Cancer Chemother Pharmacol (1982) 8:9–16

Cancer Chemotherapy and Pharmacology

Peptichemio Induction Therapy in Myelomatosis

Giampaolo Merlini, Paolo G. Gobbi, Alberto Riccardi, Guido Riva, Carlo Sardi, and Sergio Perugini †

Institute of Medical Pathology I, University of Pavia, Policlinico S. Matteo, I-27100 Pavia, Italy

Summary. *Fifteen patients with multiple myeloma, two of whom had plasma cell leukemia, were treated between May 1974 and December 1978. Peptichemio was administered intravenously at doses of 40–80 mg/48 h, courses including 4–17 administrations in association with moderate doses of prednisone (15–50 mg/day) and androstanes at high dosages (250 mg weekly). In two patients PTC was associated with vincristine (VCR) administered on the first day of the course. Eight patients were previously untreated, four had been resistant to melphalan (MPH) and/or cyclophosphamide (CTX), and three had been treated irregularly with one or both of these alkylating agents. The criteria of response to therapy are reported. Out of a total of 15 PTC courses administered we obtained 13 responses, eight complete and five partial; no response was achieved in the other two patients.*

In the four patients who were resistant to MPH and/or CTX we obtained three responses, which were maintained with the same alkylating agent to which they had been resistant previously. The time needed to obtain a response in 90% of the patients was 6 weeks. Peptichemio was shown to be effective in patients in an advanced stage of the disease, in patients with light-chain myeloma and in those with plasma cell leukemia. The association of VCR potentiated the antitumor effect, but also increased the myelotoxicity. The PTC treatment was well tolerated.

It is suggested that PTC be used in induction treatment of myelomatosis and in patients resistant to traditional alkylating agents.

Introduction

Since the introduction of effective chemotherapy with the alkylating agents melphalan (MPH) and cyclophosphamide (CTX), the median survival time for multiple myeloma patients has more than doubled, from 7–11 months to 24–50 months [3, 8, 16, 21, 32].

However, only 15% of patients achieve complete remission, and 'cures' are extremely rare [4, 10]. Thus great efforts have been made in recent years to discover new drugs active against plasma cell neoplasms and to develop new combination chemotherapy schedules to prolong survival time.

Rather recently, several drugs with different mechanisms of action have been tried in the treatment of multiple myeloma. Procarbazine [24] and adriamycin [1, 2] showed a low order of activity, whilst BCNU [30] and especially vincristine (VCR) [2, 5, 28] gave promising results.

Less attention was paid to the preliminary positive results reported by Marmont et al. [20], Astaldi et al. [6] and Luporini [19] with peptichemio (PTC) in the treatment of multiple myeloma.

Peptichemio is constituted by m-[di-(2-chloroethyl)-amino]-L-phenylalanine (sarcolysin) covalently bound to six peptides to combine the alkylating to the antimetabolic effect (Fig. 1) [11]. It is manufactured by Istituto Sieroterapico Milanese, Milan, Italy. Several studies [13, 14] have shown its broad spectrum of activity against carcinoma, lymphoma, and acute leukemia.

We tried PTC in two patients with plasma cell leukemia [25]; the good response observed led us to undertake a trial in patients with multiple myeloma. The goal of this study was the better evaluation both of the activity of PTC against myelomatous plasma cells and of its mode of action, by clinical and cytokinetic studies.

The cytokinetic modifications induced by PTC in plasma cells have been reported in a previous paper [27]. The present study concerns the clinical results obtained in 15 patients, 7 of whom had been resistant

Reprint requests should be addressed to G. Merlini at the above address

† Deceased

0344-5704/82/0008/0009/$ 01.60

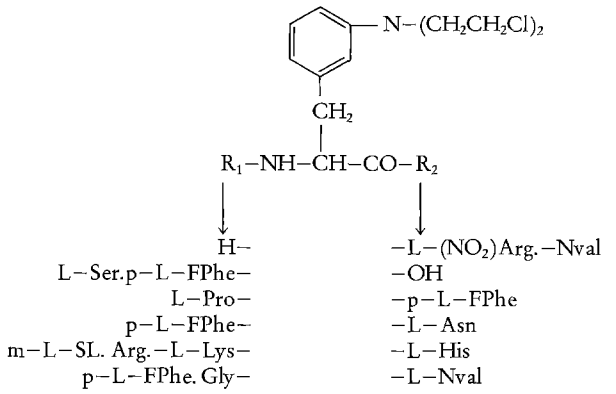

Fig. 1. Chemical structure of peptichemio

to standard alkylating agents or prednisone therapy while 8 were untreated.

