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Carminomycin Versus Doxorubicin in Advanced Breast Cancer, a Randomized Phase II Study of the E.O.R.T.C. Breast Cancer Cooperative Group

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Abstract—*Sixty-four patients with advanced progressive breast cancer resistant to conventional treatments were entered into the present study. They were randomized to receive either Carminomycin (CMM)* 20 mg/m^2 *or Doxorubicin (DOX)* 75 mg/m^2, *both drugs being administered by i.v. bolus every* 3 weeks *until progression of the disease. Five patients were not eligible and response could not be evaluated in another eight patients. Three patients had only one course due to disease-related early death. Among twenty-seven evaluable patients who received at least two courses of DOX one complete response and seven partial responses were observed for an overall response rate of* 30%. *CMM showed significantly lower* (P = 0.04) *antitumor activity with only one partial response* (4%) *among the* 24 *patients who received at least two courses of therapy.*

Median duration of response dating from the start of chemotherapy was 46 weeks *on DOX (range* 18–102+) *and* 30 weeks *for the single partial response on CMM. Although the median time to progression for all patients receiving CMM* (9 weeks) *was significantly shorter* (P = 0.04) *than for those receiving DOX* (30 weeks), *patients on DOX had only a marginally longer duration of survival* (P = .28) *than those initially treated with CMM. Myelotoxicity was more severe in the CMM treated group than in the DOX group. Other toxicities such as alopecia, nausea and vomiting were slightly more severe in the DOX treated group. On the basis of this and other similar randomized studies, CMM cannot be recommended for further application in the treatment of advanced breast cancer.*

INTRODUCTION

DOXORUBICIN is still the most active chemotherapeutic agent against advanced breast cancer [1]. The occurrence, however, of congestive heart failure with chronic administration [2] has led to investigations of the activity of new anthracycline derivates with lower cardiotoxic potential.

Carminomycin was isolated from Actinomadura carminata in the U.S.S.R. [3]. In several experimental systems the drug proved to be more active than Doxorubicin and Daunomycin [3–5]. The inhibitory effect against normal human bone marrow is substantially greater [6]. Studies employing the Zbinden rat model [7] showed that Carminomycin produced less cardiac damage than Doxorubicin as evidence by less focal necrosis [8].

Clinical data from the U.S.S.R. [9] indicated that Carminomycin was active against soft tissue sarcomas, lymphomas and acute leukemia. Initial data also suggested activity against breast, gastric, ovarian and uterine cancers [8–10]. In phase I trials leukopenia was found to be dose-limiting, whereas gastrointestinal intolerance and alopecia appeared less pronounced than with Doxorubicin [6,9,11].

This randomized phase II trial was initiated to assess the antitumor effectiveness of Carminomycin in patients with advanced breast cancer, using Doxorubicin as a control group. This design has been previously used by other E.O.R.T.C. groups [12, 13].

MATERIALS AND METHODS

Eligibility criteria

Patients, 20–75 yr of age, with histologically

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proven recurrent or metastatic breast cancer were eligible for this study. Patients were required to have measurable and/or evaluable progressive disease and a WHO performance status of 0–2. Recurrent tumor in irradiated areas was not permitted as the sole evaluable lesion. Lymphoedema, hilar enlargement, pleural effusion, ascites, marrow suppression, and osteoblastic skeletal lesions were not considered to be measurable. Previous treatment with conventional combination chemotherapy was allowed, provided the treatment had been withdrawn for at least 4 weeks prior to entry and all toxic manifestations had been resolved. Previous treatment with anthracyclines was not permitted. Other criteria for exclusion were a previous or concomittant second malignant tumor, congestive heart failure or other serious concurrent disease, and central nervous system metastases. Prior to entry patients were required to have adequate hepatic excretory function (serum bilirubin <50 μmol/l) and bone marrow reserve (leucocytes $\geq 4.0 \times 10^9$/l, platelets $\geq 100 \times 10^9$/l).

