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Short communication

Treatment of resistant non-Hodgkin's lymphomas with cisplatin, etoposide, and bleomycin

Pasquale Comella, Giuseppe Abate, Giuseppe Di Finizio, Antonio Daponte, and Donato Zarrilli

1st Division of Medical Oncology, National Tumor Institute, Cappella dei Cangiani, 80131 Naples, Italy

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Summary. A combination of cisplatin (60 mg/m^2 i.v. on day 1), etoposide (100 mg/m^2 i.v. on days 1–3) and bleomycin (15 mg i.v. on days 1 and 8) (PEB regimen) was given every 4 weeks as salvage therapy in 10 refractory and 13 relapsing patients with poor-prognosis non-Hodgkin's lymphomas. All but one of these patients had previously been treated with anthracycline-containing combination chemotherapy. We observed 4 complete remissions (CRs) and 4 partial responses (PRs), whereas 3 patients showed only a minor response (MR) and 12 were considered to be induction failures. Therefore, the objective (CR+PR) response rate was 35%. The most frequent side effect was vomiting, registered in all patients despite antiemetic treatment. Hematologic toxicity was of moderate degree, and bone marrow recovery was observed after almost all cycles after a 3-week rest period. Since objective responses were achieved only in relapsing patients, the PEB regimen seemed to be effective in these cases, whereas it was useless in early refractory non-Hodgkin's lymphomas.

Introduction

Despite the increase in complete remission (CR) rate recently obtained in advanced poor-histology non-Hodgkin's lymphomas (NHL) with aggressive treatment, a significant number of patients still either do not enter a CR or subsequently show a recurrence of disease. The life expectancy of these patients is very short, with almost all of them dying within a few months. Therefore, there is a need for new chemotherapeutic approaches to rescue these refractory patients. Unfortunately, the salvage regimens used up to now have shown significant activity in only a small fraction of these patients. To our knowledge, only the MIME (methylgag, ifosfamide, methotrexate, etoposide) regimen obtained an objective response rate as salvage treatment comparable with those achieved by first-line treatment [1].

For these reasons, at the end of 1985 we devised a new combination of cisplatin, etoposide and bleomycin (PEB) for testing in refractory NHL. The rationale of our choice involved several considerations. First of all, these drugs were previously known to be effective as single agents in NHL [2, 7], and there was some evidence of synergistic activity between cisplatin and etoposide [8, 14] as well as between cisplatin and bleomycin [5, 10] in solid tumors as well as in lymphomas. Moreover, none of these drugs was included in our first-line treatment for NHL, in hopes that there would be no cross-resistance with the PEB regimen. Finally, cisplatin, etoposide and bleomycin are slightly myelotoxic drugs and they should therefore be better tolerated in heavily pretreated patients.

Patients and methods

From September 1985 to February 1989, 25 consecutive patients with NHL were enrolled in this trial. Eligibility criteria included persistent or progressive disease after front-line therapy or a recurrence of disease after a previously unmaintained CR; a diagnosis of intermediate or high-grade histology NHL according to the Working Formulation [12] or that of a low-grade malignancy coupled with bulky tumor mass and/or B symptoms; the presence of measurable localizations; complete recovery from previous treatment, with a white blood cell (WBC) count of $>3 \times 10^9$/l and a platelet count of $>75 \times 10^9$/l and baseline serum levels of <1.5 mg/dl for creatinine and <1.2 mg/dl for bilirubin.

Pretreatment assessment included a physical examination, a chest X-ray and bone marrow biopsy with the Jamshidi needle in all cases. Subdiaphragmatic spread of disease was detected by bipedal lymphography and/or abdominal echotomography and, in selected cases, with abdominal computerized axial tomographic (CAT) scan. Other examinations were done only if necessitated by clinical conditions.

Patients that fulfilled the above-mentioned inclusion criteria were assigned to receive at least two cycles of the PEB regimen for an adequate evaluation and up to six courses if they showed any response. The PEB regimen consisted of 60 mg/m^2 cisplatin (CDDP) given i.v. after a short prehydration on day 1; 100 mg/m^2 etoposide (VP16) given as a 30-min infusion on days 1–3; and 15 mg bleomycin (BLM) diluted with 100 mg hydrocortisone, given by i.v. push on days 1 and 8. Courses were repeated every 4 weeks.

