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Phase II trial of idarubicin in patients with advanced lymphoma

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Summary. A phase II trial of idarubicin was performed in 24 patients with advanced lymphoma. The drug was administered in a dose of 10–15 mg/m^2 i.v. or 15–70 mg/m^2 p.o. (single dose) every 3 weeks. There were four partial responses and four minor responses. All but one of the responders had received prior doxorubicin therapy. The toxicities were myelosuppression, nausea and vomiting, and alopecia. Two patients with compromised cardiac function were observed to have further deterioration in the ejection fraction as measured by gated cardiac scan after idarubicin therapy. Further assessment of the activity of idarubicin against lymphoma is recommended in less heavily pretreated patients. The cardiac toxicity should be carefully monitored in future studies.

Introduction

Idarubicin (IMI-30, NSC 256439, 4-demethoxydaunorubicin) is a derivative of daunorubicin which lacks the methoxy group in position 4 of the aglycone [1]. It has entered clinical trials because of its favourable preclinical characteristics. It is more active than daunorubicin and doxorubicin against a number of experimental tumour systems: L1210 and P388 leukemias, Gross leukaemia, sarcoma 180 and T cell lymphoma EL-4 [4, 6, 8]. Idarubicin also active when given p.o. [12, 13] and is significantly less cardiotoxic than daunorubicin in animal models [7, 9]. Phase I clinical studies showed that the dose-limiting toxicity of idarubicin was myelosuppression [15], and a dose of 12.5 mg/m^2 i.v. or 40–50 mg/m^2 p.o. every 21 days was suggested for phase II trials [2, 3, 13]. This paper reports a phase II trial of idarubicin in patients with advanced malignant lymphoma.

Materials and methods

The objective of the trial was to determine the antitumour efficacy and toxicities of idarubicin administered i.v. or p.o. every 3 weeks in patients with advanced lymphoma.

Requirements for entry into the trial included a histologically confirmed diagnosis of malignant lymphoma with clinically measurable lesions, no radiotherapy or chemotherapy within the last 4 weeks (6 weeks if the last chemotherapy included mitomycin or nitrosoureas), and adequate bone marrow function unless inadequacy was due to lymphomatous infiltration of marrow (WBC $>3000/mm^3$ and platelets $>100\times10^3/mm^3$). Patients with uncontrolled infection, clinical signs of cardiac insufficiency or previous cumulative doxorubicin dose greater than 450 mg/m^2 were excluded.

The following parameters were evaluated prior to entry into the trial: history, physical examination, body height and weight, WHO performance status [17], tumour measurement, full blood counts, blood biochemistry, chest X-ray and electrocardiogram. Prior to each dose, full blood counts and blood biochemistry were obtained. Chest X-rays and electrocardidograms were performed before courses 1, 3, 6 and whenever clinically indicated. Gated cardiac scans were done, where possible, before each patient entered the study, before every treatment from course 3 onwards, and before withdrawal from the study.

Patients who had received fewer than two courses of idarubicin were considered not evaluable (NE) for response. Response criteria were: partial response (PR), >50% decrease in the size of measureable lesions for at least 4 weeks; minor response (MR), 25%–49% decrease in size for >4 weeks; no change (NC), <25% change in tumour size, and progressive disease (PD), >25% increase. All patients were evaluated for toxicities using WHO criteria [17].

Idarubicin was supplied by Farmitalia Carlo Erba and was available as 5-mg vials for i.v. injection and 5- or 10-mg capsules for administration p.o.

In all, 24 patients entered this study. The patient characteristics are shown in Table 1. A total of 70 courses of idarubicin were administered. The median number of courses per patient was 2 (range 1–7). Of the 70 courses, 16 were given i.v. (for the purpose of pharmacokinetic studies) and the others p.o. Pharmacokinetic studies were performed in the 15 patients who received idarubicin i.v. for the first course and will be reported elsewhere. The i.v. doses were 15 mg/m^2 except in one course, for which 10 mg/m^2 only was given because of the poor physical condition of the patient. The initial oral dose was 40–50 mg/m^2, but was reduced to 30 mg/m^2 in those with marrow suppression secondary to lymphomatous infiltration (2 patients). The oral doses given ranged from 30 mg/m^2 to 70 mg/m^2 (median 50 mg/m^2). Patients escalated to the higher dose if they showed no myelosuppression at all

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Table 1. Patient characteristics[a]

