosis that led to suicide; this was the only toxicity-related death during the treatment. In another patient in this group severe haemorrhagic cystitis arose. The treatment was discontinued owing to severe toxicity in 8 cases in the DC group and in 5 cases in the other group.

Discussion

The response rates in patients with advanced breast malignancy, 32 per cent in the DC group and 36 per cent in the CMFVP group, were lower than in most other reports (2, 4, 6, 11, 13). A possible

Table 3

Number of responding patients correlated to the sites of the metastases and mean duration of the response (months; in parentheses)

	Complete response	Partial response	Stable disease	Progressive disease	Total
DC regimen					
Bone	–	2	6	1	9
Soft tissues	–	–	4	–	4
Viscera	–	4	3	1	8
Multiple	3	6	13	4	26
Total	3 (6.3)	12 (8.1)	26 (8.8)	6	47
CMFVP regimen					
Bone	–	–	1	3	4
Soft tissues	3	–	2	2	7
Viscera	2	1	4	2	9
Multiple	7	6	16	6	35
Total	12 (12.0)	7 (9.9)	23 (10.5)	13	55

Table 4

Toxicity of DC and CMFVP regimens (SWOG scale) (13)

	DC regimen	CMFVP regimen
WBC		
Degree 1	8	8
Degree 2	11	17
Degree 3	8	5
Degree 4	4	2
Platelets		
Degree 1	3	4
Degree 2	2	–
Degree 3	1	2
Degree 4	1	–
Gastrointestinal		
Degree 1	23	15
Degree 2	5	–
Degree 3	1	2
Stomatitis		
Degree 1	3	10
Degree 2	–	–
Cardial	4	3
Neuropathy	–	18
Cushing's disease	–	14
Psychotic disorders	1	6
Eye irritation	–	8
Vertigo	2	6
Cystitis	1	2
Others	4	9

reason for this might be that at the time of randomization, most of the patients in the present series (60%) had multiple metastases and most of them had received hormone treatment previously; similar observations have been reported by others (3, 8). However, the response rates and mean response durations were almost identical in the two groups, this also being in agreement with some previous reports (5, 6, 10, 13). Although complete remission occurred in the CMFVP group more often (12 cases) than in the DC group (3 cases), the difference was not statistically significant, perhaps owing to the relatively small number of patients. The difference could not be explained by different distributions of the metastases.

The mean age of the responders was almost the same in the two groups, but the patients with complete remission in the CMFVP group were somewhat younger (mean age 47 years). GEORGE & HOOGSTRATEN (3) reported that patients under 50 years responded more often to non-doxorubicin combinations.

In accordance with earlier reports, severe leukopenia was more frequent after DC than after CMFVP (8, 9, 13). Haematologic toxicity occurred less frequently in patients receiving combinations that included prednisone. No severe cases of thrombocytopenia were observed in the present material. Doxorubicin has been reported to have a platelet-sparing effect (6), as well as less frequent gastrointestinal side effects (5, 10), which agreed with the present observations. Stomatitis, neuropathy, eye disorders, and cortisone-related toxicity such as psychoses, Cushing's symptoms and diabetes were relatively more frequent in our CMFVP group than previously reported (12). The toxicity of both drug

combinations could be regarded as acceptable in this material, although toxicity caused discontinuation of treatment more often in the DC group.

If hormone receptors are assayed at the primary operation it might be preferable to start cytotoxic chemotherapy in receptor-negative cases with metastases without giving hormonal treatment. However, the selection of a chemotherapy regimen is extremely difficult, and unfortunately the present results do not provide much help in this question. At present we prefer CMFVP before DC because its mean response time was longer, and since the frequency of patients with complete remission was larger. In the future, analysis of the biologic activity of the breast cancer tissue might be helpful for selection of suitable chemotherapy for patients with advanced breast malignancy.

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