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Short Communication

Combination of Oral Idarubicin and Prednimustine in Advanced Breast Cancer: a Phase II Study

A. Barnadas,[1] C. Mendiola,[2] A. Casado,[3] A. Villar,[4] J. Jimeno,[5,6] M. Clerigue,[5,7] R. Rosell,[1] E. Diaz-Rubio,[3] H. Cortés-Funes[2] and M. García de Paredes[5]

[1]Department of Medical Oncology, Hospital Germans Trias y Pujol, Crta. Canyet s/n, 08916 Badalona; [2]Department of Medical Oncology, Hospital Doce de Octubre, Madrid; [3]Department of Medical Oncology, Hospital San Carlos, Madrid; [4]Department of Oncology, Hospital Arnau de Vilanova, Valencia; [5]Medical Department, Pharmacia-Upjohn, Madrid; [6]Pharmamar R + D, Tres Cantos, Madrid; and [7]FAES R + D, Bilbao, Spain

The aim of this study was to assess the efficacy and toxicity of an idarubicin–prednimustine combination in advanced breast cancer. 19 patients received idarubicin 35 mg/m^2 day 1 and prednimustine 100 mg/m^2 days 2–6, every 21 days. Three objective responses with a median duration of 7 months were observed. Tolerance was good. A further 23 patients were given idarubicin administered at 15 mg/m^2 days 1, 2 and 3 and prednimustine at the aforementioned dosage. 8 (35%) showed an objective response (4 CRs, 4 PRs) with a median duration of 6 months. No severe toxicity was observed. Results suggest activity of idarubicin–prednimustine combinations in advanced breast cancer, and further studies are indicated since this regimen is easily administered, especially to elderly patients. **© 1997 Elsevier Science Ltd. All rights reserved.**

Key words: advanced breast cancer, chemotherapy, idarubicin, prednimustine

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INTRODUCTION

ANTHRACYCLINES, PARTICULARLY doxorubicin and 4-epidoxorubicin, have proved very active in the treatment of solid tumours. Both substances produce the same adverse effects, including nausea, vomiting, myelotoxicity and accumulated dose-related cardiotoxicity. These drugs are administered intravenously with the inherent risk of soft tissue damage due to extravasation. The oral administration of cytotoxic drugs could improve quality of life and reduce health care costs [1–4].

Idarubicin is the only oral daunorubicin analogue, and has 30–40% bioavailability. Metabolised in the liver, it is transformed into idarubicinol which shows higher cytotoxic activity than daunorubicin. The mechanism of action is similar to that of the other anthracyclines [1–4].

Several phase II studies have shown the efficacy of this drug in advanced breast cancer both as a single agent or in a combined drug regimen [1–4]. However, some studies have reported a cytotoxic effect comparable to that of doxorubicin [5], but have been unable to confirm these results [6]. Usual doses of idarubicin administered in monotherapy are between 35 mg/m^2 and around 25 mg/m^2 in combination. Preclinical studies have shown idarubicin to have lower toxicity, especially in the heart [6, 7].

To date, few studies have used oral cytotoxic drug combinations. However, the idarubicin–cyclophosphamide combination has been assessed in several studies, showing objective response rates ranging from 22 to 49% [8–10].

Prednimustine is an alkylating agent which combines a chlorambucil ester and prednisolone and has proved to be active in metastatic breast cancer, even in previously treated patients. Moreover, in a comparative study, prednimustine appeared superior to chlorambucil plus prednisolone given separately [11]. Its activity justifies its use in advanced breast cancer with a theoretically different mechanism of action [12]

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Correspondence to A. Barnadas.
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tered at two different doses in patients with disseminated breast cancer.