Total no. of patients	24
Male/female	12/12
Age (years): range	22–76
median	62
Performance status (WHO)	
0	9
1	7
2	6
3	2
Prior treatment:	
Radiotherapy	6
Chemotherapy:	24
With doxorubicin	19
Without doxorubicin	5
Median no. of prior chemotherapeutic regimens (range)	3 (1–5)
Median no. of prior chemotherapeutic agents (range)	5 (3–14)
Median cumulative dose of doxorubicin in mg/m^2 (range)	150 (0–420)
Staging: III	4
IV	20
Extranodal involvement:	
Liver	9
Spleen	8
Bone marrow	11
Skin	3
Pleura	5
Kidney	1
Stomach	1
Hard palate	1
Histology:	
Hodgkin's disease:	
Mixed cellularity	3
Nodular sclerosing	1
Non-Hodgkin's lymphoma:	
Low grade:	
Nodular lymphocytic poorly differentiated	6
Diffuse lymphocytic well differentiated	2
High grade:	
Diffuse histiocytic	3
Diffuse mixed	7
Diffuse undifferentiated	2

[a] No. of patients (unless otherwise stated)

Table 2. Clinical responses to idarubicin[a]

	NE	PD	NC	MR	PR
No prior doxorubicin	3	0	1	0	1
Prior doxorubicin	3	6	3	4	3
Hodgkin's disease	0	1	0	2	1
Non-Hodgkin's lymphoma:					
Low grade	1	3	1	2	1
High grade	5	2	3	0	2
Total	6	6	4	4	4

NE, not evaluable; PD, progressive disease; NC, no change; MR, minor response; PR, partial response

[a] No. of patients

at 40–50 mg/m^2. In addition, in one patient the plasma idarubicin concentration was undetectable after an oral dose of 50 mg/m^2, and the dose was escalated to 70 mg/m^2 when plasma idarubicin was estimated in concentrations comparable to those found in other patients. Pharmacokinetic studies were performed in 14 of the 56 oral courses of treatment. Intervals between courses were usually 3 weeks, being extended by 7 days if blood counts were low (WBC $< 3000/mm^3$ or platelets $< 100 \times 10^3/mm^3$).

All patients gave informed consent and understood that idarubicin was a drug undergoing phase II trial. The protocol was approved by the appropriate local Ethics Committees.

Results

The responses to idarubicin therapy are shown in Table 2. Six patients were considered not evaluable for response, because each of them received only one course of idarubicin. The second course of treatment was not administered because of rapidly progressing disease in all but one of these patients, who was withdrawn from the study before his second course as hypoglycaemic coma developed as a complication of insulin therapy for his diabetes. This was considered to be unrelated to idarubicin treatment.

There were no complete responses, but four partial responses were seen (duration 4, 6, 8 and 24+ weeks). Three of the patients concerned had received prior doxorubicin (cumulative doses 250, 300 and 420 mg/m^2). Minor responses were seen (duration 4, 8, 8, 10 weeks) in another four patients all of whom had received prior doxorubicin (cumulative doses 110, 155, 210, 300 mg/m^2).

The major toxicity of idarubicin was myelosuppression, and its severity is shown in Table 3. Neutropenia was complicated by two fatal cases of septicaemia and three episodes of pneumonia, which resolved with antibiotic therapy. Platelet transfusion was given when the platelet count was below $20 \times 10^3/mm^3$, but no patient had major clinical bleeding.

Nausea and vomiting were never serious with idarubicin, although they were more common after idarubicin p.o. than after treatment i.v. They occurred after 3 of the 15 courses of idarubicin i.v. (2 grade 1, 1 grade 2) and after 32 of the 55 oral therapies (24 grade 1; 7 grade 2; 1 grade 3). Diarrhoea and mucositis were not a problem, nor were changes noted in clinical chemistry or liver function tests during this study.

Serial gated cardiac scans were performed in nine patients (Fig. 1). Deterioration in cardiac function was seen in two patients after idarubicin therapy. However, the pretreatment scans were midly abnormal in both patients, suggesting the presence of compromised cardiac function before their entry on study. Both patients had previous doxorubicin therapy (cumulative doses 75, 250 mg/m^2). In the first patient, the ejection fraction dropped from 45% pretreatment to 38% after the first course and further to 26% after the second course of idarubicin. In the other patient, the pretreatment ejection fraction was 65% which dropped to 57% after two courses of idarubicin, and further to 48% after the third course.

Of the 24 patients, 16 were evaluable for alopecia. Grade I alopecia occurred in 5 of them; in 1 hair regrowth continued throughout the six courses of idarubicin administered.

