A Prospective Randomized Trial of Doxorubicin Versus Idarubicin in the Treatment of Advanced Breast Cancer

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Seventy-six patients with advanced breast cancer were entered into the current study. They were randomized to receive either idarubicin (IDA) 45 mg/m^2 orally or doxorubicin (DX) 75 mg/m^2 intravenously (IV), both drugs being administered every 3 weeks. Among 37 evaluable patients who received DX treatment the overall response rate was 46%, whereas it was 21% in 34 evaluable patients treated with IDA. This difference was statistically significant. In previously untreated patients the response rate with DX was 60% compared to 29% with IDA. Patients with prior chemotherapy had 29% response rate to DX in contrast to 12% with IDA. The median time to response, the median response duration, and the median time to progression were similar in both groups. The median survival of all patients was 20 months in DX arm and 14 months in IDA arm (95% confidence limits 16.69–23.31 and 10.77–17.23, respectively; $P = 0.09$). Both treatments produced equivalent incidence and severity of myelotoxicity. Gastrointestinal toxicity and alopecia were significantly lower in patients receiving IDA. As for cardiotoxicity, four cases of congestive heart failure were recorded among patients treated with DX whereas no cases occurred in the IDA group. The results of this study indicate that, although DX remains the best single agent available in the treatment of breast cancer, IDA may have a role in selected patients with this disease.

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DOXORUBICIN (DX) is the most active single cytotoxic agent in the treatment of advanced breast cancer, but cumulative dose-limiting cardiotoxicity has reduced its usefulness. Furthermore, pronounced vomiting, hair loss, and tissue necrosis by accidental extravasation can be severely distressing. For these reasons, during the last decade efforts have been made to produce anthracycline analogs devoid of these side effects but still retaining antitumor activity.

Idarubicin (4-demethoxydaunorubicin, IDA) is an analog of daunorubicin lacking the methoxyl group at position 4 of the aglycone, which has been shown to be active by the oral route.[1] Toxicities noted in preclinical studies paralleled those of the parent compound, but cardiac toxicity in mice and rabbits was comparatively lower.[2]

In a previous Phase II study of oral IDA in advanced breast cancer[3] we observed a 23% response rate in 22 evaluable patients previously treated with various chemotherapeutic regimens, including an anthracycline in more than 50% of the cases. Unpleasant side effects had an acceptable incidence, and were generally well tolerated.

Consequently, a comparative trial of DX and oral IDA seemed warranted to better evaluate the relative usefulness of the two drugs.

Materials and Methods

Seventy-six patients with histologically proven recurrent or metastatic breast cancer were admitted to the study. Eligibility criteria included age ≤ 70 years, Karnofsky performance status > 50, and measurable progressive disease. Lymphedema, hilar enlargement, pleural effusion, ascites, marrow depression, and osteoblastic skeletal lesions were not considered measurable lesions. Patients may have had prior hormonal treatment and one prior combination chemotherapy regimen, provided that treatment had been stopped for at least 4 weeks before entry, and anthracyclines had been excluded. Previous or concomitant radiotherapy was acceptable if it did not include marker lesions. Initial leukocyte count > 4000/mm^3 and platelet count (PLT) > 100,000/mm^3 as well as adequate hepatic and renal function (bilirubin ≤ 1.5 mg/dl, creatinine ≤ 1.5 mg/dl) were required. Patients were excluded from the trial if they had a history of congestive heart failure, active cardiac disease or a left ventricular ejection

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fraction (LVEF) at rest lower than 50%, a history of other malignancies (except for carcinoma *in situ* of the cervix or skin cancer), central nervous system (CNS) involvement, or active infection. All patients were fully informed with regard to the experimental nature of the treatment program and an informed consent was obtained.

The pretreatment evaluation included history and physical examination, automated blood cell count, biochemical profile, chest radiograph, electrocardiogram (ECG), radionuclide angiography, liver ultrasound echography, and skeletal survey. When indicated, additional studies were done. Blood counts were obtained on day 1 and then at least every 7 days. Physical examination, blood chemistry tests and ECG were repeated at each course, whereas LVEF was determined every three courses and 4 to 8 weeks after the end of the treatment. Chest radiograph and liver ultrasound scanning were repeated at every alternate course if initially abnormal. Other scans and radiographs were performed every three courses.

After stratification by previous chemotherapeutic treatment (yes or no), patients were randomly allocated to receive either DX, 75 mg/m^2 by intravenous (IV) bolus, or IDA, 45 mg/m^2 by mouth. IDA was supplied by Farmitalia Carlo Erba as a red powder in 5-mg, 10-mg, and 25-mg capsules and was administered 3 hours after dinner.