Materials and Methods

The patient sample used in this study contained 13 with multiple myeloma and two with plasma cell leukemia, who were treated with PTC at our Institute between May 1974 and December 1978. The diagnostic criteria for multiple myeloma as defined by the Chronic Leukemia-Myeloma Task Force [9] were adopted. The general characteristic of the patients are reported in Tables 1 and 2; the staging was assessed according to Merlini, Waldenström and Jayakar [23].

Eight patients (nos. 2, 5, 6, 10, 11, 12, 13, and 15) were untreated, four (4, 7, 8, and 14) had been resistant to treatment with MPH and/or CTX, and three (1, 3, and 9) had been treated irregularly with one or both of these alkylants. It was therefore impossible to evaluate their response to previous treatment.

Peptichemio was administered by IV infusion at doses of 40–80 mg/48 h in courses including 4–17 administrations, each in association with 'moderate' doses of prednisone (range 15–50 mg/day) and high doses of androstanes (testosterone enanthate or methenolone enanthate 250 mg weekly). In patients Zor P, and Cre M, PTC was associated with VCR administered on the first day of the course.

In the early stage of the study we administered 40 mg/48 h (patients 1, 2, and 3); in view of the good tolerance, we tried the dosage of 80 mg/48 h in two patients (5 and 10).

Since there were no significant therapeutic advantages with the higher dose [22], the dosage was standardized at 40 mg.

In the first two patients treated, the suspension of PTC treatment was followed by a rebound of the serum M-component (MC) concentration. Thus in subsequent patients we gave maintenance treatment with MPH or CTX after the induction treatment with PTC.

Laboratory Studies. The serum and urine MC concentrations were estimated as the scanning percentage of total serum and urine [18] proteins, serially following the initiation of PTC administration and prior to therapy with other alkylating drugs. Measurements of hemoglobin, WBC count, platelet count, levels of serum creatinine, blood urea nitrogen, serum calcium, normal immunoglobulins (by single radial immunodiffusion), roentgenographic skeletal surveys, and bone marrow plasma cell percentage were performed in all subjects and repeated at appropriate intervals.

The criteria for response to chemotherapy were based on (a) percentage reduction in MC; (b) decrease of the marrow plasma cell count by at least 20 percentage points (e.g., a decrease from 60% to 40%) or a return to less than 10%; (c) a 2 g/dl rise in hemoglobin concentration in anemic patients (Hb < 11 g/dl) sustained for more than 4 weeks; (d) return of serum calcium and blood urea nitrogen to normal values; (e) elevation of the serum albumin value up to or greater than 3 g/dl in the absence of other causes of hypoalbuminemia; and (f) absence of progression of the skeletal lytic lesions.

Patient responses were defined as follows: *Complete response* (CR): percentage reduction in MC greater than 50% and response in more than half of the other parameters; *partial response* (PR): percentage reduction in MC or in TCM greater than 25% and response in more than half the other parameters; *no response* (NR): no satisfaction of the above criteria for CR and PR.

Results

The treatment with PTC produced a rapid analgesic effect and improvement of the general condition in all the symptomatic patients. Seven patients (1, 4, 10, 12, 13, 14, and 15) who were immobilized in bed because of sharp bone pain were able to get out of bed within 7–15 days.

Tables 1 and 2 show the modifications induced by PTC treatment in some parameters used for the evaluation of therapeutic response. The parameters are considered separately.

M-Component

The treatment significantly reduced the MC in 13 of the 15 patients treated (87%). The decrease was greater than 50% (range 56–66) in five cases and greater than 25% (range 30–49) in eight. It is noteworthy that in patients 14 and 15 the addition of 2 mg VCR to the treatment on the first day of the PTC course induced a rapid marked fall (45% and 56%, respectively) of MC with small doses of PTC (see Tables 1 and 2).

The reduction of MC in responsive patients was very rapid: the median time required to obtain the response was 32 days (range 20–80 days).

Bone Marrow Plasma Cells

The modifications of bone marrow plasma cell percentages are mainly in accordance with the changes of MC.

