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Combination Chemotherapy With Epirubicin and Mitomycin C as First-line Treatment in Advanced Breast Cancer

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From December 1988 to February 1991, 112 consecutive patients were submitted to epirubicin + mitomycin C chemotherapy as first-line treatment for advanced breast cancer. Epirubicin (75 mg/m²) was given every 3 weeks and mitomycin C (10 mg/m²) every 6 weeks. Only patients with visceral involvement or with a disease-free interval of less than 12 months were considered eligible. 102 patients were evaluated for response and toxicity in the present analysis. The main sites of involvement were viscera, soft tissues, bone in 71 (69.6%), 19 (18.6%) and 12 (11.8%) patients, respectively. Multiple site involvement was present in 66 (64.7%) cases. A total of 726 courses of therapy were administered (range 2–14; mean 7.2). Follow-up ranged from 96 to 210 weeks (median follow-up 138 weeks). Response rate was complete response (CR): 21.6% [95% confidence interval (CI) ± 0.8], partial response (PR) 49.0% (95% CI ± 0.1), stable disease (SD) 12.7% (95% CI ± 0.1), progressive disease (PD) 16.7% (95% CI ± 0.1), CR+PR: 70.6% (95% CI ± 0.1). Median values of survival and time to progression were 79.4 and 42 weeks, respectively. At 2 years, 37.2±4.7% and 12.8±3.3% of the patients, respectively, were alive or without evidence of progression. Toxicity was generally mild. One hundred and four (14.3%) cycles in 53 patients were delayed due to haematological (82) or cardiac (3) toxicity, infectious disease (11) or causes not related to the treatment (8).

Key words: advanced breast cancer, chemotherapy, drug therapy, epirubicin, mitomycin C
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INTRODUCTION

ADVANCED BREAST cancer is an incurable disease and, even if many active antineoplastic agents are available, the aim of the treatment, at present, can be only palliation.

Nevertheless, availability of these agents allows us to control the disease for long periods of time and to improve the quality of life in the majority of patients. A prolongation of survival, on the contrary, can be hypothesised only in a minority of cases achieving a complete response.

With currently available first-line treatments, expected response rates range from 50 to 70% [1–12]. Anthracyclines (doxorubicin, epirubicin) are widely used in combination schedules and are considered the most effective drugs in the treatment of metastatic breast cancer. Mitomycin C has shown good activity but it is not so widely used in first-line combination chemotherapy, because of its potential for producing prolonged myelosuppression. Nevertheless, results of studies with mitomycin C–doxorubicin combinations [1, 2, 5, 9] showed response rates from 25 to 51% and demonstrated the feasibility of such treatment. The association of mitomycin C with the new anthracycline derivative epirubicin has demonstrated, in our experience with a small group of patients, comparable rates of response [12].

On this basis, a multicentric phase II study was opened to test epirubicin–mitomycin C association in a large number of patients affected by advanced breast cancer.

PATIENTS AND METHODS

Patient population

From December 1988 to February 1991, 112 consecutive patients with advanced breast cancer were allocated to receive epirubicin–mitomycin C chemotherapy. Eligibility criteria included histologically proven breast cancer, age ≤ 70 years, performance status ≤ 2 (WHO scale), progressive disease with measurable or evaluable lesions, no prior chemotherapy for the advanced disease, normal blood counts (white blood cells ≥ 4000/mm³, platelets ≥ 100 000/mm³), normal liver and kidney function tests, life expectancy ≥ 3 months. Myocardiopathy, presence of brain metastases or adjuvant chemotherapy with anthracyclines were considered criteria for exclusion. Only

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patients with visceral involvement and/or disease-free interval less than 12 months entered the study.

Therapeutic regimen

Treatment consisted of epirubicin, 75 mg/m^2 intravenously (i.v.), every 3 weeks and mitomycin C, 10 mg/m^2 i.v. every 6 weeks. Chemotherapy had to be discontinued in cases of disease progression, unacceptable toxicity or after six cycles if no response was observed. A total of eight cycles was suggested in case of response but investigators were free to continue chemotherapy according to their treatment policy. No dose reduction was allowed: in case of hematological, gastrointestinal or cardiac toxicity not permitting the scheduled administration of chemotherapy, the treatment was temporarily discontinued until recovery. Patients unable to receive chemotherapy after a maximum delay of 2 weeks were considered out of the study because of the recorded toxicity.