In patients of both arms standard antiemetics, generally metoclopramide, were used.

Cycles were repeated every 3 weeks until progression, until unacceptable toxicity precluded further therapy, or until a cumulative dose of 600 mg/m^2 for DX and 360 mg/m^2 for IDA was reached. After reaching the maximum cumulative dose, possible further treatment was decided on individual basis.

Efforts were made to administer full drug dosages. Treatment was postponed if there was no full hematologic recovery by day 21. A maximum delay of 2 weeks was allowed. Afterwards, the dose was reduced by 25% for leukocyte count between 3000 to 4000/mm^3 or PLT between 75,000 to 100,000/mm^3, and by 50% for leukocyte count between 2000 to 3000/mm^3 or PLT between 50,000 to 75,000/mm^3. In case of lower values of either leukocyte count or PLT, treatment was discontinued.

The dose of either drug was reduced by 50% if serum bilirubin was > 1.5 to 3 mg/dl. Treatment was discontinued if the bilirubin was > 3 mg/dl, or if there was a decrease in LVEF of ≥ 20% from basal values or below 50%.

Response and toxicity were evaluated according to World Health Organization (WHO) criteria.[4] Patients were required to have had a minimum of two courses of chemotherapy in order to be evaluable for response.

Survival and time to progression were measured from day of randomization.

Comparison of patient characteristics, response rates, and toxicity incidence and grade was performed using the chi-square test. Time to progression and survival curves were calculated by the Kaplan-Meyer method,[5] and were compared using the log-rank test.[6]

Results

Between October 1985 and June 1987, a total of 76 patients were entered into this study (39 DX, 37 IDA). Seventy-three were evaluable for toxicity (38 DX, 35 IDA), and 71 for response (37 DX, 34 IDA). Three patients were not considered evaluable for toxicity and efficacy because of refusal of treatment after randomization (one DX, one IDA), and being lost to follow-up after one cycle (one IDA). Two patients, although evaluable for toxicity, were considered inevaluable for efficacy: one lost to follow-up after one cycle of DX, and one died after the first course of IDA. The cause of death was unknown, but not related to toxicity.

Patient pretreatment characteristics are shown in Table 1. The two groups were comparable with respect to age, performance status, menopausal status, disease-free interval, and prior treatment. There were some differences in the distribution of patients by dominant disease site and number of metastatic sites. These differences were not statistically significant, in part because of the small sample size.

Response to treatment are outlined in Table 2. The objective response rate in patients with no prior chemo-

TABLE 1. Clinical Characteristics of Patients

	Doxorubicin	Idarubicin
Evaluable patients	37	34
Median age, yr (range)	55 (30–67)	55 (33–67)
Premenopausal/postmenopausal	3/34	4/30
Median Karnofsky performance status (range)	80 (90–60)	80 (90–60)
Disease-free interval in yr (no.)		
0–1	10	9
1–5	23	22
>5	4	3
Dominant site of disease (no.)		
Soft tissue	8	16
Osseous	14	10
Visceral	15	8
No. of disease sites		
1	32	25
2	5	5
3	0	4
Prior treatment		
Surgery	36	32
Radiotherapy	9	9
Hormonal therapy	14	18
Chemotherapy	17	17
None	1	2

TABLE 2. Response Rates

	Doxorubicin		Idarubicin	
	No.	Percent	No.	Percent
Response to treatment				
CR	4/37	11	2/34	6
PR	13/37	35	5/34	15
CR + PR	17/37	46	7/34	21
No change	18/37	49	15/34	44
Progression	2/37	5	12/34	35
Response by dominant site				
Soft tissue	4/8	50	5/16	31
Bone	3/14	21	1/10	10
Visceral	10/15	67	1/8	12.5
Response by no. of disease sites				
1	14/32	44	6/25	24
2	3/5	60	1/5	20
3	—	—	0/4	0
Response by prior chemotherapy				
No prior chemotherapy	12/20	60	5/17	29
Prior chemotherapy	5/17	29	2/17	12

CR: complete response; PR: partial response.

therapy was 60% with DX compared to 29% with IDA. Patients with prior chemotherapy had 29% response rate to DX in contrast to 12% with IDA. Overall, response rates were 46% for DX group and 21% for IDA group, with four and two CR, respectively. This difference was statistically significant ($P = 0.02$). There was no significant difference in the number of patients who achieved stabilization of disease. Responses at sites of involvement were similar for soft tissue and bone lesions, whereas patients with visceral metastases had a higher response rate in the DX arm ($P = 0.02$). With respect to number of disease sites there was no significant difference in response rate between the two groups.

