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Activity of 4-Demethoxydaunorubicin by the Oral Route in Advanced Breast Cancer

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Abstract—*The new anthracycline-analogue 4-demethoxydaunorubicin (4-DMDR) was administered orally at the dose of* 15 mg/m² *daily for three consecutive days and repeated every* 21–28 days *on* 29 *patients with advanced pretreated breast cancer. A partial remission was observed in* 7/25 *evaluable patients* (28%) *for a median duration of* 7 months. *Side-effects include leukopenia in* 93% *of the patients* (<1000 WBC/mm³ *in* 7%), *nausea in* 41%, *mild vomiting in* 17%, *diarrhea in* 10% *and alopecia in* 10% *of the patients. No definitive conclusion is possible regarding cardiotoxicity. Only mild changes in ECG were observed in two patients. This study shows that 4-DMDR administered orally is well tolerated in the majority of patients and has antitumor activity in advanced breast cancer.*

INTRODUCTION

4-DEMETHOXYDAUNORUBICIN (4-DMDR; idarubicin, IMI-30) is an analogue of daunorubicin (DN) which has shown a more potent antitumor activity in a variety of experimental tumors than the parent drug [1]. Unlike doxorubicin (DX), 4-DMDR is also active orally in mice bearing experimental leukemias and solid tumors [2]. DN is also active orally but at very high and toxic doses. In addition, 4-DMDR has been shown to have a reduced cardiotoxic effect in comparison with either DN and DX in animals [3, 4].

Phase I clinical trials (5–8) have shown the dose-limiting side-effect is myelosuppression both by i.v. and oral administration and that after a single oral dose vomiting is more frequent than after i.v. administration. The doses recommended for phase II trials were 12.5–15 mg/m² by i.v. administration and 40–50 mg/m² by a single oral administration.

A phase II study on the oral use of 4-DMDR in advanced breast cancer was carried out at the Division of Oncology, S. Orsola-Malpighi Hospital in Bologna. The dose determined by phase I clinical trials was administered over three consecutive days in order to reduce gastrointestinal toxicity. The aims of the study were to evaluate the toxicological profile and the antitumor activity of this regimen in a doxorubicin-sensitive tumor such as advanced breast cancer.

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MATERIALS AND METHODS

The study was carried out on patients with histologically proven advanced breast cancer resistant or no longer responsive to a standard treatment (at least one hormonal and cytotoxic treatment). The criteria of eligibility were the following: measurable or evaluable progressive disease, no antitumor treatment in the last 30 days, prognosis > 2 months, performance status (according to Karnofsky) > 40%, WBC count > 4000/mm³, platelet count > 100.000/mm³, hemoglobin > 9 g%/ml and cardiac, renal and hepatic functions within the normal limits. Signed informed consent was obtained from all patients.

4-DMDR, supplied by Farmitalia Carlo Erba s.p.a. in 5 mg and 10 mg capsules, was administered as a single dose of 15 mg/m² daily at noon for three consecutive days. The course was planned to be repeated every 21 days until disease progression. Before admission to the trial all patients had a history and a physical examination, a complete blood count and an SMA 12 test, EKG, chest and bone X-rays and other instrumental examinations (X-rays, isotopic scan, echography) if necessary. Patients were submitted to a complete blood count once or twice a week after

each treatment course. A physical examination, biochemical analysis and EKG were repeated before each subsequent course while instrumental assessment was made every two courses. A complete remission (CR) was defined as the disappearance of all tumor lesions for at least 1 month. A partial remission (PR) was defined as a >50% decrease of the product of the largest diameter by the greatest perpendicular diameter of all measurable lesions or the partial recalcification of osteolytic metastases for at least 1 month. A stationary condition of bone lesions for at least 3 months with a simultaneous >50% decrease of other measurable tumor lesions was considered a PR. No change (NC) was defined as a <50% decrease or a <25% increase of the tumor lesions. Progression (P) was defined as a ≥25% increase in the surface of only one lesion or the appearance of a new neoplastic lesion. Only patients who had received at least two courses were considered for response assessment.

RESULTS

From January 1983 to July 1984 29 patients were admitted to the study and their main characteristics are reported in Table 1. Many patients received their treatment on an outpatient basis. All of the female patients were postmenopausal or had previously received oophorectomy. All had received chemotherapy and/or hormonal therapy. The median number of cytotoxic drugs received previously was 3 (range 0-6). Chemotherapy included predominantly the CMF regimen (cyclophosphamide, methotrexate, fluorouracil), while hormonal therapy included medroxyprogesterone acetate and/or tamoxifen. No patient had previously received DX.

The median number of courses administered per patient was 3 (range 1-14) and the total cumulative dose of the drug was 135 mg/m² (range 45-630). Five patients received a total cumulative dose > 300 mg/m². Two patients received their first course at the reduced dose of 7.5 mg/m² daily for 3 days but on the second course the drug was administered at full dose because of the lack of side-effects.

Four patients were not evaluable for clinical response: in two patients the treatment was interrupted after the first course because of rapidly progressive disease, while the other two patients did not come back after one and two courses respectively.

The objective responses are reported in Table 2. Out of 25 evaluable patients seven achieved a PR. The remissions involved cutaneous lesions in three patients, cutaneous with stationary conditions in bone lesions in two others, bone (recalcification) in another and peritoneal metastases with ascites in the last. The median duration of PR was 7 months, with range from 4+ to 13 months. Out of seven responders five had previously received chemotherapy.