Offprint requests to: Pasquale Comella

Table 1. Main characteristics of evaluable patients

Characteristics	Patients (*n*)
Evaluable patients	23
Median age (range) in years	59 (41–75)
Men/women	7/16
ECOG performance status:	
1–2	18
3–4	5
Low-grade malignancy	5
Intermediate malignancy	14
High-grade malignancy	4
Extranodal disease (leukemic)	8 (4)
Constitutional symptoms	8
Bulky disease	20
Previous chemotherapy	23
With anthracyclines	22
Two or more regimens	4
Refractory patients	10
Relapsing patients	13

Table 2. Responses to the PEB regimen

Responses	Number	(%)	Duration in months
Complete remission	4	(17.5)	7, 8, 9, 9
Partial remission	4	(17.5)	2+, 3+, 6+, 8
Minor response	3	(13)	2, 2, 7+
No change	7	(30)	–
Progressive disease	5	(22)	–

Table 3. Responses related to disease-free status

Characteristics	Response to therapy:					Total
	CR	PR	MR	NC	PD	
Refractory patients	–	–	2	6	2	10
Relapsing patients	4	4	1	1	3	13
Totals	4	4	3	7	5	23

For evaluation of hematologic toxicity, WBC and platelet counts were done weekly during the whole treatment. Serum creatinine, electrolytes, bilirubin, SGOT and SGPT values and urinalysis were assessed befor and 7 days after each course of therapy. Furthermore, any other relevant toxicity was recorded and scored according to WHO criteria [11]. Responses to therapy were classified in the following categories: patients were considered to be in CR if clinical examination and initially abnormal tests showed no evidence of disease for at least 1 month, whereas a decrease of >50% or >25% of all measurable localizations was defined as a partial (PR) or a minor (MR) response, respectively. On the other hand, no change (NC) in preexisting sites or the appearance of new sites (PD) of disease were judged as being induction failures. The duration of responses was calculated in months, from the start of chemotherapy to the date of documented recurrence or progression of disease.

Results

Of 25 patients admitted to this trial, 2 were considered to be unevaluable for response. Indeed, one patient refused further treatment after the first cycle because of intolerable chemotherapy-induced vomiting and was therefore withdrawn from the study; another patient was lost to follow-up while still on treatment.

Table 4. Objective response rate related to prognostic factors

Characteristics (number of patients)	CR+PR	(%)
Evaluable patients (23)	8	(35)
Nodal disease (15)	7	(47)
Extranodal disease (8)	1	(12)
Low-grade malignancy (5)	2	(40)
Intermediate malignancy (14)	4	(29)
High-grade malignancy (4)	2	(50)
ECOG performance status 3–4 (5)	3	(60)
B symptoms (8)	3	(37)
Bulky disease (20)	7	(35)
Refractory patients (10)	0	–
Relapsing patients (13)	8	(62)

The main characteristics of 23 evaluable patients are presented in Table 1. Most patients had a good performance status, but some of them were also in very bad clinical condition. The subset of intermediate-grade malignancy accounted for about two-thirds of all histologies, whereas an almost superimposable number of patients were affected by low- or high-grade malignancy.

Furthermore, 20/23 (87%) patients showed bulky disease represented by either nodal masses >10 cm in their largest diameter or an enlarged spleen or both. As previously stated, all patients had received at least first-line therapy, and four patients had also undergone second-line treatment. Moreover, all but one had been treated with anthracycline-containing drug combinations (usually CHOP or CEOP regimens) [3, 4]. In all, 10 patients were considered to be refractory to prior therapy because of persistent (4 cases) or progressive (6 cases) disease, whereas 13 patients were admitted to this study with disease recurrence after a CR lasting 2–60 (median, 14) months.

The 23 evaluable patients received a median number of 4 (range, 2–6) courses of PEB. Therapeutic responses to this regimen are reported in Table 2. On the whole, 11 patients (48%) showed a response to PEB chemotherapy, whereas 12 (52%) were considered to be induction failures. More in detail, eight patients (35%) achieved a major (CR or PR) response with this treatment. Indeed, four patients achieved a CR lasting 7 (1), 8 (1), and 9 months (2), respectively. All of these patients subsequently relapsed and died of their disease within 8–39 months of starting PEB. Four patients achieved a PR with this treatment. However, one of them died at home after the fifth cycle, likely due to an infectious complication, as her last clinical evaluation had shown complete disappearance of mediastinal involvement and a substantial shrinkage of peripheral nodes. Another patient affected by lymphoblastic lymphoma during his first relapse achieved a rapid tumor regression with three courses of PEB, after which he was shifted from this trial to ablative chemotherapy and autologous bone marrow transplantation. In two other patients the PR lasted 6+ and 8 months, respectively.