The median time to response, the median response duration, the median time to progression, and the median survival time are shown in Table 3. No significant difference was found between the two treatment arms. The median times to progression were 4 months and 3 months for patients treated with DX and IDA, respectively (Fig. 1; $P = 0.36$). The median survival of all patients was 20 months (95% confidence limits 16.69–23.31) in DX arm and 14 months (95% confidence limits 10.77–17.23) in IDA arm (Fig. 2; $P = 0.09$).

As shown in Table 4, the most common side effects were nausea, vomiting, alopecia, and myelosuppression. Both treatments produced equivalent incidence and severity of bone marrow toxicity, with a much greater effect on suppression of leukocyte count than on PLT and erythrocytes. One patient treated with DX and one patient treated with IDA had prolonged leukopenia and chemotherapy had to be discontinued in both. Significantly less ($P = 0.02$) nausea and vomiting occurred in patients receiving IDA. Stomatitis was also less frequently observed in this group of patients compared to DX ($P = 0.001$). Several patients received a considerable amount of IDA without hair loss.

Cardiac toxicity is reported for the 69 patients (37 DX, 32 IDA) in whom at least two radionuclide angiographies were performed. Linear regression analysis of interval change in LVEF measurements (Fig. 3) showed a highly significant difference between the two groups ($P = 0.0001$). This difference was first detected at cumulative doses of 450 mg/m^2 of DX and 270 mg/m^2 of IDA. Absolute decreases in LVEF of $\geq$ 20% were recorded in 18 patients treated with DX and only in two patients receiving IDA. Treatment was promptly discontinued in these patients, as it was in another IDA patient whose LVEF decreased below 50%, although the absolute decrease was only 6%. However, four DX patients developed congestive heart failure (CHF) after total doses of 600, 600, 600 and 750 mg/m^2, respectively. None of the three IDA patients developed cardiac dysfunction, and their LVEF improved to normal in the months after the discontinuation of the treatment.

Discussion

In recent years it has become clear that, with the currently available drugs, the goal of treatment in advanced breast cancer is to alleviate symptoms and prolong survival with minimal alteration to the quality of life. Therefore, there has been a continuous search of new effective drugs easy to administer and causing few side effects. Virtually, IDA meets all these requirements: it has been reported to be effective in metastatic breast cancer with an acceptable incidence of unpleasant side effects,[3] and it is available in an oral formulation with obvious practical advantages.

When dealing with oral chemotherapy two frequently cited problems are patient compliance and variability of the absorption of the agent. In this study, nadir leukocyte counts were carefully assessed and their pattern suggests that all patients took the drug as prescribed. No patient admitted to not taking the prescribed drug, and in the only case in which all capsules were vomited immediately, the full dose of the drug was administered the day after.

TABLE 3. Response Duration and Survival

	Doxorubicin	Idarubicin
Median time to response, mo (range)	2 (1–6)	2 (1–6)
Median response duration, mo (range)	6 (3–15)	5 (4–22+)
Median time to progression, mo (range)	4 (1–10)	3 (1–9)
Median survival, mo (range)	20 (3–31)	14 (1–30)

