Cancer Chemother Pharmacol (1987) 20: 75–77

Cancer Chemotherapy and Pharmacology

Phase II clinical and pharmacological study of oral 4-demethoxydaunorubicin in advanced non-pretreated small cell lung cancer

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Summary. 4-Demethoxydaunorubicin (4-DMDNR) is an oral anthracycline with antitumour activity demonstrated in a number of clinical studies. We have assessed the usefulness of 4-DMDNR in 16 patients with advanced small cell lung cancer, none of whom had received previous chemotherapy. There were no complete or partial responders among the 14 evaluable patients, but 9 patients showed a minor radiographic improvement and 6 reported transient symptomatic improvement. Side effects were mostly minor or moderate, although one patient succumbed to septicaemia during neutropenia following treatment. There was no evidence of cardiotoxicity in any patient. Pharmacological studies were undertaken in 8 patients. A previously undescribed metabolite, identified as the 7-deoxyaglycone of 4-demethoxydaunorubicinol, was detected in 3 patients and these 3 patients all showed some anti-tumor response.

Introduction

The anthracyclines represent an important group of anti-tumor agents. 4-Demethoxydaunorubicin (4-DMDNR) is a derivative of daunorubicin which lacks the methoxy group at position 4 in the aglycone ring. It is an active anti-tumor agent in murine leukaemia models [4] and in solid tumour (sarcoma) models [1]. In addition, 4-DMDNR has been shown to be active when administered orally [4, 7]. Further, at equipotent doses, in animal studies 4-DMDNR appears to be significantly less cardiotoxic than daunorubicin or doxorubicin [3].

The results of phase II studies to assess the clinical usefulness of 4-DMDNR in various malignancies have in general paralleled the activity recorded for the parent drug. In leukaemia [6] and advanced breast cancer [10] there is clear evidence of anti-tumour activity. On the other hand, in tumours of the upper gastro-intestinal tract [8] and kidney [12] results have been disappointing. Since Adriamycin is one of the most active agents in small cell lung cancer [9], and because of the attractiveness of an anthracycline which can be taken orally on an out-patient basis and which appears to be less cardiotoxic than its parent compound, we have undertaken a pilot study to assess the clinical usefulness of 4-DMDNR in a group of 16 patients with advanced small cell lung cancer who had not received previous chemotherapy.

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Materials and methods

Patients. All patients (7 male, 9 female, mean age 64.7 years, range 48–78 years) had histologically proven small cell lung cancer with extensive disease demonstrated by isotope bone, liver or gallium scanning, which in all cases was measurable or evaluable. Patients were of ECOG status 2 or better. No patient had received cytotoxic therapy at any time or radiotherapy in the 4 weeks prior to study entry. The principal patient exclusion criteria were a history of active cardiac disease, bone marrow hypoplasia (total white cell count $<3.5\times10^9/l$ or platelet count $<100\times10^9/l$), significant hepatic or renal insufficiency, or proven CNS involvement by tumour. Informed consent was obtained in all cases.

Patients received 4-DMDNR (idarubicin, supplied courtesy of Farmitalia Carlo Erba), administered orally as a total dose of 50 mg/m^2 (given as three divided doses over 24 h) with routine anti-emetic cover. Dosing was repeated at 21-day intervals if the peripheral blood count had returned to baseline values. If there was evidence of haematological toxicity appropriate dose reductions and treatment delays were instituted. Patient response was assessed every 3 weeks and patients showing a response to treatment continued to a maximum of six courses. The median number of courses was three (range 2–6). The median cumulative dose was 180 mg/m^2 (range 120–510 mg/m^2). Patients with progressive disease could be withdrawn from the study at any time.

Pharmacological studies. Pharmacokinetic studies were performed in 4 patients. Blood samples were collected for drug analysis from 4 female patients (mean age 58.5 years, range 55–64 years), before treatment and then at frequent intervals up to 50 h after the last (third) dose of 4-DMDNR on the first course of treatment. In a further 4 patients a single sample of plasma was obtained at 6 h for metabolite profile. After sampling plasma was immediately separated and frozen to $-20°$ C in plain glass tubes for storage prior to analysis. 4-DMDNR and its metabolites were extracted from plasma according to the rapid method previously described for Adriamycin and its metabolites [5] and measured by high-performance liquid chromatography.

Results

Response

Two patients were not evaluable. One died of a septicaemic illness which was probably treatment-related, occurring 11 days after the first course of 4-DMDNR (total WBC 0.9×10^9/l). Another patient, an elderly man with extensive loco-regional disease, died at home some weeks after the first course of chemotherapy. The 14 evaluable patients received at least two courses of 4-DMDNR, and their responses to treatment are summarised in Table 1. None experienced a complete or partial response to treatment, but 9 patients showed some minor radiographic improvement (approximately 30% reduction in tumour mass). Six patients reported transient improvements in their well-being. These subjective minor responses were of short duration (mean time to disease progression 6 weeks). Four patients with a subjective improvement were able to receive subsequent combination chemotherapy. For the 10 patients who were treated with 4-DMDNR alone median survival was 3 months (range 2–11 months).

