Cancer Chemother Pharmacol (1988) 21: 351–354

Cancer Chemotherapy and Pharmacology

A phase II study of oral idarubicin (4-demethoxydaunorubicin) in advanced breast cancer

Nicholas S. A. Stuart[1], Michael H. Cullen[2], Terrence J. Priestman[2], George R. P. Blackledge[1], and Christopher J. Tyrrell[3]

[1] West Midlands CRC Clinical Trials Unit, Queen Elizabeth Hospital, Edgbaston, Birmingham B15 2TH, U. K.
[2] Department of Radiotherapy and Oncology, Queen Elizabeth Hospital, Edgbaston, Birmingham, U. K.
[3] Department of Radiotherapy and Oncology, Plymouth General Hospital, Plymouth, U. K.

Summary. Idarubicin (4-demethoxydaunorubicin: DMDNR) is an orally active analogue of daunorubicin that has shown promising activity in animal and early clinical studies. We gave idarubicin in a phase II study to patients with advanced breast cancer unresponsive to hormonal manipulation and in some cases to standard chemotherapeutic agents. Idarubicin was given orally every 21 days at a starting dose of 40 mg/m^2 with dose escalation until myelosuppression occurred. Nadir blood counts showed that patient compliance was good. Of 33 patients studied, 32 are evaluable for response: 4 (13%) had partial responses (95% confidence interval 1%–23%) with a duration of response between 32 and 59 weeks; 8 (25%) had static disease for between 17 and 48 weeks; and 20 failed to respond. For patients not previously exposed to chemotherapy, the response rate was 3/19 (16%). Toxicity was mild, with little or no gastro-intestinal disturbance in the majority of patients, no severe haematological toxicity and little alopecia. Two patients however, were withdrawn from the study because of toxicity; one with a skin rash and one with severe vomiting. Idarubicin produces little toxicity when given orally at a dose of 40 mg/m^2 every 21 days, but its activity in breast cancer is insufficient to justify its further use with this schedule. Further studies should be undertaken only if direct comparison can be made with doxorubicin.

Introduction

Doxorubicin (adriamycin) is the single, most active cytotoxic agent for the treatment of breast cancer but suffers from the disadvantage of subjective toxicity with frequent nausea, vomiting and alopecia as well as myelosuppression, cardiotoxicity and the risk of extravasation. Idarubicin (DMDNR:4-demethoxydaunorubicin) is an analogue of daunorubicin lacking the methoxyl group at position 4 of the aglycone ring (Fig. 1). It differs from daunorubicin and doxorubicin in several ways including absorption following oral administration [7, 11]. Activity has been shown in many animal tumour models [1, 7] and useful activity has also been demonstrated in early clinical studies [6]. There is also some evidence of an increased therapeutic ratio with less risk of cardiotoxicity than with doxorubicin or daunorubicin [5, 8, 9]. The aim of this study was to assess the activity of this drug in breast cancer when given orally and to further assess toxicity.

Offprint requests to: N. S. A. Stuart

Patients and methods

Patients selected were females under the age of 80 with biopsy-proven carcinoma of the breast who were unresponsive to hormonal manipulation. All patients had documented disease progression with measurable or evaluable disease, had received no chemotherapy or hormonal manipulation in the preceding 4 weeks and had WHO performance scores of 2 or better. Patients previously treated with anthracyclines were excluded, but those who had received the anthracenedione mitozantrone were eligible. Patients with no prior exposure to chemotherapy were included as long as they did not have life-threatening or rapidly progressive disease. Patients with WBCs (white blood cell counts) less than 3.5×10^9/l, platelet counts less than 100×10^9/l, renal insufficiency (creatinine >130 μmol/l), liver dysfunction (bilirubin >25 μmol/l), CNS involvement by tumour, history of heart failure or other malignancy, or abnormality on pre-treatment ECG were excluded. Details of the study group are shown in Table 1.