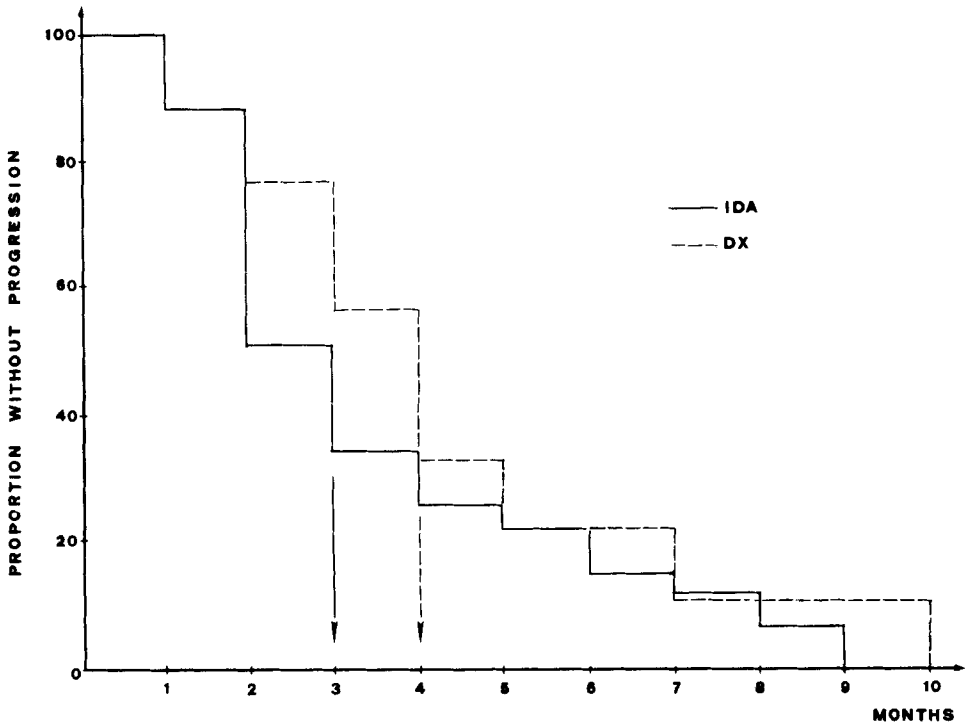

FIG. 1. Time to progression from initial treatment randomization.

The wide range of nadir leukocyte counts (600–6200/mm^3) observed suggests that erratic absorption of the drug may have occurred. Nevertheless, in only three patients myelosuppression was not recorded, and one of these benefited of a long-lasting complete response (CR). Thus, it seems that the observed response rate is not related to the poor absorption of the drug.

The main question to be answered, however, is whether IDA may have a role in the treatment of recurrent or advanced breast cancer in comparison to other anthra-

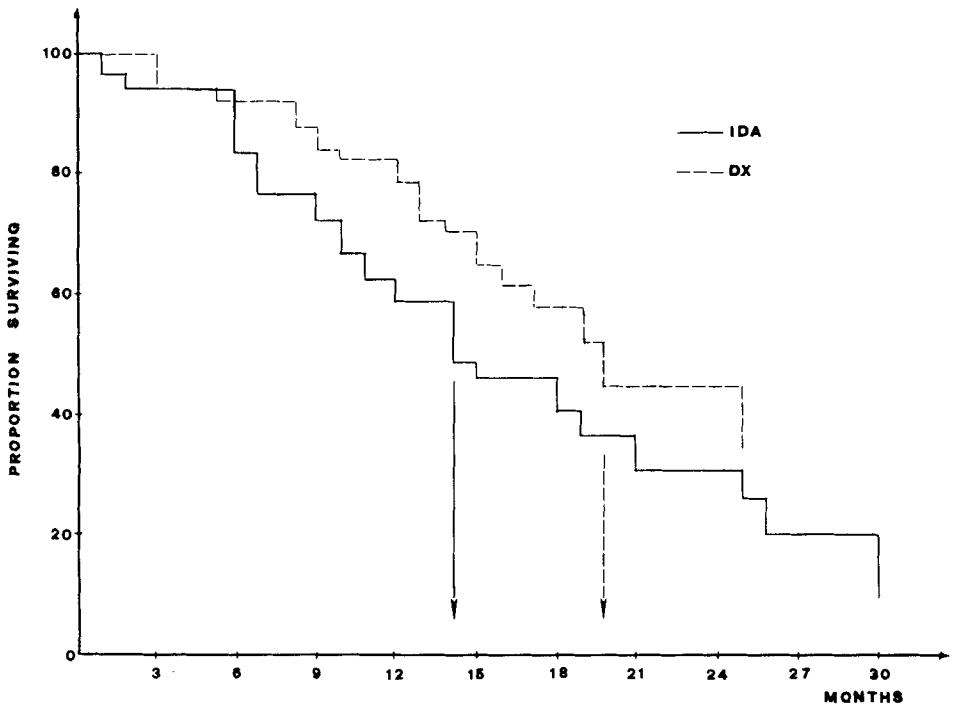

FIG. 2. Survival for all patients from initial treatment randomization.

TABLE 4. Non-Cardiac Toxicity in 73 Patients

	No. of patients resulting in grade*											
	Doxorubicin						Idarubicin					
	0	1	2	3	4	Total (%)	0	1	2	3	4	Total (%)
Nausea and vomiting	0	2	11	24	1	100	5	4	11	14	1	86
Stomatitis	18	9	6	5	0	53	33	2	0	0	0	6
Diarrhea	34	3	0	1	0	11	27	5	2	1	0	23
Alopecia	1	1	2	34	0	97	24	9	2	0	0	31
Cutaneous	34	2	0	2	0	11	35	0	0	0	0	0
Anemia	21	11	4	1	1	45	23	7	3	2	0	34
Leukopenia	4	13	9	10	2	89	5	12	6	10	2	86
Thrombocytopenia	31	1	3	3	0	18	29	3	1	1	1	17
Cystitis	33	2	3	0	0	13	33	2	0	0	0	6

* According to Miller *et al.*[4]

cyclines, namely DX, which is the single most active agent in this disease but produces considerable subjective and objective toxicity.