In Table 3, responses to the PEB regimen are related to the disease-free status of patients before their admission to this trial. Relapsing patients showed an objective (CR or

Table 5. Toxicity of PEB regimen

Toxicity	Patients	
	(*n*)	(%)
Leukocytes[a] $<2 \times 10^9$/l	17	(74)
Platelets[a]:		
$<75 \times 10^9$/l	6	(26)
$<50 \times 10^9$/l	4	(17)
Vomiting:		
grade I–II	9	(39)
grade III–IV	16	(61)
Infection grade I–II	10	(43)
Fever by bleomycin	8	(35)
Constipation grade I–II	7	(30)
Diarrhoea grade I	6	(26)
Skin pigmentation	3	(13)
Toxicity-related death (?)	1	(4)

[a] Assessed weekly during treatment

PR) response in 8/13 (62%) of cases, whereas only 2 MRs were observed among refractory patients. Table 4 shows the objective (CR+PR) response rate according to the prognostic characteristics of our patients. Only refractory or extranodal disease adversely affected the effectiveness of PEB, whereas no significant difference in response rate was related to histologic subgroups, constitutional symptoms, or bulky disease.

As regards hematologic toxicity, 17 patients (74%) experienced grade III leukopenia and 10 (43%) showed grade II (6 cases) or III (4 cases) thrombocytopenia during the interval between cycles (Table 5). However, the evaluation carried out for 93 courses of treatment ascertained that in almost all cases there was a bone marrow recovery after 3 weeks from the start of chemotherapy (Table 6).

All patients complained of moderate or severe vomiting despite antiemetic treatment (1 mg/kg i.v. metoclopramide before as well as at 1 and 2 h after CDDP infusion) and, as mentioned above, one patient refused further chemotherapy because of this side effect. At times during their treatment, ten patients suffered infectious complications, usually of the upper or lower respiratory tract. These infections were always mild or moderate, and they never required hospitalization. However, a patient died at home during the rest period between cycles, and this sudden death was ascribed by her attending physician to a fulminating sepsis. Intestinal disturbances, as well as side effects of BLM, were less frequently seen. No liver or renal damage was revealed in any patient by laboratory tests conducted after each cycle of therapy.

Discussion

Among the anticancer agents tested in phase I–II trials that showed some activity in NHL, CDDP and VP16 have more frequently been used, alone or in combination with other drugs, in the salvage management of resistant patients.

The combination of CDDP and VP16 has been tested in several trials using different doses and schedules, and conflicting results were obtained. Judson and Wilthshaw [8] used CDDP (50 mg/m^2 on day 1) and VP16 (100 mg/m^2 on days 1–3) every 3 weeks; they observed objective responses in 53% of 17 evaluable patients refractory to standard combination chemotherapy. Furthermore, Tubiana et al. [16] subjected 22 resistant or relapsed patients to a continuous infusion of CDDP (15 mg/m^2 daily) for 5 days with an i.v. push of VP16 (100 mg/m^2) given on the first 2 days; treatment was repeated every 3 weeks, and 18 patients (82%) showed a response to this regimen. However, 15/18 of these patients achieved only a PR of short duration (1–9 months). Kroner et al. [9] used a combination of CDDP (60 mg/m^2 on day 1), VP16 (120 mg/m^2 on days 3–5) and prednisone (60 mg/m^2 on days 1–5) every 3 weeks and reported only 5 PRs (38% response rate) among 13 evaluable patients in progression with front-line therapy.

CDDP or VP16 have also been combined with other active drugs in advanced resistant NHL. In fact, a combination of CDDP (80 mg/m^2 as a continuous infusion), vinblastine (0.1 mg/kg on days 1 and 2) and BLM (10 units weekly) given every 4 weeks was used by Liepman et al. [10], with objective responses in 35% of patients, whereas Corder and Clamon [5] obtained only 5 PRs (38% response rate) among 13 patients treated with a similar drug combination.