All patients received a starting dose of 40 mg/m^2 idarubicin given orally in divided doses over 24 h. Treatment was repeated every 21 days if peripheral blood counts had recovered sufficiently. Blood counts were measured before

Table 1. Details of study group

Median age (range)	55 (33–77)		
Number of previous cytotoxic agents	0	=	19 patients
	1	=	3
	2	=	1
	3	=	5
	4	=	2
	6	=	3
(Six patients previously exposed to mitoxantrone)			
Site of dominant disease	Local	=	13 patients
	Nodal	=	9
	Bone	=	3
	Liver	=	3
	Skin	=	2
	Pelvic	=	2
	Lung	=	1

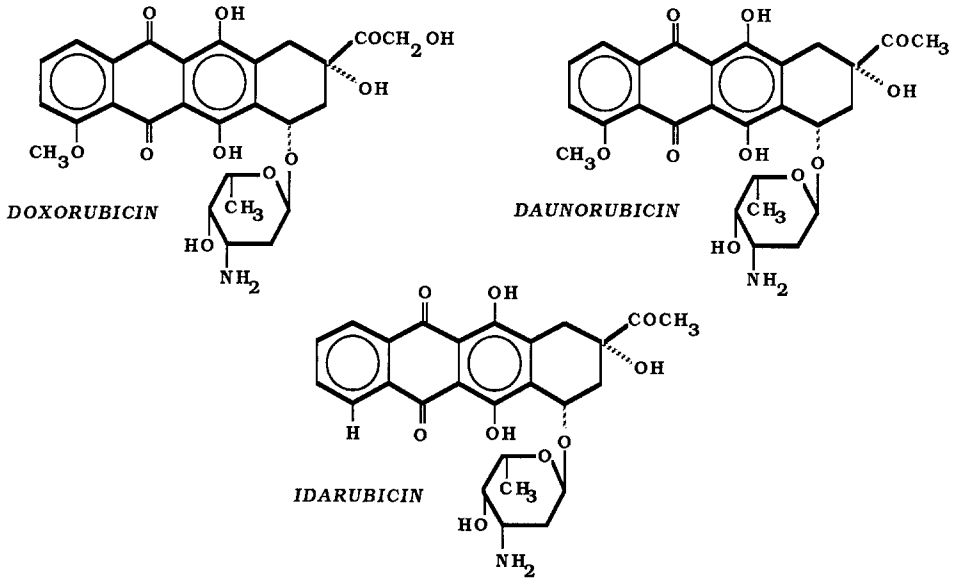

Fig. 1. Structural formulae of doxorubicin (adriamycin), daunorubicin and 4-demethoxydaunorubicin (idarubicin)

treatment and on three occasions between days 8 and 16 of the first course of treatment. They were also recorded at the beginning of each subsequent course and on one occasion between days 10 and 14 thereafter. This provided a check on patient compliance and drug absorption and allowed for dose escalation. In those patients who did not show myelosuppression between days 7 and 14 of their first course, the dose of subsequent courses was increased by 5 mg/m^2 until myelosuppression was seen.

The criteria defined by Miller et al. for the World Health Organization [17] were used to assess response. Patients whose disease remained static beyond four courses (12 weeks) were considered to have static disease as a result of treatment.

Results

A total of 112 courses (range 1–9 per patient) were received by 33 patients who entered the study. One patient is not evaluable for response because she was withdrawn from treatment after only one course due to infection not related to neutropenia. Two further patients were withdrawn after only one course because of toxicity. Of the 32 evaluable patients, 4 (13%) achieved partial remissions (95% confidence interval 1%–23%) with a duration of response from 32 to 59 weeks (sites of response: bone, skin, nodes and local disease). Eight patients (25%) had static disease for between 12 and 45 weeks and 20 (63%) failed to respond. Of those patients who failed, eight progressed during their first course of treatment, including two early deaths. For patients having two or more courses, the response rate was 17%, and there were three partial remissions (16%) among 19 patients not previously exposed to chemotherapy. No statistically significant difference was found between the first-course nadir WBCs of patients whose disease progressed and those who had static or responsive disease (pooled t-test for comparison of means; $t = 0.13$, $P = 0.90$).