Table 1. General characteristics and response to peptichemio therapy of previously treated patients

Patient	Sex	Age	Date of diagnosis	M-comp. type	Clinical staging	Previous drugs	Date of PTC course	PTC		M-comp. g/dl			BMPC %			Re-sponse	Date of death	Survival (months)
								mg/48 h	Total	BT	AT	Δ %	BT	AT	Δ %			
1 Car M[a]	M	67	Feb. 72	GK	III	MPH/CTX	May 74	40	240	5.7	5.2	− 9	95	90	− 5	NR	Jun. 74	28
3 Car D	F	63	Jun. 72	AK	II	MPH	Dec. 74	40	680	5.7	2.9	− 49	53	23	− 57	CR	Alive	−
4 Fil V	M	68	Jun. 75	LCL	II	MPH	Sept. 75	40	640	326	128	− 61	47	16	− 66	CR	Jan. 79	42
7 Cas I	F	51	Jan. 73	GL	II	MPH/CTX	Sept. 75	40	480	4.4	4.0	− 9	55	40	− 27	NR	Jun. 77	53
8 Bal M	F	60	Feb. 74	G_3K	II	MPH	Nov. 75	40	400	1.7	1.1	− 34	NV	NV	−	PR	Alive	−
9 Mon E	F	59	Oct. 74	AL	I	MPH	Apr. 75	40	440	3.0	2.1	− 30	NV	NV	−	PR	Alive	−
14 Zor P	M	53	Mar. 75	AK	III	MPH/CTX	Oct. 78	40[b]	320	4.0	2.2	− 45	90	53	− 41	PR	Alive	−

[a] Patient with plasma cell leukemia
[b] Plus VCR 2 mg on the first day of PTC course

Table 2. General characteristics and response to peptichemio therapy of previously untreated patients

Patient	Sex	Age	Date of diagnosis	M-comp type	Clinical staging	Date of PTC course	PTC		M-comp. g/dl			BMPC %			Re-sponse	Date of death	Survival (months)
							mg/48 h	Total	BT	AT	Δ %	BT	AT	Δ %			
2 Feb L[a]	M	66	Apr. 74	AK	II	Jun. 74	40	360	7.8	4.7	−40	60	40	−33	PR	Feb. 79	57
5 Scu P	M	39	Jun. 75	G_3L	I	Aug. 75	80	400	1.8	0.7	−59	60	41	−32	CR	Alive	−
6 Sal E[b]	M	65	Dec. 75	GK	II	Feb. 76	40	240	3.2	1.7	−47	38	20	−47	CR	Jul. 76	7
10 Ver V	M	58	Apr. 76	GL	III	Jul. 76	80	800	9.4	4.9	−48	41	2	−95	CR	Oct. 76	6
11 Cas M	F	74	Nov. 76	LCL	III	Oct. 77	40	400	2.2	1.2	−45	85	55	−35	PR	Dec. 77	13
12 Lil L	F	69	Jan. 78	GL	II	Feb. 78	40	400	3.5	1.2	−66	20	NV	−	CR	Alive	−
13 Pag G	M	30	Feb. 78	AK	I	Mar. 78	40	600	6.3	2.7	−57	80	NV	−	CR	Alive	−
15 Cre M	F	52	Nov. 78	LCK	III	Dec. 78	40[c]	160	20	8.7	−56	95	30	−68	CR	Alive	−

[a] Patient with plasma cell leukemia
[b] Patient with cancer of larynx
[c] Plus VCR 2 mg on the first day of PTC course

Hemoglobin

Figure 2 shows the hemoglobin changes in anemic patients after therapy and without transfusions. There was a significant increase in five (2, 10, 13, 14, and 15) of the nine (1, 2, 6, 7, 10, 11, 13, 14, and 15) anemic patients, a slight or no increase in three patients (1, 6, and 7), and a moderate decrease in one patient (1).

Serum Albumin

The treatment with PTC induced a rise of albumin level to 3 g/dl, or more, in all the five patients (2, 4, 10, 11, and 13) whose initial concentration was lower.

Normal Serum Immunoglobulins

A significant increase in depressed normal immunoglobulins (IgM increments exceeding 20 mg/dl, IgA exceeding 40 mg/dl, and IgG exceeding 400 mg/dl) occurred in five patients (33%), and in two other patients (14 and 15) there was a slight improvement.