Pharmacology

The results of the pharmacological studies are shown in Fig. 1 and Table 2. Figure 1 is a graph illustrating the terminal pharmacokinetics of the parent drug. Terminal half-lives were calculated by non-linear regression data-fitting to the terminal portion of the plasma – concentration time curve, using the computer program ELSFIT. Mean peak concentration of parent drug was 8 ng/ml, mean t½ was 8.75 h. The mean peak concentration of the alcohol metabolite 4-DMDNOL was 30 ng/ml, and the mean t½ was 61 h. As can be seen from Table 2, the parent drug (4-DMDNR) and its alcohol metabolite (4-DMDNOL), were detected in all patients. A previously undescribed terminal metabolite identified as the 7-deoxyaglycone of 4-demethoxydaunorubicinol was present in 3 of 8 patients sampled, and these 3 patients showed a minor response to treatment.

Table 1. Response to 4-DMDNR in 14 evaluable patients

	Minor response	No response/ progressive disease
Radiographic	9	5
Clinical	6	8
Node	1	5
Hepatic function	1	–

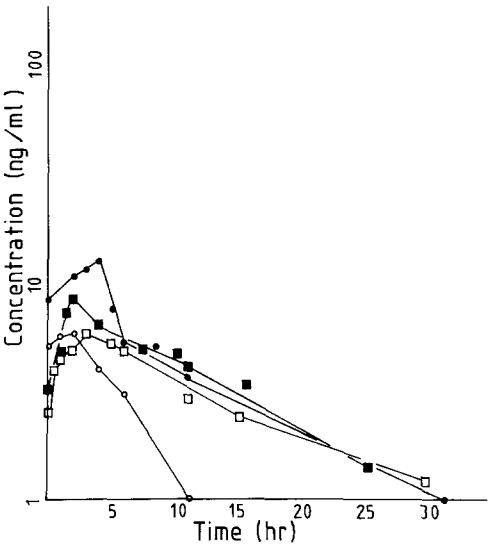

Fig. 1. Graph illustrating the terminal pharmacokinetic profile of the parent drug 4-DMDNR

Toxicity

Generally 4-DMDNR was moderately well tolerated. Gastro-intestinal side effects were most evident, with 5 patients experiencing troublesome vomiting (WHO grade 3) that was often delayed in onset (1–2 days after treatment) and somewhat protracted (2–3 days). Alopecia was encountered in 10 patients, and in 2 patients was severe. The hair loss was slowly progressive and severity seemed to relate to the total number of courses of treatment. Mid-cycle myelosuppression was evident in all but 2 patients, but sufficient to warrant a subsequent dose reduction in only 1 case. After the first course of treatment the median nadir white cell count (measured 10 days after treatment) was 2.9×10^9/l (range $0.4–6.7 \times 10^9$/l), and the median nadir platelet count, 224×10^9/l (range $116–555 \times 10^9$/l). There was no evidence to suggest significant cumulative myelotoxicity, similar nadir values being obtained with subsequent treatment courses. One patient died of septicaemia during neutropenia. No episodes of cardiac decompensation, dysrhythmia or ECG changes were noted. All patients underwent full cardiovascular examination and had an ECG performed before every course of treatment.

Discussion

The overall results of the study are disappointing, with no partial or complete response in 14 evaluable patients despite pharmacological evidence that drug levels that are as-

Table 2. Parent drug and metabolite levels measured in eight patients 6 h after last dose of first course of idarubicin

Patient	Response	4-DMDNR (ng/ml)	4-DMDNOL (ng/ml)	4-DMNOL-DONE (ng/ml)
1	Progressive disease	8	28	N.D.
2	Stable disease	3	12	N.D.
3	Stable disease	4	15	N.D.
4	Minor response	7	17	13
5	Minor response	3	23	7
6	Minor response	5	13	N.D.
7	Minor response	6	40	7
8	Non-evaluable	5	18	N.D.

N.D., not detected

sociated with response in other tumour types were attained. This suggests that the overall response rate is less than 20%, at the 5% level of significance (after Gehan 1961). Side effects, although acceptable, were significant and outweighed any possible benefit from treatment in terms of transient symptomatic improvement. Delayed and somewhat protracted nausea in a number of patients was troublesome and might perhaps relate to gastric binding of 4-DMDNR. Haematological toxicity was not severe in the majority of patients. Disturbance of liver function has previously been described [2, 6], but was not found in this study. Although we found no evidence of cardiovascular toxicity the median cumulative dose of 4-DMDNR administered was 180 mg/m^2, and indeed the maximum cumulative dose administered was 510 mg/m^2, both levels below which cardiotoxicity could realistically have been anticipated. The disappointing lack of response we found with the 4-demethoxy derivative of daunorubicin may relate to the group of patients studied, all of whom had advanced disease with a major tumour burden at outset.

Both the parent drug and its alcohol metabolite were detected in the plasma of all patients at levels that are in keeping with other published data [11], confirming that oral administration results in effective absorption of 4-DMDNR. A metabolite identified as the 7-deoxyaglycone of 4-demethoxydaunorubicinol was present in only 3 of the 8 patients sampled. This 7-deoxyaglycone has not been previously described as a terminal metabolite after oral administration of 4-DMDNR. It is interesting to note that the 3 patients in whom this metabolite was identified were those who showed the best response to treatment (Table 2), but unfortunately such responses were minor and short-lived, and median survival figures were similar in both groups (3 months). There did not appear to be any clear relationship between metabolite profile and drug toxicity.

Patients with extensive small cell lung cancer have a poor prognosis, and the present efforts at achieving palliation without undue toxicity will continue. In this context an oral cytotoxic agent which could be used on an out-patient basis in patients with advanced lung cancer remains a desirable goal.

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Received July 6, 1986/Accepted April 14, 1987