Toxicity

Figure 2 shows the nadir WBC counts for 19 patients who were assessed on two or more consecutive courses. Of 32 patients assessed, 15 had no myelosuppression with their

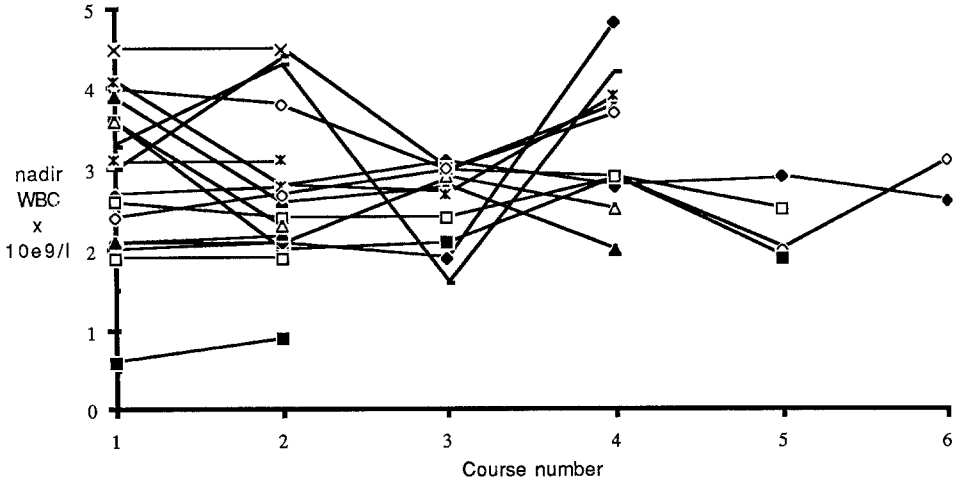

Fig. 2. Pattern of nadir WBCs during consecutive courses of idarubicin for 19 patients having nadir WBC measured in two or more courses

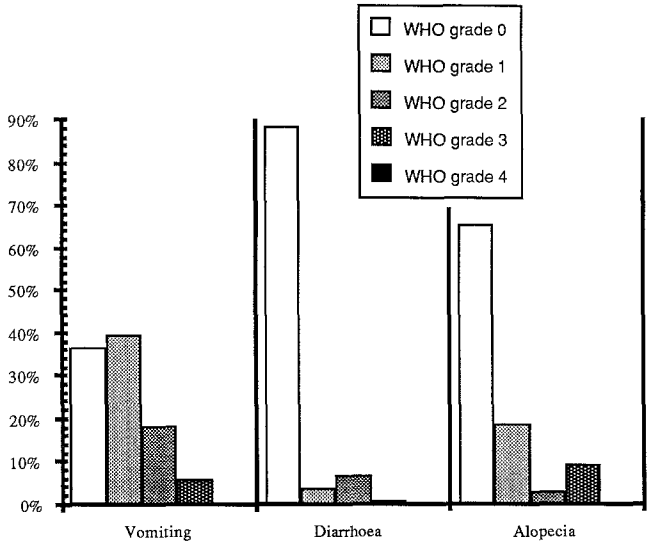

Fig. 3. Incidence and severity of toxicity during treatment: percentage of *courses* associated with nausea and vomiting or diarrhoea; percentage of *patients* having two or more courses experiencing alopecia

first course of treatment, but dose escalation ensured that of 51 second and later courses for which nadir WBC was measured, 43 (84%) had a nadir WBC below 3.5×10^9/l. Of 79 non-first courses, 28 (35%) were given at increased dose (maximum 50 mg/m^2), 2 at reduced dose because of nadir WBC less than 1.0×10^9/l, and 22 (28%) were delayed because of low WBC ($< 3.5 \times 10^9$/l) on day 21.