Bone Lesions

The bone x-ray survey of all the patients revealed normal bones in three patients (7, 9, and 11); diffuse osteoporosis in three patients (2, 5, and 6); solitary lytic lesion of the skull in patient 8; multiple lytic lesions in five patients (1, 4, 12, 13, and 15); and extensive skeletal destruction in three patients (3, 10, and 14). The treatment with PTC induced the healing of the solitary parietal lytic lesion observed in patient 8. No progression of the skeletal destruction occurred in the other patients.

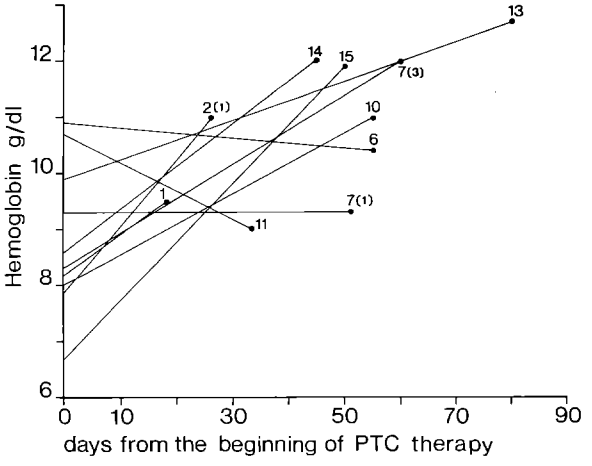

Fig. 2. Hemoglobin modifications in anemic patients (hemoglobin less than 11 g/dl) after therapy

Response to Treatment

Tables 1 and 2 show that the treatment induced eight CR (53%), five PR (33%) and two NR (13%). It must be noted that in the unresponsive patient observed in the leukemic terminal phase at 26 months from the diagnosis and dead of acute heart failure only 18 days from the beginning of therapy (patient 1) PTC was certainly active, inducing quick regression of bone pain and a fall of circulating plasma cells from 42.2 to 4.7 $\times$ 10^3/mm^3 [25]. The early death did not allow the evaluation of the fall of MC.

The therapeutic results do not seem to be correlated with the dosage of PTC [22].

Eight patients were treated with low or medium doses of MPH or CTX after PTC. This treatment was able to prolong remission for 5–31 months, inducing in cases 2 and 10 a further reduction of serum MC levels of 62% and 33%, respectively.

Survival

The patients had been treated with different alkylating agents, so the effect of treatment, i.e., survival, cannot be ascribed to PTC alone. Nevertheless, as shown in Tables 1 and 2, eight patients are still alive and the median survival time of the population studied is 43+ months from diagnosis and 16+ months from the beginning of PTC therapy.

Toxicity

The most serious non-hematologic side-effect was phlebothrombosis of the injection vein (observed in (6/15 patients), sometimes avoided by adding 2,000 U heparin to the vein-washing solution. Alopecia was observed in three cases.

Table 3 shows the hematologic side-effects: in 3/15 courses leukocytes dropped below 1,500/mm^3, and in six there was thrombocytopenia (less than 50,000/mm^3) without bleeding. The cytopenic effect was rapidly reversible at the suspension of the treatment. It was also possible to treat cytopenic patients (1, 2, 7, 9, 11, and 14) without serious problems.

In addition to the results presented above a few remarks on the following *particular cases* seem to be called for.

In case 2, with plasma cell leukemia (see Fig. 3), the first course of PTC induced a dramatic response, which was strengthened and maintained for 7 months by small discontinuous doses of MPH. The treatment was stopped because a viral hepatitis developed; nevertheless, the clinical remission was maintained, without treatment, for 7 months. The resumption of