Trial design

After stratification by institution, patients were randomized to receive either Doxorubicin (NSC-123127) or Carminomycin (NSC-180024). Patients showing disease progression after two courses of Carminomycin were crossed over to the Doxorubicin arm, while those failing on Doxorubicin went off-study. In the event of disease stabilisation or response patients continued therapy until progression or until the maximum cumulative dose of the drug was received.

Therapeutic regime

Doxorubicin (DOX) 75 mg/m^2 was given as an i.v. bolus once every 3 weeks. Continuation of therapy beyond a cumulative dose of 550 mg/m^2 was not recommended, but was left at the discretion of the individual investigator.

Carminomycin (CMM) 20 mg/m^2 was given as an i.v. bolus once every 3 weeks. The potential for cardiotoxicity was unknown and no specific recommendations were made about cumulative dose. (Carminomycin was supplied by Bristol–Myers, New York.)

Dose modifications during treatment

For both drugs (DOX or CMM) the dose was reduced by 50% if serum bilirubin was between 35 and 50 μmol/l. Treatment was discontinued if the bilirubin went above 50 μmol/l. If the WBC count was below 3.0×10^9/l or the platelets below 100×10^9/l 3 weeks after the last course, treatment was postponed for 1 week. At this time, if the WBC were between 2.0 and 2.9×10^9/l or platelets between 75 and 99×10^9/l, therapy was continued at 50% dose. If the counts were below these levels treatment was postponed by another 1–2 weeks.

Adjustments for the nadir count in previous courses were: WBC $2.0–2.9 \times 10^9$/l or platelets $50–74 \times 10^9$/l, Doxorubicin 75% dose, Carminomycin 90% dose; WBC $<2.0 \times 10$g/l or platelets $<50 \times 10$g/l, Doxorubicin 50% dose, Carminomycin 75% dose. Dose escalation was not permitted. Patients went off-study if haematological toxicity delayed retreatment for more than 3 weeks.

Pretreatment and follow-up investigations

Baseline studies included history and physical examination, WHO performance status, tumor measurements, complete blood count, biochemical tests (alkaline phosphatase, aminotransferase, LDH, bilirubin), chest X-ray, ECG and, when indicated to estimate tumor size, CT-scanning or ultrasound scanning. Echocardiography and radionucleide cardiac scans were performed in some centres.

Haematology had to be evaluated every 3 weeks at least, in order to adjust dosage according to WBC and platelet values. All other investigations were repeated after every two to four courses of chemotherapy.

Definition of response

Patients were considered evaluable for response if they had received a minimum of two courses of chemotherapy and if tumor measurements had been repeated 3 weeks after the second cycle. Response criteria were those defined by WHO [15]. Patients dying before 6 weeks were classified as early death.

Toxicity

All side effects due to treatment were systematically recorded and graded according to WHO criteria [15].

Statistical design

An initial patient entry of 29 evaluable patients in each arm was required, with termination of the study if three or fewer responses were observed in either arm. There was provision to stop the study if no response was reported in the first 19 patients in either arm. This plan ensured that if the anthracycline analogue had a true response rate of at least 25%, the probability of rejecting it from further study was <0.05.

RESULTS

Patient Characteristics

A total of 64 patients from five institutions were entered from March 1981 to May 1982. Of the 34 patients randomized to Doxorubicin, 5 were not

fully evaluable for the following reasons: protocol violation (1), loss to follow-up (1), only one course of therapy due to early death (3) (disease-related in two and unrelated in one).

Of the 30 patients randomized to Carminomycin 25 were evaluable for response. Three were ineligible, two had inadequate blood counts and one was too old, and another three were not fully evaluable: one patient had only one course due to disease-related early death, one patient refused treatment and another one received insufficient treatment, less than 75% of the calculated dose.

Nearly all patients had been pretreated with the Cyclophosphamide, Methotrexate and 5-Fluorouracil combination and had received prior hormonal therapy.

Patient characteristics are shown in Table 1.