Of 112 courses, 104 were assessed for subjective toxicity. Figure 3 shows the incidence of gastrointestinal toxicity and alopecia. Of 32 patients assessed, 7 had no nausea or vomiting at any time during the study. When vomiting did occur, its duration was generally less than 48 h. In one patient the severity of vomiting was sufficient for the refusal of further treatment. Diarrhoea affected 6 of 32 patients but was never severe. Alopecia was infrequent.

One patient developed a generalized, desquamating, erythematous rash 3 days after her first dose of idarubicin. The rash persisted for 4 weeks before subsiding spontaneously. There was no previous history of atopy or skin rashes in this patient, and the only other medication she was taking was oral metoclopramide. It was felt that this rash could be a reaction to idarubicin and that further courses could not be given; the patient was therefore withdrawn from the study. No other toxicity was observed.

Discussion

For patients with advanced or recurrent breast cancer, treatment is essentially palliative. There is a need for treatments which are effective and easily given and cause few side effects. Doxorubicin is the single, most active drug in breast cancer but produces subjective and objective toxicity. Idarubicin is an anthracycline analogue that has shown activity in early clinical studies when given orally and may produce fewer side effects. It is thus an attractive drug to assess in advanced breast cancer.

A frequently cited objection to oral chemotherapy is the the problem of non-compliance. In this study, nadir WBCs were carefully assessed and the pattern of blood counts suggests that all patients took their drugs as prescribed. Only one patient for one course admitted that she did not take her prescribed drugs, and in only one other case was poor compliance considered possible. A further problem is that nausea and vomiting produced by oral chemotherapy may stop patients from taking a full course of treatment. One patient in this study vomited two of seven capsules and probably received less than the full protocol dose; this patient progressed during her first course.

In addition to the problem of patient compliance, the efficacy of any oral drug may also be compromised by erratic absorption. That this occurs is suggested by the wide range of nadir WBCs after the first course ($0.6-7.2 \times 10^9$/l). Other studies have also shown this [3, 10] and, although there may be other explanations for this variability, dose titration for individual patients must be considered essential for studies of oral idarubicin. In this study 35% of non-first courses involved dose escalation that continued until myelosuppression was seen, and it is unlikely that poor absorption of the orally administered drug accounts for the low response rate seen.

Reported response rates to idarubicin in groups of patients largely unexposed to previous chemotherapy have ranged from 36% of 50 patients receiving 45 mg/m^2 as a 1-day regime [2], to 31% of 29 patients receiving 15 mg/m^2 for 3 days [14] or 22% of 31 patients given a fixed dose of 30 mg for 3 days [18]. In groups of patients previously exposed to chemotherapy, excluding anthracyclines, response rates have ranged from 21% of 48 patients to 26% of 29 patients, both studies using 15 mg/m^2 for 3 days [12, 16]. One earlier study included 12 of 27 patients who were previously exposed to standard anthracyclines and showed a response rate of 19% at 30–55 mg/m^2 on 1 day [15]. These reports were all of nonrandomized phase II studies and, although no direct comparison can be made, the response rates shown are probably less than would be expected from doxorubicin [4]. These published results do not suggest the superiority of any one schedule over the others.

The response rate for all patients in this study is less than 15% (the accepted criterion for activity of a new chemotherapeutic agent) and is undoubtedly less than would be expected from doxorubicin alone. Even for those patients not previously exposed to chemotherapy, the response rate was only 18%, a level which makes it unlikely that idarubicin given in this way will fulfil its theoretical potential for the treatment of advanced breast cancer. Other schedules for oral (e.g. treatment each week) as well as intravenous administration are being assessed in phase II studies of breast cancer, but at present, despite the low level of subjective toxicity, idarubicin cannot be recommended for the treatment of advanced or recurrent breast cancer. Further studies should only be undertaken if direct comparison can be made with the activity of doxorubicin.

Acknowledgements. We would like to thank Farmitalia Carlo Erba Ltd (U. K.) for supplying capsules of idarubicin and for their assistance throughout this study.

