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Short communication

Etoposide and cisplatinum in resistant lymphomas

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Summary. Etoposide and cisplatinum have used separately to treat refractory lymphomas. This report describes 22 patients in whom these two agents were used in conjunction. All had been extensively treated with standard therapies previously. The combination of etoposide and cisplatinum was chosen on the basis of preclinical evidence for synergy and because these agents do not cross-react. Cisplatinum was continuously infused for 5 days at a dose of 15 mg/m^2/d. As a push a 100 mg/m^2/d dose of etoposide was injected on days 1 and 2 of treatment. This schedule produced good responses in 18 patients, i.e. 15 partial remissions and three complete remissions. The side effects were acceptable.

Key word: Lymphomas treatment

Introduction

Patients with advanced-stage lymphoma who relapse or become refractory to aggressive combined-modality treatment have a very poor prognosis. Both etoposide (VP 16) and cisplatinum (CDDP) are known to be effective single agents in heavily pretreated patients with malignant lymphomas, the positive-response rate for VP 16 being 20%–30% [2, 7, 10] and for CDDP 26% [1] Greater success can be achieved by using these drugs together [3, 5, 8]. Our combination regimen was designed to be non-cross-resistant with standard therapy [4].

Patients and methods

Twenty-six patients entered this study in 1985 and 1986. All had been extensively treated beforehand either by chemotherapy or by radiochemotherapy. The combination protocol used called for continuous infusion of 15 mg/m^2/d of CDDP for 5 days with a push of 100 mg/m^2/d of VP 16 for the first 2 days. The overall dose of CDDP, which was at all times shielded from light, never exceeded 25 mg/d. The regimen was repeated every 21 days. All toxic effects of previous therapy were resolved before entry into the study. Abnormal creatinine level ($>150\ \mu M/l$) was the only absolute contraindication.

Results were assessed at the end of the second treatment session. Twenty-two patients showed evaluable effects at that time. Therapy was discontinued if the disease progressed. The patient was considered to have a complete response (CR) if clinical examination and tests (bone marrow, abdominal and thoracic CT scan and appropriate investigations) were normal for more than 1 month. Partial remission (PR) was defined as a greater than 50% decrease in measurable lesions.

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Results

The characteristics of the patients included in this study are listed in Table 1. Most were between 40 and 60 years of age. They had Karnofsky scores of 70%–100%. Nine had low-grade lymphomas and 13 intermediate or high-grade. All had undergone extensive therapy prior to the study. Seventeen were progressing despite therapy and five were relapses. The nine patients with low-grade lymphoma had become refractory to standard therapy and were in the final progressive stage of disease. At the time of treatment 18 presented visceral involvement: nine bone marrow (five high grade), eight lung and six gastrointestinal.

Toxic effects were moderately severe. Myelotoxicity dependent on their prior treatment was mild, with four pa-

Table 1. Patient characteristics

Characteristics	No. of patients
Total entered	22
Age distribution	
<40 years	4
40–60 years	12
>60 years	6
Sex distribution	
Male	17
Female	5
Working formulation	
Low-grade	9
Intermediate-grade	6
High-grade	7
Prior therapy	
Radiotherapy	11
Chemotherapy	
Anthracycline	18
<4 drugs	9
6–8 drugs	13

Table 2. Response to CDDP/VP 16

Type of disease	Response (no. of patients)		
	PD	PR	CR
Resistant lymphomas			
Low grade	2	7	1
Intermediate and high grade	1	6	0
Relapse lymphomas			
Low grade	0	0	0
Intermediate and high grade	1	2	2

PD, Progressive disease; *PR*, partial response; *CR*, complete response

tients showing grade-III leukopenia (WHO codes) and two grade-IV. Grade-III thrombocytopenia was observed in six patients. Adverse digestive effects, which were tolerable, included nausea and grade-II and -III vomiting in ten patients. Renal toxicity in the form of a grade-I increase in creatinine occurred in five cases. Renal toxicity was reversible in three cases and permanent in two. These results point up the advantages of administering CDDP by infusion. There were no treatment-related deaths.

Responses to the combined regimen tested in this study are shown in Table 2. Each patient underwent an average of three sessions (range 2–7). Progressive disease was observed in four patients, three with refractory lymphoma and one relapse. Partial responses were recorded in 15 patients, 13 with resistant lymphomas and two relapses. Of the 13, nine subsequently died of the disease after an average response time of 4 months (1–7). In the remaining four living patients, the average duration of response was 6 months (2–9). The duration of response for the two relapsed patients who achieved a partial response in this study was 4 and 8 months.

Complete responses were obtained in three patients, one with resistant lymphoma and two relapses. The duration of remission in these cases was 10, 4 and 17 months respectively.

Discussion

The combination of etoposide and cisplatinum used in this study was chosen on the basis of preclinical evidence of synergy between cisplatinum and epipodophyllotoxin [9] and because these agents had previously been shown to be effective in phase-II therapy. Like the findings of Judson et al. [6], who used the same regimen but a different mode of administration, our results suggest that this combination therapy deserves further attention. An interesting line of study would be to incorporate this regimen into a protocol of alternating regimens used as initial treatment.

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