Table 3. Toxic effects of peptichemio therapy

Patient	PTC dose		WBC cells/mm^3 × 10^3			Platelets cells/mm^3 × 10^3			
	mg/48 h	Total	BT	Nadir	No. of days WBC < 1.5	BT	Nadir	No. of days $P < 50 < 100$	
Previously treated patients									
1 Car M[a]	40	240	36.9	20.8	0	65	25	Until death	
3 Car D	40	680	4.9	1.5	0	145	44	5	20
4 Fil V	40	640	4.0	3.9	0	335	105	0	0
7 Cas I	40	480	3.3	1.8	0	135	85	0	15
8 Bal M	40	400	5.2	3.2	0	150	30	10	50
9 Mon E	40	440	3.2	3.2	0	195	100	0	0
14 Zor P	40[b]	320	3.1	1.9	0	107	65	0	25
Untreated patients									
2 Feb L[a]	40	360	26.7	1.8	0	75	50	0	21
5 Scu P	80	400	6.6	6.6	0	135	135	0	0
6 Sal E	40	240	7.7	1.7	0	190	110	0	0
10 Ver V	80	800	4.9	1.0	4	180	30	9	22
11 Cas M	40	400	3.5	3.0	0	85	20	15	17
12 Lil L	40	400	6.5	0.6	7	139	25	5	11
13 Pag G	40	600	8.8	1.7	0	170	75	0	12
15 Cre M	40[b]	160	9.6	2.0	0	86	86	0	15

[a] Patients with plasma cell leukemia
[b] Plus VCR 2 mg on the first day of PTC course

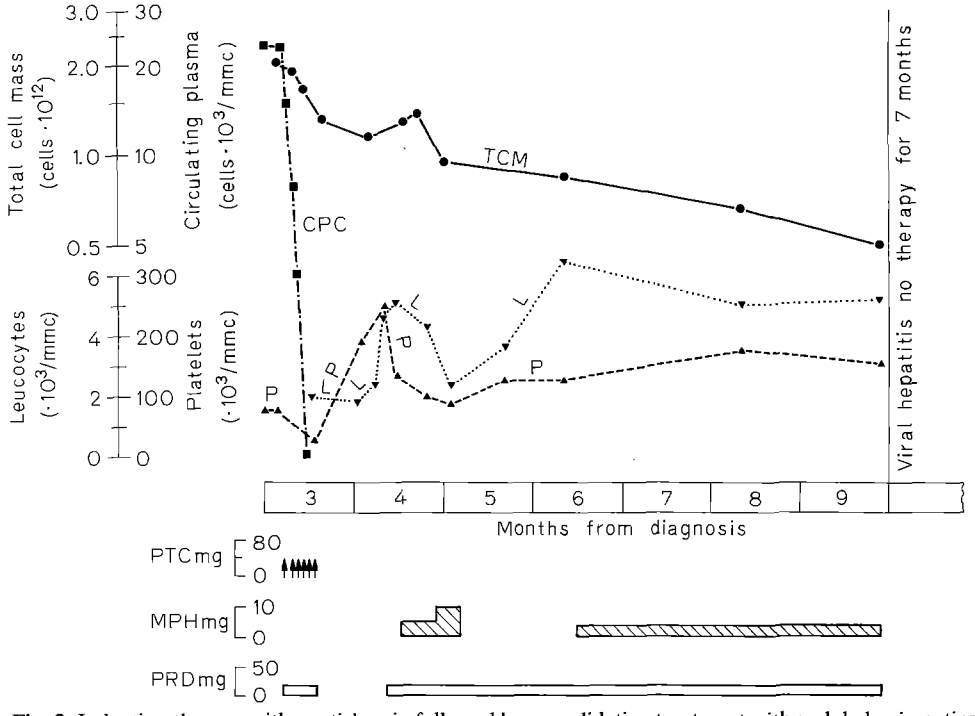

Fig. 3. Induction therapy with peptichemio followed by consolidating treatment with melphalan in patient Feb. L. (no. 2). See text for the complete clinical course

maintenance treatment with MPH and prednisone induced a further reduction of MC, which disappeared on serum electrophoresis. Since such remission was maintained for 14 months the treatment was stopped. The suspension of the therapy induced the first relapse 34 months from diagnosis. The second course of PTC applied on that occasion is not evaluable because of lack of data. After another 23 months, when the patient showed signs of being resistant to MPH and CTX and no longer treatable with the M2 protocol [17] because a severe cytopenia arose after the second M2 course, the association of 1 mg VCR on the first day of the PTC course again induced reduction of 36% of MC. The patient died in an acute terminal phase [7] at 57 months from diagnosis.

Figure 4 shows the course of case 4 who, suffering from lambda light-chain myeloma, survived 42 months. The patient was admitted to our Institute in very poor condition because of multiple lytic skeletal lesions involving the skull, ischium, and pubis, with tearing bone pain which had immobilized him in bed for more than 2 months. In this patient, PTC was effective both in the first course and in the second, which was given 22 months later on the occasion of the first relapse. The third course was also effective, while the fourth reduced the MC but did not succeed in preventing the rapid progression of the acute terminal phase.