Response and toxicity criteria

Physical examination and blood counts were repeated before each cycle. Instrumental evaluation was performed every three cycles. Left ventricular ejection fraction measurements were optional, so no formal gradation of cardiac toxicity was attempted. Tumour response and toxicity were evaluated according to the WHO scoring system [13]. Response duration and survival were calculated from the first day of therapy. The calculation of life probability and time to progression was performed by the Kaplan–Meier method.

RESULTS

102 patients, out of the 112 who entered the study, are evaluable for response and toxicity. 10 were considered ineligible for evaluation: 7 did not satisfy the inclusion criteria (2 were > 70 years old, 3 had received prior chemotherapy for the advanced disease and 2 had received prior adjuvant chemotherapy including doxorubicin), 2 received an incorrect dose of epirubicin and 1 patient died before starting chemotherapy, for causes other than breast cancer.

Ages ranged from 28 to 70 years (mean age 55.8, median 55). 51 patients were pre- and 51 were postmenopausal. 24 patients had been submitted to adjuvant chemotherapy (cyclophosphamide/methotrexate/5-fluorouracil, CMF) and 29 to adjuvant hormonotherapy (tamoxifen), 43 had received hormonal therapy for the advanced disease and 30 had not received any treatment before starting epirubicin–mitomycin C chemotherapy. 42 patients had been submitted to previous irradiation of the breast (6 cases), breast plus supraclavicular nodes (6 cases), skeleton (12 cases), chest wall (left: 1 case; right: 2 cases), chest wall plus mammary chain (left: 5 cases; right: 1 case), chest wall plus mammary chain, axilla and supraclavicular nodes (left: 4 cases; right: 3 cases), mammary chain (2 cases). No patient received radiotherapy concurrently with chemotherapy. Multiple site involvement was present in 66 (64.7%) cases. The main sites of involvement were viscera, soft tissues and bone in 71 (69.6%), 19 (18.6%) and 12 (11.8%) patients, respectively. In 3 cases the skeleton was the only site of involvement. Sites of disease were soft tissue 40 (39.2%), nodes 45 (44.1%), lung 38 (37.2%), liver 43 (42.1%), bone 44 (43.1%), pleural effusion 11 (10.8%), peritoneal effusion 1 (0.9%). A total of 726 courses of therapy were administered (range 2–14; mean 7.2). 8 patients received more than eight cycles. Follow-up period ranged from 96 to 210 weeks (median follow-up 138 weeks).

Table 2. Response according to disease site

		No. of patients (%)				
	n	CR	PR	NC	PD	CR+PR
Bone	44	3(6.8)	12(27.3)	24(54.5)	5(11.4)	34.1%
Lung	38	13(34.2)	14(36.8)	6(15.8)	5(13.2)	71.8%
Liver	43	11(25.6)	18(41.8)	7(16.3)	7(16.3)	67.4%
Serosal effusion	12	7(58.3)	3(25.0)	2(16.7)	—	83.3%
Soft tissue	40	11(27.5)	18(45.0)	8(20.0)	3(7.5)	72.5%
Nodes	45	26(57.8)	13(28.9)	4(8.9)	2(4.4)	86.7%

CR, complete response; PR, partial response; NC, no change; PD, progressive disease.

Response rates (Table 1) were complete response (CR) 21.6% [95% confidence interval (CI) ± 0.8], partial response (PR) 49.0% (95% CI ± 0.1), stable disease (SD) 12.7 (95% CI ± 0.1), progressive disease (PD) 16.7% (95% CI ± 0.1). The overall response rate (CR+PR) in the total series was 70.6% (95% CI ± 0.1). In Table 2 the response rates by site of involvement are reported.

Survival (Figure 1) was 69.6±4.5% at 1 year and 37.2±4.7% at 2 years (median survival 79.4 weeks). Median time to progression was 42 weeks with 36.6±4.7% and 12.8±3.3% of the patients without evidence of progression at 1 and 2 years, respectively (Figure 2).

Table 3 shows the toxicity scores recorded as the worst episode appeared during treatment.

