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A Phase II Study of Oral Weekly 4-Demethoxydaunorubicin in Advanced Breast Cancer

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Abstract—*Thirty-eight patients with advanced breast cancer were treated with oral 4-demethoxydaunorubicin in a continuous weekly schedule at a dose of* 15 mg/m^2*/week. Subjective toxicity consisted of mild nausea (grade* 1*) in* 52% *with more severe GI side effects (grade* 2*) in* 15%. *Three patients developed grade* 1 *alopecia and there were no episodes of cardiac failure. Significant neutropenia (grade* 2/3*) only occurred in patients with marrow involvement or widespread bone disease. There was one CR and* 5 *PRs, an overall response rate of* 15.7% (95% *confidence limits* 6–31%). *In addition* 6 *patients had disease stabilization for at least* 6 *months. Fourteen patients progressing on 4-demethoxydaunorubicin have received adriamycin* 60 mg/m^2 21 *days. There have been* 5 *PRs in this group indicating possible non-cross-resistance between these two agents.*

INTRODUCTION

4-DEMETHOXYDAUNORUBICIN (Idarubicin, 4-DMDNR) is a synthetic analogue of daunorubicin which lacks the methoxy group at position 4 of the aglycone ring. In pre-clinical testing it had similar antitumour activity to both daunorubicin and doxorubicin [1, 2]. In addition the major metabolite of 4-demethoxydaunorubicin, 13-OH4DMDNR, was of equal potency to the parent compound [3]. Pharmacokinetic studies in man have demonstrated an oral bioavailability of 25–30% for 4-demethoxydaunorubicin. This is confirmed by clinical data which suggests that the maximum tolerated dose is 3–4× higher when the drug is used orally compared to intravenously [4]. In addition, although the parent compound is undetectable in the serum after 72 hr, 13-OH4DMDNR has a plasma half-life of 36–48 hr [5, 6] significant amounts still being present 7 days after administration [6].

Experience with adriamycin in breast cancer has shown that toxicity can be reduced by using a weekly rather than *q*21 day schedule without compromising therapeutic effect [7–9]. Since 4-demethoxydaunorubicin is available in an oral preparation it would be particularly suitable for use in this manner. Moreover in view of the antitumor activity and long serum half-life of the 13-OH metabolite it was possible that a weekly schedule might mimic a continuous cytotoxic infusion which may be of benefit in tumours with relatively slow doubling times.

4-Demethoxydaunorubicin had demonstrated activity in advanced breast cancer during phase I testing [4] and we therefore decided to test this drug in a weekly oral schedule in such patients.

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PATIENTS AND METHODS

A phase I study by De Sloover *et al.* [10] using a weekly × 4 oral schedule demonstrated minimal toxicity with doses up to 15 mg/m^2 but increasing nausea, vomiting and neutropenia at higher doses. Since one of our aims was to use a continuous therapy we did not wish to choose a dose that would result in frequent delays. 4-Demethoxydaunorubicin was therefore given at a dosage of 15 mg/m^2 in a weekly oral schedule. Patients were seen at 14 day intervals for the first 4 weeks and subsequently every 28 days. The dose was reduced by 5 mg/week when the wbc fell to $< 2.5 \times 10^9$/l and treatment was delayed by one week if the wbc was $< 2.0 \times 10^9$/l. Following a delay 4-demethoxydaunorubicin was not restarted until the wbc was $> 3.0 \times 10^9$/l. Treatment was given for at least 8 weeks, unless progression of life-threatening disease dictated a change to intravenous chemotherapy,

and continued until relapse. When progression occurred it was our intention to use adriamycin 60 mg/m^2 in a $q21$ day schedule in order to obtain data on cross-resistance between these two agents.