Table 3. Haematological toxicity

		No. of courses	No. of patients
Total no.		70	24
WBC or neutrophils	$<2.0\times10^3/mm^3$ $<1.0\times10^3/mm^3$	30	15
Platelets	$<50\times10^3/mm^3$	9	3
WBC or neutrophils	$<1.0\times10^3/mm^3$ $<0.5\times10^3/mm^3$	14	10
Platelets	$<20\times10^3/mm^3$	3	2

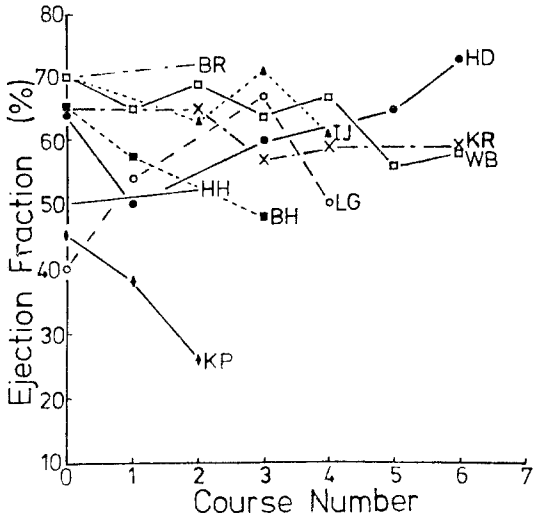

Fig. 1. Cardiac ejection fraction determined from gated nuclear scan for nine patients receiving idarubicin in a schedule of 15 mg/m^2 i.v. in the first course, then 50 mg/m^2 p.o. for subsequent courses at 3-weekly intervals

Discussion

Idarubicin was observed to have some activity against lymphoma in this study. There were four partial responses and four minor responses. Considering that our patient population was very heavily pretreated and most of the patients had received prior doxorubicin, any responses observed, despite their transience, must be considered significant. It is particularly important to note that seven of the eight responses were seen in patients with prior doxorubicin treatment. This was not observed in another phase II trial of i.v. idarubicin in advanced lymphoma [10]. However, responses to idarubicin have been reported in patients with leukaemia resistant to previous anthracycline therapy [5, 11]. In addition, preliminary results from other pilot studies suggest that idarubicin has activity in lymphoma. Thus, in one study [14], one out of three patients with non-Hodgkin's lymphoma went into complete remission when idarubicin was used in a combined regimen, and another was maintained in remission with idarubicin alone. In another study [16] partial responses were noted in five of six previously untreated and four of six previously treated patients with non-Hodgkin's lymphoma following treatment with 40–45 mg/m^2 p. o. idarubicin every 3 weeks. The balance of the evidence therefore suggests that this drug has significant activity in lymphoma.

The side effects on this regimen appear to be predictable and acceptable. The dose-limiting toxicity was myelosuppression. The degree of neutropenia and thrombocytopenia was as anticipated in this heavily pretreated patient population, with the median numbers of prior chemotherapeutic regimens and agents being three and five, respectively. The two episodes of fatal septicaemia were seen in patients with rapidly progressing disease that was not responsive to therapy. In a study in which 20–45 mg/m^2 idarubicin was given i.v. for 3 consecutive days in patients with acute leukaemia [11], liver function abnormalities were seen in a quarter of the patients. In the present study, in which lower (and largely oral) doses of idarubicin were used, these changes were not present; nor was mucositis, which was seen in over one-third of patients receiving high i.v. doses [11], found to be a problem. These effects are probably dose-dependent and at these lower oral doses of idarubicin they apparently do not occur frequently.

It is very difficult to derive any statement from the results of the present study on differences between p.o. and i.v. treatment with regard to response or myelosuppression. The difficulty arises because the order of i.v. and p.o. treatments was not randomized and only 15 of the 24 patients studied received treatment by both routes. Treatment was given i.v. for the first course for all these 15 patients, to enable pharmacokinetic studies to be carried out, and subsequent treatment was given p.o. (except for 1 patient who received two treatments i.v. before switching to the oral route). Thus, as in general only one i.v. treatment was given, and always for the first drug administration, there is little point in comparing either response or myelotoxicity referred to the two methods of administration.

One of the advantages of idarubicin over other available anthracyclines is that it is active when given p.o. [2, 4, 12]. Administration of idarubicin p.o. seems to be followed by a higher incidence of nausea and vomiting than i.v. administration, but they are usually mild. Although preclinical studies suggest that idarubicin is probably less cardiotoxic than doxorubicin, cardiac impairment was observed in 2 of our patients after idarubicin. However, it is important to note that both patients already had some degree of cardiac impairment before receiving idarubicin.

We therefore recommend further assessment of the activity of idarubicin against lymphoma, possibly in less heavily pretreated patients or in combination with other drugs. It is important that the cardiac toxicity of this drug should be carefully monitored in future studies.

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