In case 6 multiple myeloma was associated with a widespread metastasizing cancer of the larynx. A course with PTC (40 mg × 6), followed by a reinforcement course with CTX (400 mg IV × 3), induced prompt reduction of total cell mass [31] from 1.46 to 0.62 × 10^{12} cells, lasting 2 months. During radiotherapy and the subsequent treatment with adriamycin and methotrexate that was needed for the epithelial neoplasm, there was an exponential growth of the total cell mass from 0.62 to 2.2 × 10^{12} cells in 2.5 months. The patient died from cancer of the larynx.

Discussion and Conclusions

The preliminary positive results of PTC treatment in myelomatosis reported by Marmont et al. [20], Astaldi [6], and Luporini [19] led us to undertake the present study. Our aim was to verify their preliminary observation, trying to improve our knowledge concerning the clinical and laboratory changes induced by the drug.

Analysis of the clinical and laboratory data clearly demonstrates the effectiveness of PTC in improving the general condition of the patients (reduction of bone pain, increase of hemoglobin and albumin concentrations) and in reducing the level of MC. The results reported above showed that: (1) PTC has a

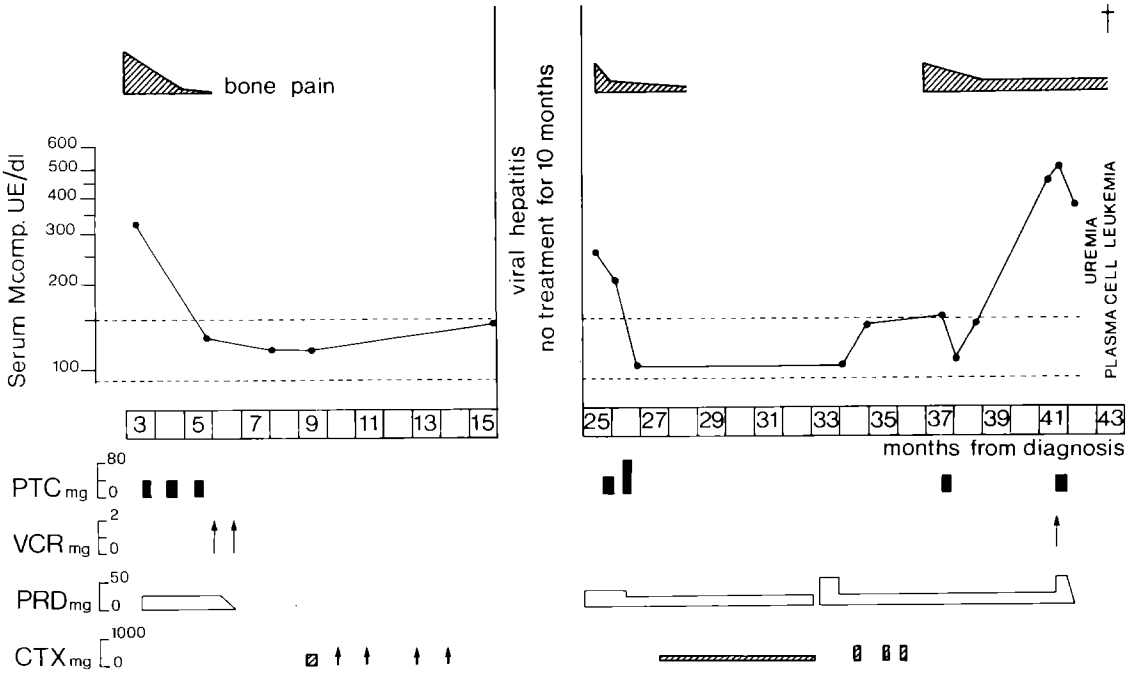

Fig. 4. Clinical course of patient Fil. V. (no. 4). The serum M-component (lambda light chain) was determined by radial immunodiffusion: the *dotted lines* delimit the mean value ± 1 SD found in the normal population at our laboratory. Bence-Jones proteinuria (0.4 g/24 h) appeared during the second relapse at 34 months from diagnosis

remarkable rapidity of action: the time needed to achieve a response in 90% of the patients with PTC is 6 weeks; (2) PTC is effective in patients who had been resistant to MPH or CTX (it is remarkable that in patients 4, 7, and 8 it was possible to maintain the remission induced by PTC by giving the same alkylating agent to which they had previously been resistant); (3) PTC was effective in patients in an advanced stage of the disease (1, 2, 10, 11, 14, and 15) and with a high tumor mass, which is usually correlated with short survival [23] and, according to Durie and Salmon [12], with a low response rate. Patients with plasma cell leukemia and with light-chain myeloma also have a poor prognosis [15, 23, 26, 33].