PATIENTS

Thirty-eight evaluable patients with a median age of 63.5 years, a WHO performance status of 0 or 1, and an anticipated survival of at least 3 months were entered into the study. Patients with cardiac failure, major rhythm disturbances or significant ECG abnormalities were excluded. Patient characteristics are summarized in Table 1. No patient had received prior chemotherapy but 32 had one or more trials of hormone treatment. Reasons for not using hormone therapy included rapidly advancing liver disease (3) and receptor negative inflammatory carcinomas (3).

Among the 18 patients with soft tissue metastases as the dominant site of disease there were 10 with locally advanced primary tumours, 3 with involved lymph nodes and 5 with cutaneous disease. In the group of 8 patients with dominant bone disease only 2 did not have evaluable disease elsewhere.

All patients were assessed according to UICC criteria [11] with duration of remission measured from the date of starting chemotherapy. Toxicity had been graded using the WHO scale [12].

RESULTS

The 38 patients received a median of 12 weeks' treatment (range 2–60 weeks). Three patients with rapidly progressing liver disease had to be switched to adriamycin after 2–4 weeks' therapy. Six patients received in excess of 450 mg/m^2 total dose of 4-demethoxydaunorubicin.

Table 1. Patient characteristics

Characteristic			%
Age, median (range)		63.5 (33–79)	
Menopausal status: pre-		1	3
post-		37	97
Post-surgery radiation		11	29
Disease free interval, months median (range)		19 (0–204)	
Time from first relapse to 4-DMDNR months median (range)		10 (0–132)	
Receptor status:			
oestrogen + progesterone +		15	48
+	−	3	10
−	+	2	6
−	−	11	35
Response to hormone therapy:			
Progression		18	56
Static (6 months +)		4	12
PR		8	25
CR		2	6
Dominant site of disease:			
Soft tissue		18	47
Bone		8	21
Lung		6	16
Liver		4	11
Retroperitoneal		2	5

One CR (cutaneous) and 5 PRs were seen providing an overall response rate of 15.7% (95% confidence limits 6–31%). Partial remissions occurred in patients with the following dominant sites of disease. Inflammatory carcinoma (1), lymph nodes (1), retroperitoneal infiltration + bone (1) and cutaneous deposits (2). In addition, 6 patients had static disease for a period of at least 6 months. The duration of the remissions was 13 months for the CR and 5+, 5+, 9+, 10+ and 14+ months for the PRs. The median time to objective remission was 8 weeks (range 4–10 weeks) and responses were evenly distributed between patients with receptor-positive and receptor-negative tumours.

Toxicity

The toxicity of 4-demethoxydaunorubicin administered in this schedule was mild. Seven patients (17.9%) required treatment delays, 6 due to neutropenia (grade 3) and 1 to a severe radiation recall reaction. Dose reductions were necessary in 13 patients (33.3%), 9 because of haematological toxicity (grade 2/3 neutropenia) and 4 as a result of unacceptable nausea and vomiting (grade 3). Bone marrow examinations were performed in 6 of the 9 patients who had dose reductions following episodes of neutropenia and in all cases the marrow was involved with tumour. Two of the remaining 3 patients had widespread bone disease.

Gastrointestinal toxicity was variable. Twelve patients (31%) experienced no nausea or vomiting while 14 (36.8%) had mild nausea (grade 1) affecting < 25% of their doses. Six patients also reported grade 1 nausea but affecting 25–75% of doses and a further 6 (5.7%) had nausea and vomiting (grade 2–3) with every treatment, in 4 cases requiring dose reductions. Three patients developed mild alopecia not requiring a wig (grade 1) and there were no episodes of cardiac failure or ECG abnormalities seen during the study.

Treatment on progression with adriamycin

Thus far 32/38 patients have progressed on treatment with 4-demethoxydaunorubicin and 14 of these have received adriamycin. Reasons for not using adriamycin in the remaining patients included: too ill to warrant further therapy (6), fear of alopecia (2), elderly and frail (5), asymptomatic (2), radiation recall with 4-demethoxydaunorubicin (1), cirrhosis with rising bilirubicin (previously normal) (1) and prolonged pancytopenia (1).