One hundred and four (14.3%) cycles in 53 patients were delayed due to haematological (82) or cardiac (3) toxicity, infectious disease (11) or causes not related to the treatment (8). More than one delay was observed in 29 patients. Treatment delay (mean value 8.3 days) was 1 week in 88 cycles and 2 weeks in 12 cycles. 4 patients required treatment discontinuation for

Table 1. Response rates in the total series and according to previous treatments

		Number of patients (%)				
	n	CR	PR	SD	PD	CR+PR
Total series	102	22(21.6)	50(49.0)	13(12.7)	17(16.7)	70.6%
Adjuvant chemotherapy	24	4(16.7)	10(41.7)	3(12.5)	7(29.1)	58.4%
Adjuvant hormone therapy	29	5(17.3)	17(58.6)	3(10.3)	4(13.8)	75.9%
No treatment	30	8(26.7)	15(50.0)	4(13.3)	3(10.0)	76.7%
Hormonotherapy for advanced disease	43	10(23.3)	21(48.8)	5(11.6)	7(16.3)	72.1%

CR, complete response; PR, partial response; NC, no change; PD, progressive disease.

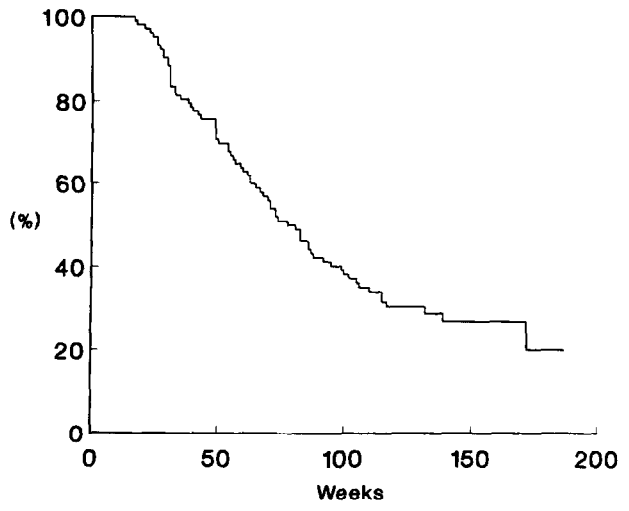

Figure 1. Overall survival in the total series.

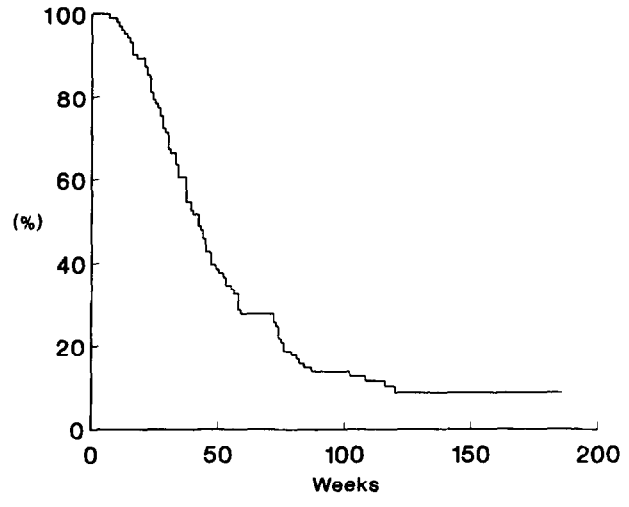

Figure 2. Time to progression in the total series.

longer than 2 weeks and went off study because of haematological toxicity (3 patients: 2 after six cycles while still responding and 1 after four cycles with no change of the disease) or causes not related to the treatment (1 patient). In 1 case the chemotherapy was discontinued after six cycles because of grade 3 oral mucositis. No discontinuation of chemotherapy was related to gastrointestinal toxicity. Cardiac toxicity was limited to rhythm alteration but one of these patients, who discontinued the chemotherapy after four cycles, died of heart infarction 2 weeks later without restarting the treatment. No patient required hospitalisation because of infectious disease or haematological toxicity.