Peptichemio is well tolerated, apart from the risk of phlebothrombosis, from both the clinical and the hematological points of view. The cytopenias were of short duration. Furthermore, it has been possible to treat with PTC some patients who did not tolerate MPH because of excessive cytopenia. Since we almost always add androstanes to the various drugs used in the therapy of multiple myeloma we do not think that the better tolerance of PTC depends exclusively on such an association.

Forty percent (w/w) of the PTC molecule consists of sarcolysin, so the injection of 34.37 mg PTC is equivalent to the administration of 16 mg of such an alkylating agent, which is a huge amount considering that the usual dose of sarcolysin is 2–5 mg. This suggests the hypothesis that the aminoacid moieties in some way (by slowing down the releasing of the alkylant? and/or by selectively increasing the uptake of the drug by the tumor cells?) reduce the myelotoxic effect of sarcolysin, which can thus be administered at a high dosage with consequent quick, marked damage to the neoplastic cell mass. Furthermore, recent studies [29] have shown that PTC, unlike MPH, can inhibit the DNA repair activity, damaging the replication system of the cell; this may contribute to the effectiveness of PTC.

A protocol concerning the association of PTC with VCR for the treatment of myelomatosis has recently been devised and its effectiveness is under study.

In conclusion, PTC seems particularly indicated for induction treatment of myelomatosis, for a rapid marked reduction of the tumor mass, and in patients resistant to MPH and/or CTX before polychemotherapy.

Acknowledgements. We are indebted to Prof. Jan Waldenström for his critical reading of the manuscript.

The investigation described in this paper was supported in part by grant no. 78.02857.96 from the Consiglio Nazionale delle Ricerche, Roma (Progetto Finalizzato Controllo della Crescita Neoplastica). GM is in receipt of a fellowship from the A. Villa Rusconi Foundation.

References

1. Alberts DS, Salmon SE (1975) Adriamycin (NSC-123127) in the treatment of alkylator-resistant multiple myeloma: a pilot study. Cancer Chemother Rep 59: 345
2. Alberts DS, Durie BGM, Salmon SE (1977) Treatment of multiple myeloma in remission with anticancer drugs having cell cycle specific characteristics. Cancer Treat Rep 61: 381
3. Alexanian R, Bergsagel DE, Migliore PJ, Vaughn WK, Howe CD (1968) Melphalan therapy for plasma cell myeloma. Blood 31: 1
4. Alexanian R, Balcerzak S, Haut A, Hewlett J, Gehan E (for the Southwest Oncology Group) (1975) Remission maintenance therapy for multiple myeloma. Arch Intern Med 135: 147
5. Alexanian R, Salmon S, Bonnet J, Gehan E, Haut A, Weick J (1977) Combination therapy for multiple myeloma. Cancer 40: 2675
6. Astaldi G, Meardi G, Yalçin B, Krc I, Taverna PL, Krcova V (1974) Ricerche sperimentali e cliniche con il Peptichemio. In: Atti del Simposio sul Peptichemio. I.S.M., Milano, p 173
7. Bergsagel DE, Pruzansky W (1975) Treatment of plasma cell myeloma with cytotoxic agents. Arch Intern Med 135: 172
8. Bergsagel DE, Griffith KM, Haut A, Stuckey WJ Jr (1967) The treatment of multiple myeloma. Adv Cancer Res 10: 311
9. Chronic Leukemia Myeloma Task Force, National Cancer Institute (1968) Proposed guidelines for protocol studies. II. Plasma cell myeloma. Cancer Chemother Rep [3] 1: 17
10. Costa G, Engle RL, Schilling A, Carbone P, Kochwa S, Nachman RL, Glidewell O (1973) Melphalan and Prednisone: an effective combination for the treatment of multiple myeloma. Am J Med 54: 589
11. De Barbieri A, Chiappino G, Di Vittorio P, Golferini A, Maugeri M, Mistretta AP, Perrone F, Tassi GC, Temelcou O, Zappelli P (1974) Il Peptichemio: sintesi di ricerche farmacologiche, morfologiche, biochimiche e biologico-molecolari. In: Atti del Simposio sul Petiochemio. I.S.M., Milano, p 13
12. Durie BG, Salmon SE (1975) A clinical staging system for multiple myeloma. Correlation of measured cell mass with presenting clinical features, response to treatment, and survival. Cancer 36: 842
13. EORTC (1977) A phase II clinical trial of Peptichemio. Biomedicine 27: 290
14. Gingold N, Pittermann E, Stacher A (1974) Peptichemio in the therapy of malignancies. Int J Clin Pharmacol 10: 90
15. Hobbs JR (1969) Immunochemical classes of myelomatosis. Br J Haematol 16: 599
16. Korst DR, Clifford GO, Fowler WM, Lovis J, Will J, Wilson ME (1964) Multiple myeloma. II. Analysis of cyclophosphamide theraphy in 165 patients. JAMA 189: 758
17. Lee BL, Sahakian G, Clarkson BD, Krakoff IH (1974) Combination chemotherapy of multiple myeloma with Alkeran, Cytoxan, Vincristine, Prednisone and BCNU. Cancer 33: 533
18. Lindstrom FD, Williams RC, Swaim WR, Freier EF (1968) Urinary light-chain excretion in myeloma and other disorders – an evaluation of the Bence Jones test. J Lab Clin Med 71: 812