PATIENTS AND METHODS

42 patients with histologically confirmed advanced breast cancer were studied. Inclusion criteria were: age younger than 75 years, general physical status lower than 3 on the ECOG scale, locally advanced or measurably disseminated disease, absence of previous hormone- or chemotherapy (with the exception of adjuvant therapy without anthracyclines, stopped 4 weeks prior to inclusion in the study), adequate cardiac function (analysed by ventricular ejection fraction determination, which should be over 50%), blood counts and renal function within normal limits, liver function lower than twice normal values and absence of other neoplasms. Informed consent was obtained from all patients.

Pretreatment evaluation consisted of complete clinical history and physical examination, complete blood and biochemical studies, chest X-ray, serial bone X-ray, bone scintigraphy, abdominal ultrasound and an isotopic ventriculogram at rest. Chest and abdominal CT were performed when indicated.

Blood count was measured on days 1, 14 and 21 of each cycle. Biochemical studies, response and toxicity evaluation were performed every 21 days. EKG was recorded every two cycles and the ventriculogram and other studies every three cycles.

Regimen I consisted of oral idarubicin 35 mg/m^2 day 1 and prednimustine 100 mg/m^2 days 2–6, every three weeks. Regimen II consisted of idarubicin 15 mg/m^2 days 1–3 and prednimustine as before. Treatment was maintained provided there was no disease progression or until a total idarubicin dose of 600 mg/m^2 was reached.

The prednimustine dose was reduced by 25% if leucocyte or platelet counts on day 14 were below 1×10^9/l or 25×10^9/l, respectively. Similarly, treatment was delayed one week if the leucocyte count on day 21 was not above 4.5×10^9/l or platelet count was below 100×10^9/l. If on day 28, the leucocyte and platelet counts failed to reach 2.5×10^9/l and 100×10^9/l, respectively, the next cycle was postponed for 7 days. Treatment was suspended if these blood counts had not been recovered by day 35. Treatment was also withdrawn if there was a 25% reduction in the ventricular ejection fraction relative to the baseline value.

Idarubicin was supplied by Pharmacia-Upjohn in 5, 10 and 25 mg capsules and administered correspondingly in a single daily dose. Similarly, prednimustine (Pharmacia-Upjohn) in 20 and 100 mg capsules was administered in a single daily dose.

WHO criteria were used to evaluate response and toxicity [13]. Only patients who received at least two cycles were considered for response evaluation. The Kaplan–Meier method was used to estimate probability of time to progression and survival.

RESULTS

Regimen I included 19 patients and regimen II 23; patient characteristics are shown in Table 1. Bone and soft tissue were the predominant disease locations and most patients had more than one metastasis.

Four cases in regimen I could not be evaluated for response: one due to rapid disease progression in the first cycle, another due to death from intercurrent disease (cerebro-vascular accident) and the remaining two because they refused to continue treatment; all patients were evaluated for toxicity. All women included in regimen II were evaluated for response and toxicity.

Table 1. Patient characteristics and overall response

	Regimen I Idarubicin (35 mg/m^2)	Regimen II Idarubicin (45 mg/m^2)
No. of patients	19	23
Mean age (years)	60	57
Disease location		
Soft tissues	2	8
Soft tissues + bone	6	4
Soft tissues + viscera	4	6
Soft tissues + viscera + bone	1	2
Bone + viscera	3	2
Viscera	3	1
Previous treatment		
Adjuvant	9	10
Disseminated disease	3	4
Adjuvant + disseminated	1	2
Mean number of disease locations	2	2
Complete remission	1 (5%)	4 (17%)
Partial remission	2 (11%)	4 (17%)
Stable disease	7 (37%)	5 (23%)
Progression	5 (26%)	10 (43%)
Not evaluable	4	
Overall response rate	16%	35%
95% CI	3–40%	15–54%

CI, confidence interval limits..

Table 2. Toxicity grades III and IV

	Regimen I Idarubicin (35 mg/m^2)		Regimen II Idarubicin (45 mg/m^2)	
	G-3	G-4	G-3	G-4
Leucocytes	0	0	0	0
Neutrophils	0	0	0	0
Haemoglobin	0	1	2	0
Platelets	1	0	0	0
Nausea—vomiting	0	0	3	1
Mucositis	0	0	1	0
Diarrhoea	1	0	3	0
Infection	1*	0	1	0
Haemorrhagia	0	0	0	1†

G, WHO grade toxicity.