Patient characteristics of these 14 patients are

Table 2. Characteristics of patients treated with adriamycin

Characteristic		%
No.	14	
Age, median (range)	60 (33–65)	
Number of weeks 4-DMDNR therapy, median (range)	14 (2–32)	
Response to 4-DMDNR:		
Static (6+ months)	2	14
Progression	12	86
Dominant site:		
Soft tissue	4	28
Bone	1	7
Lung	3	21
Liver	6	43
Number of courses of adriamycin, median (range)	4 (2–8)	
Reason for stopping adriamycin:		
Toxicity	1	7
Reached maximum dose	4	28
Progression	8	57
Continues on therapy	1	7

shown in Table 2. Six patients had rapidly advancing liver disease in 2 cases occurring as a new site after 12 and 17 weeks' 4-demethoxydaunorubicin.

There were 5 PRs (35.7%) in this group of patients. A further 3 patients had < 50% regression of their disease with good symptomatic response for 5, 5, and 8+ months. One responding patient has relapsed after 5 months but the remaining 4 continue in remission at 6+ months after commencing adriamycin.

Two patients who responded to adriamycin had previously had static disease on 4-demethoxydaunorubicin for 6+ months. These were patients with lung metastases as the major site. The remaining 3 all had liver metastases and in two cases were switched to adriamycin after less than 4 weeks' 4-demethoxydaunorubicin because of rapidly advancing disease.

DISCUSSION

In recent years it has become clear that with the currently available drugs advanced breast cancer is not a curable disease [13]. This realization has prompted the search for less toxic treatments which can be administered with minimal disturbance to normal lifestyle. Attention has therefore focussed on oral chemotherapy which avoids the trauma of venous canulation and may reduce the frequency of clinic visits while retaining therapeutic activity [14]. 4-Demethoxydaunorubicin is the first anthracycline analogue to be available in an oral form and is therefore of considerable interest in the management of breast cancer in view of the activity of the parent compounds in this disease [13].

In this study oral 4-demethoxydaunorubicin in a weekly schedule was well tolerated with limited GI toxicity affecting 59% of patients and no significant alopecia. There were no episodes of cardiac failure seen during the study despite 6 patients receiving more than 450 mg/m^2, a cumulative dose that might be expected to result in myocardial dysfunction allowing for an oral bioavailability of 30%. This suggests that 4-demethoxydaunorubicin is less cardiotoxic than the parent drug although the weekly schedule may also have contributed to a reduction in this side effect.

Haematological toxicity was also mild. There was no thrombocytopenia and neutropenia only occurred in patients with marrow infiltration or widespread bone disease. There was no evidence of cumulative myelosuppression. The objective response rate of 15.7% was disappointingly low and does not compare favourably with preliminary data on 4-demethoxydaunorubicin used in a q21 day schedule in patients with advanced breast cancer. These studies have obtained response rates of 30–50% [15, 16] using doses in the range 40–50 mg/m^2 and thus it appears likely that in contrast to adriamycin there is a loss of therapeutic effect when 4-demethoxydaunorubicin is used in a weekly schedule. The inference that may be drawn from these data is that high peak levels of 4-demethoxydaunorubicin or 13-OH4DMDNR, or both, are important for antitumour activity rather than the more continuous lower levels achieved by weekly administration. However a randomized trial would be required to finally answer this question.

For the reasons outlined above the number of patients in the adriamycin arm of this study was too small to draw any firm conclusions on cross-resistance between thee two drugs. Moreover 2 of the 5 patients who responded to adriamycin had only 2 weeks' therapy with 4-demethoxydaunorubicin due to rapidly advancing liver disease. However there were 3 patients who progressed after more than 8 weeks' 4-demethoxydaunorubicin therapy (lung 2, liver 1) who subsequently achieved a partial remission with adriamycin suggesting that there may be a degree of non-cross-resistance between these two agents.