Table 1. *Patient characteristics*

Characteristic	Carminomycin	Doxorubicin
No. of patients	30	34
Age (yr)		
Median	57	58
Range	30–69	37–73
WHO Performance		
Score		
Median	1	1
Range	0–3	0–3
Prior treatment		
None	1	0
Surgery	24	28
Radiotherapy	24	30
Hormonal therapy	18	23
Chemotherapy	26	31
Predominant metastatic site		
Soft tissue	3	8
Bone	12	13
Visceral	15	13

Antitumor effect

Of the 25 evaluable patients in the Carminomycin group, one patient (4%), having soft tissue lesions only, achieved a partial response lasting for 23 weeks. Eleven patients had no change after two courses while the 13 remainders showed progressive disease. Of the 29 patients in the Doxorubicin arm one complete response of visceral metastases lasting for 30 weeks and seven partial responses were observed (see Table 2).

The overall response rate of 28% with Doxorubicin is significantly higher than the 4% yielded by Carminomycin ($P = .04$).

Twelve patients crossed over from Carminomycin to Doxorubicin. Eight only are evaluable for response, whereas among the four remainders one died within 6 weeks and three are not evaluable because of inadequate treatment, the only measurable lesion was irradiated and refusal after one course. One partial response, five no-changes and two progressions were observed in this cross-over group.

The median duration of response was 46 weeks on DOX (range 18–102+ weeks). The median time to progression in all evaluable patients was 9 weeks in the Carminomycin-treated group and 30 weeks in the Doxorubicin group ($P < .001$, logrank test).

The median duration of survival in all eligible patients was 7 months in the Carminomycin and 12 months in the Doxorubicin treated group (Fig. 1). Although the response rate in the Doxorubicin treated arm is significantly higher than that with Carminomycin, the difference in survival is not statistically significant ($P = .28$, logrank test).

Toxic effects

The haematological toxicity observed during the first two courses resulted in a median leucocyte nadir of 1.6×10^9/l (range 0.6–2.6) for CMM and 2.5×10^9/l (range 1.8–3.7) for Doxorubicin. The corresponding median platelet nadir was 35.5×10^9/l (range 17–118) for Carminomycin and for Doxorubicin 125×10^9/l (range 90–165).

Table 2. *Response to first-line anthracycline by dominant site of disease*

	No. of patients with Carminomycin				No. of patients with Doxorubicin				
Dominant site of disease	Total	PR	NC	PD	Total	CR	PR	NC	PD
Soft tissue	3	1	1	1	6	0	3	3	0
Osseous	8	0	5	3	11	0	3	6	2
Visceral	14	0	5	9	12	1	1	2	8
Total	25	1	11	13	29	1	7	11	10

Note: CR = Complete response; NC = No change; PR = Partial response; PD = Progressive disease.

