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Peptichemio in Pretreated Patients with Plasmacell Neoplasms

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Abstract—*Twenty-one patients with alkylator-resistant plasmacell neoplasms were treated with Peptichemio (PTC) at a dose of* 40 mg/m^2 *for* 3 days *every* 3 weeks *or, in the case of persistent leukopenia and/or thrombocytopenia, at the single dose of* 70 mg/m^2 *every* 2–3 weeks *according to haematological recovery. Seventeen patients,* 10 *with multiple myeloma and seven with extramedullary plasmacytoma (EMP), were fully evaluable. Six of* 17 *patients* (35%) *responded: three of seven EMP patients had a complete remission and* 3 *of* 10 *multiple myeloma patients had an objective response* > 50%. *The median duration of response was* 8.5 months. *An EMP patient obtained a complete response lasting for* 16 months. *The most frequent toxic effect were phlebosclerosis, occurring in all the patients, and myelosuppression, which was severe in only one case. PTC appears to be an active drug in patients with plasmacell neoplams even if resistant to alkylating agents.*

INTRODUCTION

PEPTICHEMIO (PTC) is a peptidic compound, consisting of a mixture of six different synthetic peptides containing *m*-L-phenylalanine mustard [1]. Its mechanism of action is that of an alkylating agent, but in vitro it has also shown antimetabolic activity. At the molecular level it inhibits DNA synthesis, DNA polymerase, reverse transcriptase and protein synthesis [2–4]. The cell phase sensitivity patterns do not coincide with those observed for L-phenylalanine mustard [5]. The antitumour activity of PTC has already been demonstrated in experimental tumours (i.e., L 1210 Leukemia, Yoshida sarcoma, Sarcoma 180, and Adenocarcinoma 755) [2, 3]. In clinical studies PTC proved to be active against a variety of solid tumours [6–10] and lymphoproliferative diseases [11–13].

In myeloma patients resistant to intermittent melphalan–prednisone or to other drug combinations various drugs have been tested, but only a few have shown some activity, i.e. adriamycin [14], hexamethylmelamine [15], vincristine [16], vindesine [17] and procarbazine [18].

Two recent studies in a small number of patients have demonstrated the possibility of obtaining objective responses with PTC in pretreated patients [12, 13]. The use of this drug in plasmacell neoplasms seems particularly interesting for its double mechanism of action, combining the alkylating to the antimetabolic effect.

We report here the results obtained in a group of patients with plasmacell neoplasms resistant to prior chemotherapy with alkylating agents.

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MATERIALS AND METHODS

Patients

Between January 1978 and June 1985, 21 patients, 14 with multiple myeloma and seven with extramedullary plasmacytoma (EMP) were treated with PTC. Diagnosis of multiple myeloma was established according to the criteria of the Chronic Leukemia–Myeloma Task Force guidelines [19]; the diagnosis of extramedullary plasmacytoma was histologically proven. Patients with multiple myeloma were divided in stages using the quantitative staging system proposed by Salmon [20]; those with EMP were staged according to the system adopted by Wiltshaw [21].

All patients had previously received as first line therapy and at relapse the M-2 regimen (melphalan, cytoxan, vincristine, BCNU and prednisone) [22]. In addition, prior to PTC 14 patients had also received monochemotherapy with a single

alkylating agent and/or a cyclospecific agent (vindesine). All patients entered in PTC study had resistant disease as shown by progression while on M-2 regimen: three of them were initially resistant and 18 became resistant at reinduction.

Treatment

PTC was diluted in 100 ml of 5% dextrose solution and was administered i.v. over a period of 20–30 min at a dose of 40 mg/m^2 for 3 consecutive days every 3 weeks, according to the schedule proposed by Grose *et al.* [23]. In patients starting with myelosuppression (WBC < 3.500/μl and/or platelets < 120.000/μl), PTC was given at the single dose of 70 mg/m^2 every 2–3 weeks according to haematological recovery [24]. To avoid allergic reactions due to the peptide content, PTC was preceded by chlorphenamine maleate (10 mg i.m.) 30 min. before PTC influsion.

In patients with complete remission, therapy was discontinued; in patients with partial remission therapy was continued until relapse.

Evaluation

Myeloma cell mass changes were calculated from changes in serum paraprotein production rate using a computerized system developed by Salmon and Wampler [25]. In patients with multiple myeloma an objective response was defined as a reduction of 50% or more of the paraprotein production rate and a decrease of 90% or more of urinary Bence Jones protein. In patients with EMP complete remission was defined as the complete disappearance of all measurable lesions and of paraprotein from serum and urine for at least 1 month, and partial remission as a > 50% reduction in the product of the two longest perpendicular diameters at all sites of measurable disease and a decrease of 50% or more of the paraprotein production rate. Blood haemoglobin concentration above 9.0 g/dl, serum albumin above 3.0 g/dl and calcium level below 12 mg/dl were necessary requirements for a response to be accepted. Toxicity was evaluated according to the WHO criteria.