In this comparative trial of DX *versus* oral IDA, response rate was significantly higher in patients treated with DX (46%) than in those receiving IDA (21%). This difference, however, probably due to the small sample size, did not translate into a significant improvement of other parameters of treatment efficacy. Response duration and time to progression were virtually identical in both groups, and survival times were not significantly different in the two treatment arms.

Idarubicin was better tolerated than DX. Overall, gastrointestinal toxicity and alopecia were significantly more pronounced in patients treated with DX than in those given IDA. However, most important is the evidence of the lower cardiotoxic potential of IDA.

Although a > 20% decrease in LVEF was recorded in two cases (at cumulative doses of 225, and 270 mg/m^2), this was transient in nature, and seven patients received > 315 mg/m^2 of IDA, with two patients having 540 mg/m^2, without cardiac toxicity. In the DX group there were four instances of CHF, and ten patients were withdrawn from the study for toxicity while on remission (two CR, eight partial responses [PR]). It could be debatable whether the higher response rate with DX has really produced a greater and longer palliation of the disease.

Several other studies of oral IDA, using a 21-day sched-

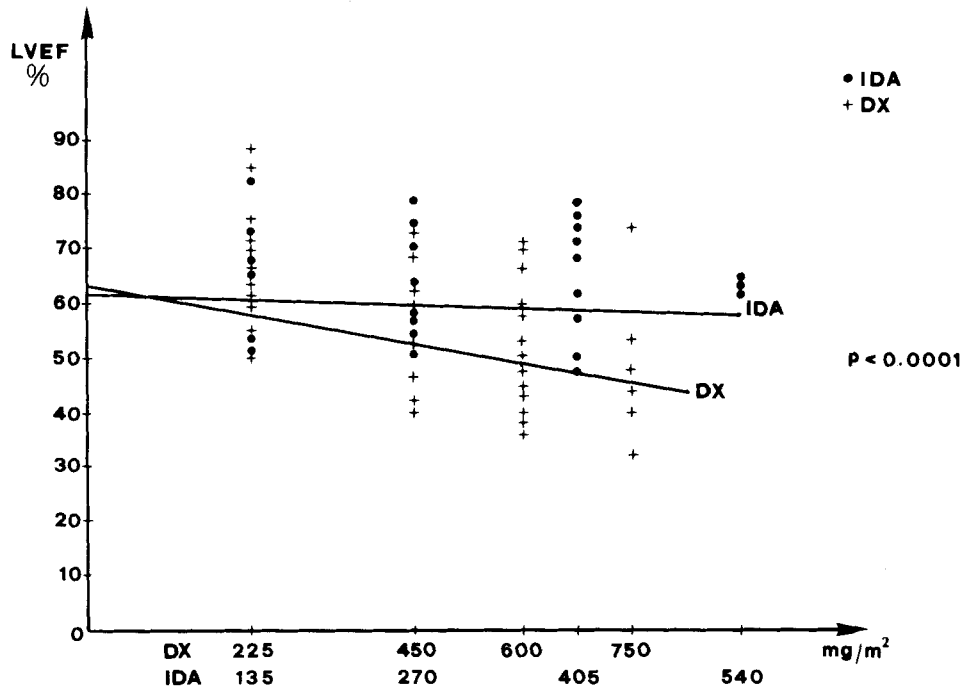

FIG. 3. Linear regression analysis of interval change in LVEF measurements in patients receiving DX or IDA.

ule in patients with advanced breast cancer, have reported response rates ranging from 5% to 41%.[3,7-15] The overall response rate in these studies has been 25% (76/307), which is similar to the one observed in the current trial. As in this study, responses were seen in all disease sites, although more frequently in soft tissue, and sometimes they were long lasting. Better results have been observed in previously untreated patients with an overall response rate of nearly 39%.[9,12]

On the whole, the current results provide further evidence that DX remains the best single agent available in breast cancer treatment. Nevertheless, as reported in other studies,[16,17] the high activity of the drug in terms of response rates only minimally affects ultimate survival, and the risk of severe toxicity precludes its use in some patients and reduces its usefulness in others. Therefore, there may be some circumstances (slow-growing tumors, metastatic lesions confined to soft tissues, patients with psychologic disturbances or living in remote areas or refusing to take intravenous chemotherapy) in which the use of less active but better tolerated drugs could be more appropriate. In these instances, as well as in patients with poor venous access, IDA can be of value. Furthermore, it is not unlikely that in the future, with more information about the different degree of cardiotoxicity of the two drugs, the cardiac status of the patient will be the most important selection criterion.

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