*Herpes zoster infection on the leucocyte nadir.

†Gastrointestinal bleeding coinciding with altered hepatic function due to liver metastases.

Regimen I*: idarubicin* 35 *mg/m^2: response and toxicity evaluation*

The õverall objective response was 16% (95% CI limits: 3–40%). One patient with previous adjuvant tamoxifen and lymph-node disease achieved complete remission. Two others showed a partial response, observed in skin–lymph nodes. Skin and lymph nodes showed the highest response rate when analysed by locations (33%). Finally, all patients with an objective response had a single-site metastasis. Median response duration was 7 months while median time to progression was 27 weeks. Median survival was 12 months. An average of four cycles per patient was administered (range: 1–17). Haematological toxicity, grades III and IV, registered in a small number of patients with this therapeutic combination and is described in Table 2. No chemotherapy-related deaths occurred. However, subsequent cycles were delayed in some patients owing to mild leucopenia (grades I and II), leading to a decrease in dose intensity. Non-haematological toxicity was also slight in most patients. No cardiac toxicity was observed.

Regimen II*: idarubicin* 45 *mg/m^2: response and toxicity evaluation*

The overall objective response was 35% (95% CI: 15–54%). A complete response was recorded in four cases, two in lymph nodes and two in soft tissue. A partial remission, also in skin–lymph nodes, was detected in four cases (Table 1). The median response duration was 6 months, median time to progression 18 weeks and median survival 11 months.

An average of four cycles per patient was administered (range: 1–15). Haematological toxicity, grades III and IV, is described in Table 2. Mild leucopenia or thrombocytopenia delayed the start of subsequent cycles. One patient showed a 12% decrease in the ventricular ejection fraction compared with basal values, but no clinical congestive heart failure.

DISCUSSION

The anthracycline idarubicin has proved to be active in disseminated breast cancer, both in monotherapy and polychemotherapy regimens [3, 4, 8–10, 14, 15]. The activity spectrum of idarubicin has been compared with that of doxorubicin, but results are inconclusive [5, 6].

In combination, idarubicin resembles that of other therapeutic regimens, with a mean response duration of 6 or 7 months [8–10].

However, to date, there have been no results of studies comparing the efficacy of an oral polychemotherapy regimen with that of a therapeutic regimen with anthracyclines, such as FAC, which might serve as a reference. In our experience, the idarubicin–prednimustine combination has shown a cytotoxic effect in breast cancer with response rates similar to those of other treatment combinations [5, 6, 8–10, 14, 15]. As in other studies [8, 9], the highest response rate was observed in skin and lymph nodes. No tumour regression, although reported by others [9, 15], was observed in bone or viscera. Other authors used a lower idarubicin dose than that used in our study, but combined with cyclophosphamide [9, 10] or doxifluoridin [15].

Tolerance and toxicity of the treatment were acceptable and there were no therapy-related deaths. Nevertheless, some cases presented mild leucopenia which slowly recovered by day 21. This led to a delay of subsequent cycle administration and a reduction in prednimustine doses with a slight decrease in dose intensity of the regimen. Furthermore, no cases of permanent alopecia, mucositis or cardiac toxicity were observed.

The advantage of such regimens lies in their oral administration which avoids the risk of extravasation inherent in the use of the other anthracyclines, and offers better tolerance leading to improved quality of life, although this aspect was not evaluated in detail in this study.

Finally, oral chemotherapy combinations may constitute a valid alternative in the therapy of disseminated breast cancer, particularly in elderly women. Further studies evaluating higher-dose oral idarubicin combined with other less myelotoxic drugs, which permit increased dose intensity and minimise the risk of severe haematological toxicity, should be undertaken.

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