RESULTS

Responses

Of the 21 patients entered into this study, four patients having multiple myeloma were not evaluable: two because of non-treatment related early death before the beginning of the second course and two because of major violation of the protocol. The patients received a median dose of 530 mg of PTC (range 160–1840 mg). The main characteristics of the patients and therapeutic results are presented in Table 1.

Among the 17 evaluable patients there were six responses (35%): three complete remissions and three objective responses (> 50%). On the average the maximum degree of response was observed after five courses (range: three to eight); the median duration of responses was 8.5 months.

Complete remissions occurred in EMP patients: one patient, with a gross thoracic mass, IgG secreting, after an initial response to M-2 regimen, progressed with pleural, pericardial and mediastinal involvement. Abnormal plasmacells and monoclonal immunoglobulins were found in both pleural and pericardial effusions; the patient was treated with PTC and obtained a complete remission lasting for 16 months and relapsed with an abdominal mass. Another patient with an EMP arising in the nasal passage, after an initial response to M-2, developed diffuse subcutaneous nodules no longer responsive to the same chemotherapy and resistant also to vindesine plus high dose prednisone: PTC was started and the patient obtained a complete response lasting for 3 months. A third complete remission was obtained in a relapsing EMP of the maxillary sinus, which was resistant to M-2 regimen and to Vindesine.

In multiple myeloma there were three objective responses: one of more than 75% (lasting 4 months) and two of more than 50% (lasting 2 and 12+ months). In addition three other patients had a stable disease for more than 2 months. All the patients responsive to PTC had previously responded to the M-2 regimen. The low number of patients does not permit a correlation between the response to PTC and the previous dosage of alkylating agents.

Toxic effects

The treatment was generally administered on an outpatient basis. Myelosuppression, evaluated on the day of the subsequent drug injection, was the most prominent side effect (Table 2) and was more frequent in heavily pretreated patients, especially after the third course. The median duration of leukopenia and thrombocytopenia was 8 days, with no important difference between the two dose schedules. Almost all the patients suffered clinical phlebitis, consisting of firm oedema evolving in sclerosis of the vein. Hydration or eparine infusion after PTC did not reduce the occurrence of phlebosclerosis. Gastrointestinal toxicity (nausea and vomiting) was noted rarely and was never severe. In one instance generalized skin rashes associated with bronchospasm, promptly responded to corticosteriod therapy, appeared soon after PTC infusion.

DISCUSSION

The standard therapy of multiple myeloma is based on the use of melphalan and prednisone. Most patients, especially with combination chemo-

Table 1. Patient characteristics and therapeutic results of the 17 evaluable patients

				Prior chemotherapy							Response Parameters				
No.*	Age	M-Protein	Clinical stage	Regimen-drugs†	Response‡	Total dose (mg) of EX†	MLF†|B/CCNU		Disease duration prior to PTC (mo.)	Dose of PTC (mg)	Response‡	Changes§ (%)	Site of disease (EMP)	Response duration (mo.)	Survival from PTC (mo.)
1 EMP	35	IgGk	IA	M-2	CR	5000	420	760	30	320	SD	−15	nose		2
2 EMP	67	non secretory	IIIA	M-2	P	2400	135	120	3	360	P	+130	abdominal masses		1.5
3 EMP	45	IgGk	IIIA	M-2,VDS	CR	12750	1350	1275	38	720	P	+50	frontal sinus		7
4 EMP	54	IgGλ	IA	M-2,VDS	CR	6300	630	360	17	700	CR	−100	thoracic mass	16	19
5 EMP	47	non secretory	IIA	M-2	CR	3000	200	160	21	990	CR	−100	maxillary sinus	5+	6+
6 EMP	45	IgGk	IA	M-2,VDS, DDP+VP16	CR	4800	900	760	36	630	CR	−100	maxillary sinus, subcutaneous nodes	16	19
7 EMP	50	non secretory	IIIA	M-2	P	3200	185	480	18	160	P	+70	abdominal masses		4
8 MM	58	IgGk	IIIA	M-2,ADR	SD	6840	720	60	30	680	SD	+113			33
9 MM	54	IgGk	IIIA	M-2	OR	1440	480	240	18	540	P	+26			
10 MM	48	Lk	IIIB	M-2,VDS	OR	10400	1020	610	70	1180	OR	−92		12+	13+
11 MM	46	Lk	IIIA	M-2	OR	14580	1215	1125	27	1840	P				48
12 MM	57	IgGk	IIA	M-2,EX	OR	31200	320	520	101	240	SD	+12			8
13 MM	55	IgAk	IIIB	M-2,VDS	P	3000	50	620	4	320	SD	+1			4
14 MM	66	IgGλ	IIA	M-2,ADR, BCNU,VDS	OR	11350	1175	1130	70	260	P	+58			5
15 MM	37	IgAλ	IIA	M2,EX,CCNU ADR+BCNU	OR	23400	2000	540	9	520	OR	−80		4	8
16 MM	53	IgAk	IIIA	M-2	OR	7260	1040	560	31	480	OR	−65		2	8
17 MM	66	IgGk	IIIA	M-2,EX,CCNU	SD	13200	80	730	36	160	P	+30			4