19. Luporini G (1974) Esperienze cliniche con il Peptichemio. In: Atti del Simposio sul Peptichemio. I.S.M., Milano, p 152
20. Marmont A, Gori E, Damasio E, Rossi F, Bordo D, Giordano D, Santini G (1974) Esperienze cliniche con il Peptichemio nel trattamento delle emoblastosi e dei tumori solidi. In: Atti del Simposio sul Peptichemio. I.S.M., Milano, p 173
21. Medical Research Council: Myelomatosis comparison of Melphalan and Cyclophosphamide therapy. Br Med J 1: 640
22. Merlini G, Riccardi A, Gobbi P, Perugini S (1978) Trattamento del plasmocitoma con Peptichemio. In: Atti XXVI Congresso Nazionale Società Italiana di Ematologia. Tipografia Viscontea, Pavia, p 554
23. Merlini G, Waldenström JG, Jayakar S (1980) A new improved clinical staging system for multiple myeloma based on analysis of 123 treated patients. Blood 55: 1011
24. Moon JH, Edmonson JH (1970) Procarbazine (NSC-77213) and multiple myeloma. Cancer Chemother Rep 54: 245
25. Perugini S, Bobbio Pallavicini E, Ghizzi A, Riccardi A, Martinotti A, Merlini G (1976) Peptichemio in the treatment of plasma cell leukemia. Haematologica 61: 248
26. Pruzanski W, Platts ME, Ogryzlo MA (1969) Leukemic form of immunocytic dyscrasia (plasma cell leukemia). A study of ten cases and a review of the literature. Am J Med 47: 60
27. Riccardi A, Martinotti A, Perugini S (1978) Cytokinetic changes in two cases of plasma cell leukemia treated with a multipeptide derivative of m-[di(2-chloroethyl)amino] L-phenylalanine (Peptichemio). Eur J Cancer 14: 1099
28. Riccardi A, Merlini G, Montecucco CM (1980) Treatment of multiple myeloma with vincristine. Acta Haematol 64: 176
29. Ringborg U, Lambert B, Lewensohn R, Turesson I (to be published) Different levels of DNA-damage in human cells treated with the closely related alkylating agents Petichemio, *m*-L-sarcolysin and melphalan. Eur J Cancer
30. Salmon SE (1976) Nitrosoureas in multiple myeloma. Cancer Treat Rep 60: 789
31. Salmon SE, Wampler SB (1977) Multiple myeloma: quantitative staging and assessment of response with a programmable pocket calculator. Blood 49: 379
32. Waldenström J (1964) Melphalan therapy of myelomatosis. Br Med J 1: 859
33. Woodruff RK, Malpas JS, Paxton AM, Lister TA (1978) