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Phase II Trial of Idarubicin (4-Demethoxydaunorubicin) in Advanced Breast Cancer

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Abstract—*A phase II trial of idarubicin (IDR-4 demethoxydaunorubicin) was carried out in patients with advanced breast cancer. A dose of* 45 mg/m^2 *was given orally once every* 3 *weeks. A total of* 66 *eligible patients were entered into the trial,* 56 *of whom were evaluable for response* (65 *were evaluable for toxicity at least). Therapeutic activity was demonstrated with an overall objective response rate of* 21% (95% *CI*: 11–32%). *When used as a first-line treatment, the response rate was* 33% (95% *CI*: 9–57%) *but this dropped to* 17% *when the treatment was administered after chemotherapy. Nausea-vomiting was the most frequent and severe non-hematological toxicity observed (WHO grade* 3–4: 29%). *Loss of hair was noticed in* 48% *of the patients but only* 4% *suffered from complete alopecia. Moderate myelotoxicity was reported but no cardiac dysfunction was noticed. IDR could be very advantageous as compared to other anthracyclines, due to its simplicity of administration associated with the lack of risk of extravasation or chemical phlebitis and also the possibility of it being able to reduce cardiotoxicity. Even if the equiefficacy of IDR and DXR has not, as yet, been clearly demonstrated, IDR should be chosen with preference to DXR when administration is not suitable.*

INTRODUCTION

IDARUBICIN (IDR) is a new derivative of daunorubicin (DNR) synthesized by Farmitalia Carlo Erba, Milan, and obtained by substituting the C-4 methoxyl group in the D-ring of the aglycone moiety by an atom of hydrogen [1]. IDR was found to be active in a variety of experimental murine tumors and significantly more potent than doxorubicin (DXR) or DNR [1, 2] by both oral and parenteral routes of administration [3]. It was shown to have less cardiotoxicity in mice [4, 5] at equieffective dosages.

Pharmacokinetic studies initially conducted in rats showed, after oral and i.v. administration, an oral absorption of about 50% of the dose [6].

Pharmacokinetic studies conducted in man showed that the mean bioavailability of the unchanged compound was about 30% of the dose [7]. These studies showed that much higher and longer lasting plasma levels of the 13-hydroxy derivative (idarubicinol) were obtained compared to those of the parent compound. The high levels of idarubicinol observed, already reached within the first hour of administration [8], can be explained by an extensive metabolization of IDR in the liver through a first-pass effect process [9, 10]. Bearing in mind that idarubicinol has been shown to be as potent and active as IDR, either *in vitro* or *in vivo* [11–13], this metabolic characteristic could certainly contribute to the clinical activity of IDR when it is administered orally.

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Phase I studies carried out with IDR given orally showed that myelosuppression, in particular leukopenia, was the dose-limiting toxicity. The recommended dosage for phase II trials was 40–50 mg/m^2 for a single administration given every 3 weeks [14–16]. In September 1983, the Clinical Screening Group of the European Organization for Research and Treatment of Cancer (EORTC) initiated a phase II study of oral idarubicin in patients with advanced breast cancer.

MATERIALS AND METHODS

The study was confined to patients with histologically proven breast cancer. IDR was administered to both previously treated and untreated patients. All patients presented a progressive disease (WHO criteria [17]). The patients had to fulfill the following conditions to be considered eligible for entry into the study: be aged between 15 and 75 years,* have a performance status (according to the ECOG scale) of 0–2, have documented and measurable or evaluable lesions (primary tumor, cutaneous or subcutaneous metastases, nodal or visceral metastases); have not received prior chemotherapy within the preceding 3 weeks; granulocytes (PNM) ≥2000/mm^3; platelet count ≥100,000/mm^3; have a normal hepatic or renal function; have an estimated survival time >2 months; no prior clinical history of cardiovascular disease (an isotopic or echocardiographic assessment of the left ventricular ejection function was a prerequisite for entry into the trial).

Patients who had inflammatory breast cancer, a history of pre-existing heart disease, a history of other malignancy (with the exception of skin cancer or carcinoma *in situ* of the cervix), or an active infection were not eligible for this trial.

Informed consent was obtained from each patient according to the standard procedures followed by every participating institution.

Idarubicin was supplied by Farmitalia Carlo Erba Research Laboratories, and provided as hard gelatin capsules containing doses of 1, 5, 10 and 25 mg. Idarubicin was given in a single oral dose of 45 mg/m^2 and repeated at an interval of 21 days.

In conformity with the prescriptions of our EORTC protocol, at least two cycles of treatment must have been given to be able to consider the patient as being evaluable for efficacy. The patients who had received a minimum of one cycle of therapy were only considered evaluable for toxicity. Therapeutic activity and toxicity were evaluated according to the World Health Organization criteria [17]. Non-responding patients were considered as 'stable disease' if they had not progressed by the time the third course was due to be given. Bone lesions, brain metastases, ascitic and pleural effusions were not considered as being evaluable lesions, but the progression or occurrence of new lesions at those sites were considered as being a progressive disease.

*Patients younger than 70 years of age who had received a prior cumulative anthracycline dose between 250 and 400 mg/m^2 had to have a normal resting left ventricular ejection fraction (LVEF). Patients over 70 had to have received a cumulative anthracycline dose of less than 250 mg/m^2 and have a normal LVEF.

RESULTS

Sixty-six eligible patients were entered in the study between September 1983 and December 1985, 56 of whom were evaluable for response (65 were evaluable at least for toxicity).

One patient was not considered evaluable for toxicity and efficacy because she had been undertreated. Nine patients (13.6%) were not considered evaluable for efficacy although they were evaluable for toxicity. There were four early deaths: two patients did not receive the second course of treatment due to a rapid deterioration of their general performance status (the WHO PS given as grade 2 at entry was probably overestimated); one patient died 2 weeks after having received the first administration of IDR and the other less than 4 weeks after; one patient reported a septic shock; one patient had peritonitis which was not drug-related; five other patients were not considered as being evaluable because only one cycle of treatment had been given (four early progressions, one increase of bilirubin level above the maximal limit allowed by the protocol).

The main characteristics of the patients evaluable for response are reported in Table 1. Fifteen patients did not receive any prior chemotherapy. Forty-one received prior chemotherapy (adjuvant treatment only: 16, chemotherapy for advanced disease: 25). The median number of drugs previously administered was four (range: 3–7). Thirty-one out of these 41 received a prior anthracycline (adjuvant: 11, advanced: 20). Seventeen of these 31 patients

Table 1. Patient characteristics

Patients	Sex	Female	56
	Age	Median	57
		Range	35–73
Performance status at entry		WHO grade 0	12
		1	28
		2	16
Dominant site		Soft tissue	28
		Visceral	28
Pretreatment with chemotherapy			41
with adriamycin			31
Number of prior drugs			Median: 4, Range: 3–7

received at least 250 mg/m^2 of doxorubicin (three of these 17 patients were considered to be resistant to doxorubicin).

THERAPEUTIC ACTIVITY

An overall objective response rate of 21% (95% CI: 11–32%) was obtained (Table 2). This response rate was clearly related to prior chemotherapy. IDR used as first-line treatment induced a response rate of 33% (95% CI: 9–57%), but when used after chemotherapy (with or without an anthracycline) the rate dropped to 17% (P value = 0.01: chi-square test for trend). Five patients responded after having received an anthracycline treatment (adjuvant treatment: 3 patients, advanced treatment: 2 patients). The response rate according to the tumor site is shown in Table 3; interestingly enough, the response rate observed in the visceral target lesions is in the same range as that observed in the soft tissue and node target lesions. There was a 42% response rate in pulmonary metastases which demonstrated a high sensitivity to IDR treatment. The median duration of response measured from the date of first treatment administration to the date of relapse was 30 weeks (Kaplan–Meyer estimate). For six patients the treatment was stopped while in PR, and the duration of response was censored at the date of last treatment administration. Reasons for stopping treatment were: treatment refusal: 3 patients, maximal cumulative dose (730 mg/m^2): one patient, surgical resection of the remaining lesion: one patient, patient remaining in partial remission after eight courses, cross-over to another treatment, one patient. One to four courses of treatment with IDR were needed to be able to observe a PR in the responding patients (median 3).

TOXICITY

The incidence and intensity of the treatment side-effects are reported in Tables 4–6. Nausea and vomiting were the most frequent side-effects reported and also the most severe non-hematological toxicities. Severe vomiting (WHO grade 3–4) was recorded in 28% of the patients (2 patients grade 4). Hair loss was seen in 47% of the cases; complete alopecia was noticed in only 4% of the patients. Patients were considered as being evaluable for the assessment of hematological toxicity if weekly blood counts had been taken. In 43 patients this was done at least once during the whole treatment. Myelotoxicity was found to be moderate in the evaluable patients. The median WBC of the nadir was 1.7 × 10^3/mm^3 (range 0.3–8.8 × 10^3/mm^3) reported on day 15 as a median (range 7–24) after the first course of IDR. As shown in Table 5, 33% of the evaluable patients recovered at day 21 of each cycle (20 out of 60 patients with 4000+

Table 2. Responses according to prior treatment

			Pretreated		Non-pretreated
	Non-pretreated	Pretreated	Without DXR	With DXR	With DXR*
PR	5	7	2	5	7
SD	9	11	4	7	13
PD	1	23	4	19	5
Total	15	41	10	31	25
RR	33%	17%	20%	16%	28%
95%	9–57%	6–29%	0–45%	3–29%	10–46%

*I.e. patients pretreated or not but no DXR previously given.