*MM: Multiple myeloma; EMP: extramedullary plasmacytoma.

†VDS: Vindesine; EX: endosan; DDP: cisplatin; ADR: adriamycin; VLB: velbe; MLF: melphalan; BLM: bleomycin.

‡CR: Complete remission; SD: stable disease; OR: objective response (≥50%, in multiple myeloma); P: progression.

§Per cent reduction in M-protein (MM) or measured tumor area (EMP).

Table 2. Toxicity according to WHO criteria

Haemathological:	
Hb (g/100ml)	
9.5–10.9	6
8.0–9.4	5
6.5–7.9	2
< 6.5	–
WBC count (1000/cmm)	
3.0–3.9	5
2.0–2.9	6
1.0–1.9	3
< 1.0	–
Platelet count (1000/cmm)	
75–99	2
50–74	1
25–49	1
< 25	1
Gastrointestinal:	
nausea	2
transient vomiting	4
vomiting requiring therapy	1
Allergic reaction with bronchospasm	1

therapy, can achieve a 50–75% tumour regression remaining in remission for 12–24 months before the onset of relapse [26, 27]. At relapse a number of single agents and combination chemotherapy approaches have been used, but generally the results have been disappointing. Bergsagel in 1972 reported a 58% response rate with a median survival of 21 months in patients refractory to melphalan therapy who were subsequently treated with cyclophosphamide [28]. However, most investigators have found only occasional responses in this situation [29] and recently White and Bergsagel also reported a response rate of only 9% with cyclophosphamide [30]. Only a few other chemotherapeutic agents have shown activity in melphalan-resistant patients: adriamycin, hexamethylmelamine, videsine and procarbazine have reduced tumour masses in occasional patients [14–18]. More recently with a regimen that combined 4-day infusions of Vincristine and Doxorubicin and intermittent high dose dexamethasone about one-half of myeloma patients with advanced refractory disease achieved tumour reduction of at least 50%: in responding patients, remissions were of excellent quality and survival was prolonged significantly [31].

Peptichemio is an antitumour drug with alkylating and antimetabolic activity: it has already shown effectiveness in several types of solid tumours and blood malignancies. Cavo *et al.* [12] and Merlino *et al.* [13] obtained responses respectively in 3 of 11 and in two of four initially resistant or relapsing patients with multiple myeloma. However, in both studies the patients received also prednisone in addition to PTC.

We administered PTC to a group of patients with plasmacell neoplasms: the drug was given intravenously and without prednisone. Of 17 evaluable patients six responded: there were three complete remissions among seven patients (43%) with EMP and three objective responses among 10 patients (30%) with multiple myeloma. Our patients were relapsing or had resistant disease while on treatment with M-2; some of them had also received before PTC a single alkylator and/or vindesine plus prednisone.

McElwain and Powles obtained responses with high dose (100–140 mg/m^2) intravenous melphalan in five of eight patients resistant to standard doses of oral melphalan plus prednisone [32, 33]. It was shown that melphalan given per os is irregularly and incompletely absorbed, with a higher blood concentration if it is taken fasting [34]. Since PTC contains *m*-L-phenylanine mustard these data could suggest that the effectiveness of PTC in our study may be due to the way of administration (intravenus) rather than to a real non-cross resistance with melphalan. In the study of McElwain and Powles, however, high dose i.v. melphalan was followed by severe haematological toxicity and multiple infections, requiring massive supportive therapy in all patients. On the contrary in our study the haematological toxicity was mild, suggesting a true non-cross resistance between PTC and melphalan.

The responses were obtained administering PTC for 3 days as well as with the single dose administration, with no important difference in the response rate between the two dose schedules.

In conclusion, this study on PTC in plasmacell neoplasms patients shows that this drug is active in patients who have acquired resistance to alkylating agents. Further studies are necessary to define the best schedule of administration and the response rate in a wider group of patients with plasmacell neoplasms.

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