In summary 4-demethoxydaunorubicin used in a weekly schedule is well tolerated and has activity in advanced breast cancer. This mode of administration, however, appears to be inferior to giving the same total dose of drug in a q21 day regimen. Low-dose weekly treatment was clearly inadequate therapy for rapidly progressive liver disease. There was some evidence of non-cross-resistance between 4-demethoxydaunorubicin and adriamycin.

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REFERENCES

1. Suppino R, Necco A, Dasida T, *et al.* Relationship between effects on nucleic acid synthesis in cell cultures and cytotoxicity of 4-demethoxy derivatives of daunorubicin and adriamycin. *Cancer Res* 1977, **37**, 4523–4524.
2. Dimarco A, Casazza AM, Pratesi G. Antitumour activity of 4-demethoxydaunorubicin administered orally. *Cancer Treat Rep* 1977, **61**, 893–894.
3. Barbieri B, Casazza AM, Penco S, Cassinelli G, Poesta A. Biological activity of 1-OH-anthracyclines. *Proc 13th Int Cong Chemother* 1983.
4. Bonfante V, Ferarri L, Villani F, Bonnadonna G. Phase I study of 4-demethoxy-daunorubicin. *Investigational New Drugs* 1983, **1**, 161–168.
5. Berman E, Wittes RE, Leyland-Jones B, *et al.* Phase I and clinical pharmacology studies of intravenous and oral administration of 4-demethoxydaunorubicin in patients with advanced cancer. *Cancer Res* 1983, **43**, 6096–6100.
6. Smith DB, Margison J, Wilkinson PM, Howell A, Crowther D, Thomas G. Pharmacokinetics of oral weekly Idarubicin. *Proc ASCO* 1986, **5**, 212.
7. Chlebowsky RT, Paroly WS, Pugh RP, *et al.* Adriamycin given as a weekly schedule without a loading course: clinically effective with reduced incidence of cardiotoxicity. *Cancer Treat Rep* 1980, **64**, 47–51.
8. Weiss AJ, Metter GE, Fletcher WS. Studies on adriamycin using a weekly regimen demonstrating its clinical effectiveness and lack of cardiotoxicity. *Cancer Treat Rep* 1976, **60**, 813–822.
9. Mattson W, Borgstroem S, Landberg T. A weekly schedule without a loading course: clinically effective with reduced incidence of cardiotoxicity. *Clin Ther* 1982, **5**, 193–203.
10. DeSloover C, Rosencweig M, Nicaise C, Gerard B, Crespeigne N, Kenis Y. Phase I study of oral Idarubicin with a weekly schedule. *Proc ASCO* 1984, **3**, 79.
11. Hayward JL, Carbonne PP, Heuson J-C, Kumaoka S, Segaloff A. Assessment of response to therapy in advanced breast cancer. *Br J Cancer* 1977, **35**, 292–298.
12. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer* 1981, **47**, 207–214.
13. Harris JR, Hellman S, Canellos GP, Fisher B. Cancer of the breast. In: DeVita VT Jr, Hellman S, Rosenberg SA, eds *Cancer. Principles and Practice of Oncology* 2nd edition. Philadelphia, Lippincott, 1985, 1119–1178.
14. Wagstaff J, Bramwell VHC, Wilkinson M, Howell A. Rotating oral cyclophosphamide, methotrexate and fluorouracil (oral CMF) for patients with advanced carcinoma of the breast. *Proc ECCO* 1985, **3**, 166.
15. Pannuti F, Martoni A, Pacciarini MA, Fruet F. A phase II trial of oral Idarubicin in advanced breast cancer. *Proc ECCO* 1985, **3**, 70.
16. Bastholt L, Ejlertsen B, Dalmark M, Sygenhus RO. A phase II trial of oral 4-demethoxy-daunorubicin (DMDR) in patients with measurable advanced carcinoma of the breast. *Proc ECCO* 1985, **3**, 169.