All the patients were evaluated for toxicity. The incidence and intensity of the observed side-effects are reported in Table 3. Leukopenia (WBC <

Table 1. Characterization of the patients

		Breast cancer (29 patients)
Sex: M/F		1/28
Age: median (range)		55 (25-72)
Performance status: median (range)		60 (40-90)
Free interval (months): median (range)		24 (0-87)
Dominant lesion		
ST		7
O		9
V		13
No. of sites		
1		9
2		10
3 or more		10
Prior treatments		
Radiotherapy		20
Chemotherapy:	1 regimen	19
	2 regimens	5
Hormonotherapy:	1 regimen	12
	2 regimens	15

Table 2. Objective response

	No.	%	Median duration (range) (months)
CR	—		—
PR	7	28	7 (4+ - 13)
NC	7	28	4 (1-9)
P	11	44	
Total evaluable patients	25		

Table 3. Side-effects (29 patients)

	Grade*				
	1	2	3	4	Total (%)
Leukopenia	10	10	5	2	27(93)
Thrombocytopenia	1	1	—	—	2(7)
Anemia	7	4	—	—	11(38)
Nausea	12	—	—	—	12(41)
Vomiting	—	4	1	—	5(17)
Diarrhea	3	—	—	—	3(10)
Stomatitis	1	—	—	—	1(3)
Alopecia	—	3	—	—	3(10)
Fever	2	1	—	—	3(10)
Headache	3	—	—	—	3(10)
Asthenia	—	1	1	—	2(7)
ECG	2	—	—	—	2(7)

*Grading according to Miller *et al.* [9].

4000/mm³) was seen in 93% of the patients. The median nadir was 3350 leucocytes/mm³ (range 0.5–9200) on day 15 (range 5–27) after the first course of 4-DMDR. Recovery occurred on average on day 25 (range 8–51). Consequently in the majority of the patients the interval between the first two courses was longer than the planned 21 days. Two patients had a nadir of 500 WBC/mm³, one after the first course and one after the third. Both patients were heavily pretreated with radiotherapy and chemotherapy and one had widespread bone involvement. In the second of these patients the next course was administered at a dose reduced by 50% while in the first the treatment was interrupted because of rapidly progressive disease. Transient anemia occurred in 38% while thrombocytopenia was seen only in 7%. Nausea was observed in 12 (41%) patients and mild vomiting occurred 2–3 hr after the administration of the drug in five (17%). In only one case was vomiting severe and required intense antiemetic treatment. Alopecia was observed only in three patients and it was partial and reversible. No liver dysfunction was evident.

Only mild and transient EKG variations were observed in two patients (atrial premature beats, left anterior hemiblock). There were no cases with signs of clinical cardiotoxicity. Angiocardiography was performed at the end of the treatment in three patients who had received a cumulative total dose of 405, 495 and 630 mg/m². The left ventricular ejection fraction (EF) was 45, 63 and 50% respectively. In the subsequent follow-up none of these patients developed symptoms or signs of congestive heart failure.

DISCUSSION

DX is probably the most active antitumor drug in the treatment of advanced breast cancer but its use is limited by a cardiotoxic effect.

4-DMDR is one of the new anthracycline-analogues which is currently being studied in an effort to identify drugs with a better therapeutic index and particularly with a lower cardiotoxicity. Preclinical studies have suggested that 4-DMDR has antitumor activity also when given orally, unlike DX and DN which are inactive and less active respectively by the oral route [3, 4]. After oral administration 4-DMDR gave tumor to heart and spleen concentration ratios twice those after i.v. DN and 1.5 times higher than after i.v. 4-DMDR in murine experimental tumors, suggesting a better selectivity of the oral over the i.v. schedule [10].

The results of this study indicate that 4-DMDR administered by the oral route induced a PR in 28% of 25 patients with advanced breast cancer (confidence limits at $P < 0.05$: 12–49%). This result is interesting in that it was achieved in patients pretreated with chemotherapy.

The administration of the dose of 45 mg/m² over three consecutive days and repeated every 21–28 days is well tolerated in the majority of the patients. Myelosuppression was the most frequent side-effect, but it was generally moderate. However, some patients presented severe leukopenia and therefore care must be taken in treating patients who had previously received intense myelosuppressive treatments and/or who have diffuse bone involvement. Vomiting occurred in 17% of the patients and its intensity was mild in all but one instance. The incidence of vomiting in our study is lower than that reported in a phase I trial which, using a single oral dose of 48 mg/m², reported vomiting in 67% [6]. This difference may be due to the distribution of the dose over 3 days. Moreover, alopecia was rare and incomplete.

No definitive conclusion is possible regarding cardiotoxicity because more data are needed. We observed only mild EKG changes in two patients and an EF in the lower normal limits in two other patients who had received a total dose > 400 mg/m².

In conclusion, 4-DMDR is to our knowledge the first anthracycline which has proved to be active in human breast cancer when given orally. The low incidence of vomiting and alopecia, the suitability of the oral administration and, possibly, the lower cardiotoxicity could be important advantages over DX. For these reasons we think that a controlled trial of this new anthracycline in comparison with DX is warranted.

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