Moreover, Tseng et al. [15] reported an overall response of 43% in patients treated with CDDP (60 mg/m^2 on day 1), cytarabine (90 mg/m^2 on days 1–3) and teniposide (60 mg/m^2 on days 1–3), every 3 weeks, whereas a combination of CDDP (80 mg/m^2 on day 1), cytarabine (300 mg/m^2 given by continuous infusion on day 1) and VP16 (200 mg/m^2 on day 1) was given by O'Donnel et al. [13] to 35 recurrent or refractory patients resulting in a 32% overall response rate. On the other hand,

Table 6. Median WBC and platelet counts assessed weekly during treatment[a]

Blood count	Day 1	Day 7	Day 14	Day 21	Day 28
WBC ($\times 10^9$/l):					
Median	6.3	3.5	2.4	4.6	6.3
Range	3–57	0.25–39	0.65–31	1.8–	
%>3 $\times 10^9$/l	100%			83%	96%
Platelets ($\times 10^9$/l):					
Median	213	155	153	225	229
Range	48–480	19–374	20–485	40	
%>100 $\times 10^9$/l	98%			95%	95%

[a] Evaluated for 93 courses of chemotherapy

VP16 was also a component of the aforementioned MIME regimen [1], which purportedly attained a 74% remission rate in recurrent lymphomas. However, it should be borne in mind that this proportion falls to about 40% if we consider only patients who either failed to respond or progressed while on front-line therapy. Such a variability in the results could perhaps be ascribed to the heterogeneity of the patient population included in the reported series.

Therefore, the 35% objective response rate (95% confidence limit, 16%–57%) obtained in our trial using the PEB regimen is in the range of activity reported for other salvage treatments. The addition of BLM to CDDP and VP16 in the present trial did not seem to enhance the effectiveness of the latter drugs, but our results may have been influenced by pretreatment characteristics of patients; on the other hand, a synergism between CDDP and BLM in NHL has been stressed by other authors [5, 10].

As reported for other salvage regimens [1, 10, 13], the highest degree of antitumor activity of PEB was documented in relapsing patients (62% overall response rate). Furthermore, CRs+PRs were also observed in patients who had previously been treated with regimens containing anthracyclines [3, 4]. Although not strictly probative, this finding suggests a lack of cross-resistance between PEB and the previously used drugs. In contrast, no major responses occurred in patients refractory to the front-line treatment. An early pleiotropic drug resistance could probably account for this discouraging result [6]. Furthermore, 5/10 of these patients had stage IV disease and it seemed to us that the extranodal spread of disease adversely affected the response to PEB. Therefore, the PEB regimen does not seem to be usefull in patients who have not achieved a CR with standard induction chemotherapy, namely, in whom a progression to extranodal sites has occurred.

The hematologic toxicity of PEB was of moderate degree. Indeed, although 74% of patients developed grade III leukopenia at some time during the interval between cycles, complete bone marrow recovery occurred during the planned rest period after almost all courses of chemotherapy. Furthermore, thrombocytopenia was less frequently seen, and it was often mild. These findings suggest that it should be possible to shorten the interval between cycles to 3 weeks.

Cisplatin-induced vomiting was the most distressing side effect of PEB chemotherapy. It was severe in the majority of patients, and in one case it precluded the continuation of treatment. We are aware that this troublesome side effect should be minimized or, if possible, avoided in physically and psychologically debilitated patients. Therefore, in this regard we cannot consider the PEB regimen to be an easily tolerable therapy.

Infection was also a frequent complication in our patients, and it was likely related to the transient granulocytopenia occurring between cycles. However, this complication was usually manageable on an outpatient basis, and only one case of a sudden death at home, probably due to sepsis, was recorded in our series. Other relevant toxicities did not affect the completion of treatment by any patient.

In conclusion, in our trial the PEB regimen obtained an objective response in about one-third of the patients treated. A higher effectiveness was observed among relapsing patients, in whom complete remissions, although short in duration, were also reached. For this reason, we think that it would be justifiable to incorporate the PEB regimen, alternated with other well-tried multidrug combinations, in the management of advanced aggressive-histology NHL. However, we cannot suggest the use of this combination chemotherapy in early refractory patients, and we think that new approaches of therapy should be investigated.

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