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HOAP-Bleo as salvage therapy for diffuse aggressive non-Hodgkin's lymphoma

R. Liang, D. Todd, and T. K. Chan

Department of Medicine, University of Hong Kong, Queen Mary Hospital, Hong Kong

Summary. A total of 30 patients with recurrent or unresponsive diffuse, aggressive non-Hodgkin's lymphoma, who had previously received doxorubicin, cyclophosphamide, vincristine, and prednisone with or without bleomycin were treated with a combination of doxorubicin, vincristine, ara C, prednisone, and bleomycin (HOAP-Bleo). Complete remissions were achieved in 33.3% of the patients and partial remissions in 13.3%. Four of the ten complete responders relapsed at 4, 10, 11, and 18 months. Myelosuppression was the major toxicity and nonhematological toxicities were acceptable. Their median survival from the date of first relapse was only 4–5 months.

Introduction

Patients with intermediate and high-grade lymphomas usually have very poor prognosis if they are refractory to first-line therapy or relapse after inital responses. Various salvage chemotherapeutic regimes have been used, but their response rates are low and the duration of response is short [1, 12]. A regime consisting of doxorubicin, vincristine, ara C, prednisone, and bleomycin (HOAP-Bleo) has been reported to produce a complete remission rate of 36% in patients who failed first-line CHOP therapy [3]. We present the treatment results of this regime in our patients who were refractory to or relapsed after initial responses to first-line CHOP or BACOP therapy [8, 10].

Patients and methods

Between June 1983 and December 1986, 30 evaluable patients with recurrent or poorly responsive intermediate or high-grade non-Hodgkin's lymphoma were included in this study. Their histology was classified according to the Working Formulation [9] and they were staged according to the Ann Arbor system [4]. Their performance scores were <2 [14]. The patient characteristics are shown in Table 1.

Pretreatment assessment included clinical examination, full blood counts, blood biochemistry, chest X-ray, computerized axial tomography of the abdomen, and bone marrow trephine biopsy. All patients had cardiopulmonary evaluation including pulmonary function tests and echocardiograms.

The patients were given a second-line regime (HOAP-Bleo) consisting of 40 mg/m^2 doxorubicin i.v. on day 1, 1.4 mg/m^2 vincristine (maximum, 2 mg) i.v. on day 1, 14 mg/m^2 ara C s.c. every 6 h on days 1–5, 100 mg prednisone orally on days 1–5, and 15 mg bleomycin i.m. on days 1 and 5 [3]. The treatment course was repeated every 28 days if blood counts allowed. A total of 89 courses were given and each patient received 1–8 (median, 2) courses. Bleomycin was omitted in three patients (five courses) because of poor pulmonary function, and vincristine was substituted with 6 mg/m^2 vinblastine (maximum, 10 mg) in two patients (six courses) because of severe neuropathy. Doxorubicin was omitted and the ara C dose escalated to 20 mg/m^2 in seven patients (37 courses) either because of

Table 1. Patient characteristics (No. of patients)

1. Total no of patients			30
2. Sex: male			19
female			11
3. Age (years): median			56
range			23–72
4. Histology:			
(a) Diffuse mixed small cleaved, and large cell			9
(b) Diffuse large cell			19
(c) Diffuse lymphoblastic			1
(d) Diffuse small noncleaved, Burkitt's			1
5. Clinical staging:			
III			8
IV			22
6. Extent of disease:			
lymph node	30	Skin	3
Waldeyer's ring	5	Nervous system	3
Bone marrow	5	Lung	2
Liver	4	Stomach	1
Spleen	3	Ileum	1
7. First-line therapy:			
CHOP	15		
BACOP	15		
8. Response to first-line therapy:			
Complete response	(CR): >12 months		8
	<12 months		9
Partial response	(PR)		11
No response	(NR)		2

Offprint requests to: Raymond Liang, University Department of Medicine, Queen Mary Hospital, Hong Kong

clinically poor cardiac function (two patients) or because the total doxorubicin dose reached 450 mg/m^2 (five patients). Five patients (12 courses) required 50% dose reduction due to marked myelosuppression.

Tumor responses were assessed using standard criteria [14]. The Kaplan-Meier product limit method was used to generate disease-free survival (from the date of the second complete remission to the date of the second relapse) and overall survival (from the date of the first relapse to the date of death or the last follow-up) rates [6]. The complete response rate is expressed with a confidence interval [11].

Results

Complete remissions (CR) were achieved in ten of the 30 patients (33.3%; 95% confidence interval, 19.0%–50.9%). Four of the ten complete responders (40%) relapsed at 4, 10, 11, and 18 months. There were four partial responses (PR) (13.3%), which lasted for 1, 2, 2, and 3 months. Responsiveness to HOAP-Bleo appeared to correlate with neither the first-line regime used nor the previous response to first-line therapy, but the number of patients in each subgroup was too small for proper statistical analysis. Patients who had previously received CHOP or BACOP had a similar response rate of 5/15 (33.3%) following HOAP-Bleo. The CR rates of patients with previous CR (>12 months), CR (<12 months), PR, and no response (NR) following first-line therapy were 3/8 (38%), 3/9 (33%), 4/11 (36%), and 0/2 (0%), respectively.