Table 3. Response by site

	Primary	Lymph node	Cutaneous	Lung	Liver
CR	—	—	—	1	1
PR	3	8	5	4	2
NC	7	16	12	3	3
PD	1	1	8	4	9
Total	11	25	25	12	15
Response rate	27%	32%	20%	42%	20%
95% CI	1–54%	14–50%	4–36%	14–70%	0–40%

Table 4. Grade (WHO)

	0	1–2	3–4	Total evaluable
Nausea-vomiting	6	40	18	64
Diarrhea	51	11	3	65
Oral	60	5	—	65
Renal	65	—	—	65
Fever	65	—	—	65
Alopecia	33	24	5	62
Infection	57	5	2	64
Cardiotoxicity	64	1	—	65

WBC/mm^3) and 58% reported at least 3000+ WBC/mm^3 (35 out of 60 patients). Seventy-four per cent of the evaluable patients (i.e. 32 out of 43) reported nadir values below 2000 WBC/mm^3 at least once during the whole treatment period. The median nadir of the platelet count, after the first course, was 148 × 10^3/mm^3 (range, 15–545 × 10^3/mm^3). Only one patient had less than 75,000 platelets at day 21 during the whole treatment period.

No cases of congestive heart failure were reported and none of the patients had to receive any modification of the IDR treatment due to cardiac dysfunction. Only one case of tachycardia was reported (the treatment had not been modified). No reduction of FEV normal values was recorded after the administration of IDR.

CUMULATIVE DOSES OF ANTHRACYCLINES

Patients evaluable for response (i.e. 56 patients) received a median of four courses (range 2–17). Responders received a median of eight cycles (range 3–17). A total dose of 161 mg/m^2 of IDR was given (range 65–722 mg/m^2). Four patients received more than 450 mg/m^2 of IDR.

Patients pretreated with DXR (i.e. 31 patients) had received a median of 250 mg/m^2 DXR (range 39–450 mg/m^2) before entering the trial.

Thirteen patients received DXR after failure on IDR. The median dose received was 240 mg/m^2 (range 61–397 mg/m^2). Consequently, cumulative doses of IDR + DXR reached a median of 390 mg/m^2 (range 74–722 mg/m^2). Ten patients received more than 600 mg/m^2 of IDR + DXR (Table 6).

DISCUSSION

When IDR is used as a single drug given orally every 3 weeks at a dose of 45 mg/m^2, it has been proved to have a certain activity against breast cancer. In this trial, IDR showed an interesting response rate in visceral lesions, which recommends its use in advanced breast cancer. From a clinical point of view, it seems obvious that IDR is sufficiently rapidly and well absorbed if we take into consideration the clinical activity and toxicity recorded.More than 70% of the evaluable patients

Table 5. Leucopenia (WBC/mm^3)

	<1 × 10^3	1–2 × 10^3	2–3 × 10^3	3–4 × 10^3	>4 × 10^3	Total
Nadir first course	7	16	12	4	4	43
Nadir (all courses)	10	22	6	3	2	43
Day 21 first course	—	4	10	17	22	53
Lowest value at day Day 21 (all courses)	1	4	20	15	20	60

Table 6. Cumulative doses of anthracyclines

	DXR before	IDR	DXR after	Total DXR + IDR
Doses mg/m^2			Nbr patients	
<100 mg/m^2	2	16	1	2
<200	9 (2)	16 (2)	3	10 (1)
<300	7 (1)	13 (4)	6 (1)	8 (2)
<400	11 (1)	7 (3)	3	9 (1)
<500	2 (1)	2 (1)	—	7 (2)
<600	—	1 (1)	—	10 (3)
<700	—	—	—	8 (1)
700+	—	1 (1)	—	2 (2)

( ) responders.

reported a nadir value of less than 2000 WBC/mm^3 at least once during the whole treatment period, despite the fact that 60% of the patients had had vomiting events (grade 2–4). To be more precise, 43 patients were evaluable for assessment of both nausea-vomiting and leucopenia after the first cycle of treatment. Thirty-six patients suffered from no nausea-vomiting to moderate nausea-vomiting (WHO grade 0–2), five of whom reported a WBC count lower than 1×10^3/mm^3 (i.e. 14%). Seven patients suffered from severe nausea-vomiting (grade 3–4), two of whom reported WBC <1000/mm^3 (i.e. 29%). The above results show that the dose of IDR given to patients suffering from severe nausea-vomiting has been properly absorbed, although it has been orally administered. In our data, severe gastro-intestinal toxicity does not seem particularly correlated with less leucopenia (i.e. an impaired oral intake of idarubicin). The results obtained in this study are consistent with those reported earlier by other investigators [18–22].

Another interesting point to take into consideration is the drastic difference in activity between oral and intravenous administration of IDR. IDR given intravenously at myelotoxic doses is minimally active against breast cancer [21]. The first-pass effect of IDR giving high plasma levels of idarubicinol could explain this difference since idarubicinol is an active metabolite and has a terminal half life at least twice as long as IDR.

The major side-effects of IDR given orally are nausea and vomiting. A significant decrease of this toxicity might be obtained by using more effective anti-emetic drugs and/or by dividing the total dose into three daily administrations [22].

Due to the small number of patients involved in an on-going comparative study [23], no conclusive demonstration as to the equiefficacy of IDR and DXR can, at the present time, be proved. However, there exists at least one major indication when i.v. administration of anthracyclines is not suitable. The IDR compound could be advantageous as compared to other anthracyclines, because of the possible reduction of cardiotoxicity and the absence of risk of phlebitis associated with leaking through the vein wall.

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