Table 3. General toxicity

	Grade				
	1	2	3	4	3+4(%)
Leukopenia	32	22	2	0	1.9
Anaemia	38	9	2	0	1.9
Thrombocytopenia	0	2	1	0	0.9
Nausea/vomiting	22	38	18	1	18.6
Stomatitis/mucositis	15	14	1	0	0.9
Diarrhoea	2	1	0	0	—
Alopecia	1	13	86	0	84.3
Hepatic	1	0	1	0	0.9
Infection	7	5	0	0	—
Cardiac rhythm	4	4	3	0	2.9

All the 7 patients who experienced grades 2 or 3 cardiotoxicity had been submitted to radiotherapy of the following volumes: mammary chain (2 cases), chest wall plus mammary chain, supraclavicular nodes and axilla (right: 1 case; left, 2 cases), right chest wall (2 cases including the patient who died of heart infarction).

Apart from the 3 cases who went off study because of cytopenia, haematotoxicity did not represent a major problem during the administration. Long-lasting cytopenia after the completion of the treatment was infrequent and only 3 patients showed a grade 2 leucopenia, for periods ranging from 3 to 5 months. At the time of disease progression, 34 patients were submitted to second-line chemotherapy, mainly with regimens containing platinum derivatives. No patient was considered ineligible for this treatment because of cytopenia and no treatment discontinuation, apart from 3 cases of anaemia, was related to myelosuppression.

DISCUSSION

No consensus yet exists regarding which cytotoxic combination to employ as first-line treatment in advanced breast cancer, nevertheless it has been demonstrated that anthracycline-containing regimens, with respect to other cytotoxic combinations, increase response rates and improve time to progression and survival [14].

Our results with epirubicin–mitomycin C combinations are superimposable with those reported in the literature for first-line chemotherapy of advanced breast cancer.

The use of other regimens [1–11], with one or both the drugs employed in the present study, does not seem to further improve response rates.

The administration of the new anthracycline derivative epirubicin instead of doxorubicin, comparing the results of the present study with those employing the doxorubicin–mitomycin C association [1, 2, 5, 7–9], does not seem to affect the results as far as response rate, survival and time to progression are concerned.

Anthracycline dose intensity is probably the major factor influencing the outcome when epirubicin-containing regimens are adopted. Comparing the results of the present study with our previous experience [12], an increase in the epirubicin dose from 60 to 75 mg/m^2 produced a higher overall response rate (from 45.0 to 70.6%) and a slight improvement in response duration.

The response rate (70.6%) observed in the present study might be partially influenced by the criteria adopted in the selection of our cases. A higher number of patients with bone lesions, as usually reported in unselected series, might determine an increase of SD cases and lower the overall response rate. The difficulty in assessing the response of bone lesions is, in fact, well known [15]. Nevertheless, the results of the present study demonstrate that epirubicin–mitomycin C combination chemotherapy can be considered a safe and active treatment of advanced breast cancer.

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The Costs of Managing Severe Cancer Pain and Potential Savings from Transdermal Administration

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The economic evaluation of any new or existing therapy should include a comprehensive appraisal of costs. When evaluating pharmaceutical interventions, it is inappropriate to identify the purchase price alone. Other relevant costs include the costs of time of doctors, nurses and other personnel in administering and monitoring the effects of the therapy, and the costs of treating any side-effects. This study estimates direct National Health Service (NHS) costs in the U.K. of current medical practice in managing severe cancer pain, using a review of the published literature and constructing a cost analysis for four 'typical' patients. Costs are estimated for patients with severe cancer pain in a hospital and an ambulatory setting, with oral and subcutaneous routes of drug administration. The study includes costs of drugs, supplies, equipment and personnel time. The results demonstrate the importance of personnel time costs, and potential cost savings which could result from the use of transdermally administered opioid analgesics.

Key words: costs and cost analysis, opioid analgesics, pain management, transdermal administration
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INTRODUCTION

WORLDWIDE INFLATION in health care budgets has led to the emphasis of the need to investigate the costs of existing therapy, and to demonstrate the cost-effectiveness of any new therapies. In economic evaluation, drug therapy should not be considered in isolation but in the context of all other costs of patient care [1], for example, the costs of treating side-effects and the value of time savings in an industry where personnel costs exceed 70% of total expenditure.

In this study, estimates were made of the direct National