Myelosuppression was the major toxicity of the regime. The nadir counts usually occurred within the first 1–2 weeks. The median nadir white cell and platelet counts were 1.5×10^9/l (range, $0.3–3.8 \times 10^9$/l) and 66×10^9/l (range, $13–169 \times 10^9$/l), respectively. There were seven febrile episodes in five patients; in three of these, infective organisms were cultured from the blood. Severe bleeding occurred in two patients (one gastrointestinal and one cerebral hemorrhage). There were three aplastic deaths (two cases of septicemia and one cerebral hemorrhage).

All patients experienced nausea and vomiting and had alopecia. Four patients had severe mucositis, one had intestinal obstruction probably related to vincristine, and one had pulmonary fibrosis due to bleomycin. Two patients had severe peripheral neuropathy requiring a change from vincristine to vinblastine.

Eleven patients who had progressive disease following HOAP-Bleo were offered third-line chemotherapy (IMVP-16) consisting of ifosfamide, methotrexate, and VP-16 [2, 3] but none of them responded.

The disease-free survival of the ten complete responders and the overall survival of all 30 patients are shown in Fig. 1. The median survival of all patients from the date of their first relapse were 4–5 months. Only three patients survived beyond 24 months, and one of them died of recurrent disease at 30 months.

Discussion

A previous report has shown that the HOAP-Bleo regime can achieve CR in 36% of patients refractory to CHOP [3]. A similar CR rate of 33.3% was observed in our patients using a similar regime, although a significant proportion of our patients required treatment modifications for various reasons. Our patients received two different first-line regimes (CHOP and BACOP), and the responses to HOAP-Bleo of the two groups were identical. The previous responsiveness to first-line therapy did not appear to predict response to HOAP-Bleo.

As all our patients received doxorubicin, vincristine, prednisone, and half of them bleomycin, in their first-line

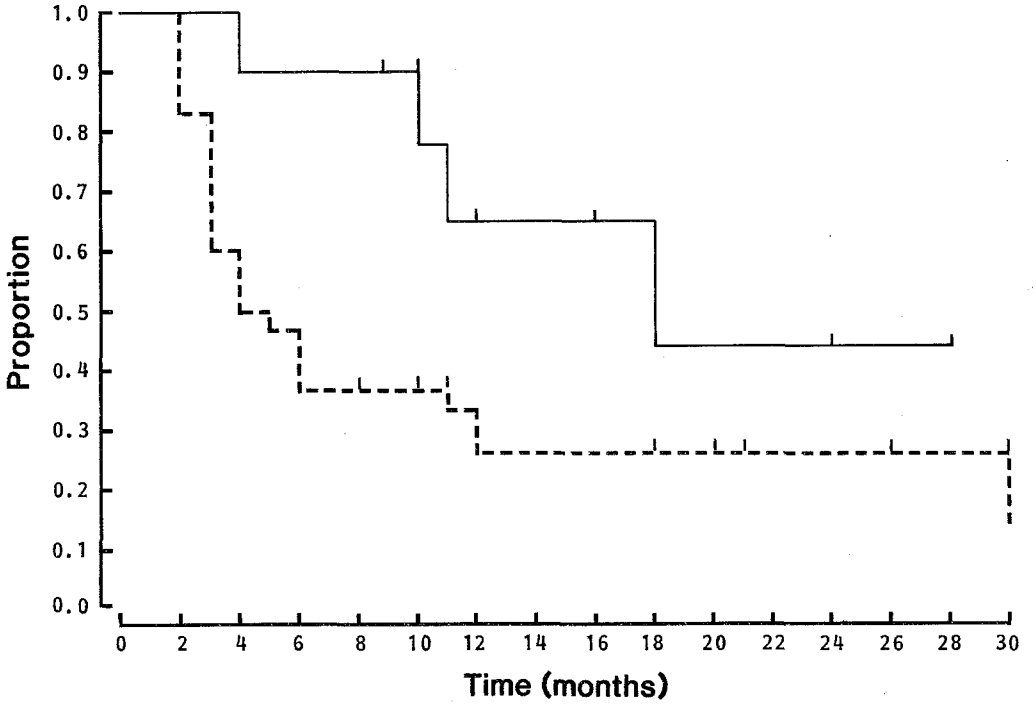

Fig. 1. The disease-free survival of the ten complete responders (———) and the overall survival of all 30 patients following HOAP-Bleo (– – – –)

therapy, ara C is probably the most active drug in the HOAP-Bleo regime. Ara C has been incorporated into various first-line regimes achieving good results [1, 12].

Myelosuppression was the major toxicity of the HOAP-Bleo regime. Our three aplastic deaths were contributed to by uncontrolled lymphoma as well as myelosuppression. Nonhematologic toxicities of the regime appeared to be acceptable.

The response rates of other salvage regimes are variable, with CR rates ranging from 5% to 37% and PR rates, from 13% to 47%, and their response durations are generally short (< 12 months) [12]. The efficacy of the HOAP-Bleo regime appears to be comparable to other salvage regimes currently available. The newer generations of more intensive first-line regimes may be able to reduce the number of treatment failures [1, 12]. However, these first-line regimes incorporate most of the active agents, and patients who fail this intensive treatment will have very few salvage regimes available [1, 5, 7, 12, 13].

Experimental approaches using high-dose chemotherapy, total body irradiation, and autologous bone marrow transplantation are being explored. The value of these new treatment approaches remains to be determined [1, 12].

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