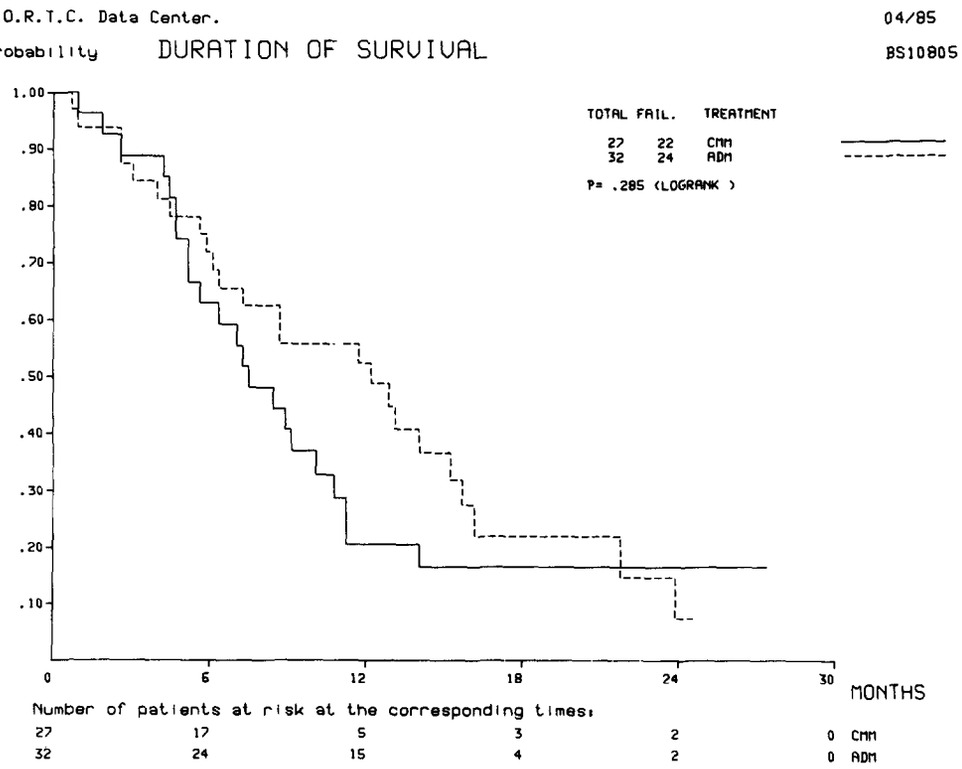

Fig. 1. Survival curves with Carminomycin (——) and with Doxorubicin (-----). Curves were determined according to the Kaplan–Meier method.

The non-haematological toxicities encountered are summarized in Table 3. The frequency and the grade of alopecia seemed less severe with Carminomycin than with Doxorubicin. It must be mentioned that all but one patient who switched from Carminomycin to Doxorubicin stated that they subjectively tolerated Carminomycin better than Doxorubicin. This better tolerance is not very well substantiated in the toxicity grading.

Table 3. Percentage of patients with non-haematological side-effects

Toxic effect	Carminomycin (25 pts)	Doxorubicin (31 pts)
Nausea/vomiting	90	93
Alopecia	76	89
Stomatitis	19	21
Diarrhoea	14	7
Cardiac	14	20
Infection	29	17

DISCUSSION

The results of this study are in agreement with earlier reports in the literature of a response rate of 25–30% for single agent Doxorubicin as second line treatment in advanced progressive breast cancer.

Our data and the data reported by the EORTC Early Clinical Trials Group [13] in a similar group of patients show that Carminomycin has only marginal activity in breast cancer with response rates of 4 and 3% respectively. The earlier reports (summarized in [10]) about the activity of Carminomycin could not be confirmed. Even recently Aboud *et al.* [14] reported a 29% response rate with Carminomycin in CMF (VP) resistant patients. There have been suggestions that these discrepancies could be attributed to the different treatment regimens. The M.D. Anderson Group [14], however, applied the same regimen as the E.O.R.T.C. Groups. In the U.S.S.R. reports a twice weekly regimen has been applied.

A recent publication about the pharmacokinetics of Carminomycin applied in different regimens failed to show major pharmacokinetic differences [16]. The bi-weekly regimen in pretreated breast cancer patients has also been demonstrated to be myelotoxic but devoid of activity [17]. The lack of activity of Carminomycin is disappointing also in relation to its toxicity because notwithstanding the higher myelotoxicity observed, the other non-haematological toxicities were inferior in grade to Doxorubicin. This was especially apparent in the group of patients who switched after failure on Carminomycin to Doxorubicin, where all but one

patient claimed that the side effects were more tolerable with the initial drug.

The requirement of the cross-over in failing patients which was adhered to in most patients, makes it ethically less difficult to perform this type of study in which a drug known to be active is compared to a new derivative which may potentially be less active. This is also supported by the nearly superimposable survival curves for both groups, whatever their initial treatment was.

In conclusion, on the basis of our data and others obtained in similar randomized studies with Carminomycin, this drug cannot be recommended for further use in advanced breast cancer.

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