References

1. Arcamone F, Bernardi L, Giardino P, Patelli B, DiMarco A, Casazza AM, Pratesi G, Reggiani P (1976) Synthesis and antitumour activity of 4-demethoxydaunorubicin, 4-demethoxy-7,9-diepidaunorubicin and their β anomers. Cancer Treat Rep 60: 829–834

2. Bastholt L, Dalmark M (1987) Phase II study of Idarubicin given orally in the treatment of anthracycline-naive advanced breast cancer patients. Cancer Treat Rep 71 (5): 451–454
3. Berman E, Wittes RE, Leyland-Jones B, Casper ES, Gralla RJ, Koward J, Williams L, Boratz R, Young CW (1983) Phase I and clinical pharmacology studies of intravenous and oral administration of 4-demethoxydaunorubicin in patients with advanced cancer. Cancer Res 43: 6069–6101
4. Bonfante V, Ferrari L, Brambilla C, Rossi A, Villani F, Crippa F, Valagussa P, Bonadenna G (1986) New anthracycline analogs in advanced breast cancer. Eur J Cancer Clin Oncol 22: 1379–1385
5. Casazza AM, Bertazzoli C, Pratesi G (1979) Anti-leukaemic activity and cardiac toxicity of 4-demethoxydaunorubicin (4-DMDNR). Proc Am Assoc Cancer Res 20: 16
6. Casazza AM, Pratesi G, Giuliani F, Di Marco A (1980) Anti-leukaemic activity of 4-demethoxydaunorubicin in mice. Tumori 66: 549–564
7. Di Marco A, Casazza AM, Pratesi G (1977) Antitumour activity of 4-demethoxydaunorubicin administered orally. Cancer Treat Rep 61: 893–894
8. Di Marco A, Zunio F, Casazza AM (1978) Comparison of biochemical and biological methods in the evaluation of new anthracycline drugs. Antibiot Chemother 25: 12–20
9. Farmitalia Carlo Erba (1981) 4-demethoxydaunorubicin investigational brochure
10. Kaplan S, Sessa C, Willems Y, Pacciorini MA, Tamasia V, Cavalli F (1984) Phase I trial of 4-demethoxydaunorubicin (idarubicin) with single oral doses. Invest New Drugs 2: 281–286
11. Kavanagh JJ, Yeung KY, Savaraj N, Krakoff IH (1985) Phase I clinical evaluation of oral and intravenous 4-demethoxydaunorubicin. Eur J Cancer Clin Oncol 21: 1187–1189
12. Kolaric K, Mechi Z, Potrebica V, Sopkova B (1987) Phase II study of oral 4-demethoxydaunorubicin in previously treated (except anthracyclines) metastatic breast cancer patients. Oncology 44: 82–86
13. Lambertenghi-Deliliers G, Pogliani E, Maiolo AT, Pacciorini MA, Polli EE (1983) Therapeutic activity of 4-demethoxydaunorubicin (idarubicin) in adult acute leukaemia. Tumori 69: 515–519
14. Lionetto R, Pronzato P, Conte PF, Sertoli MR, Amoroso D, Rosso R (1986) Idarubicin in advanced breast cancer: A phase II study. Cancer Treat Rep 70: 1439–1440
15. Lopez M, Di Lauro L, Papaldo P, Lazzaro B, Ganzina F, Di Petro N (1986) Phase II trial with oral 4-demethoxydaunorubicin (DMDR) in advanced breast cancer. Invest New Drugs 4: 39–42
16. Martoni A, Pacciarini MA, Pannuti F (1985) Activity of 4-demethoxydaunorubicin by the oral route in advanced breast cancer. Eur J Cancer Clin Oncol 21: 803–806
17. Miller AB, Hoogstraten B, Staquet M, Winkler A (1981) Reporting results of cancer treatment. Caner 47: 207–214
18. Wander H-E, Meyer D, Schuff-Werner P, Nagel GA (1986) Phase-II trial of oral idarubicin (4-demethoxydaunorubicin) in advanced breast cancer. Onkologie 9: 236–238

Received October 14, 1987/Accepted December 17, 1987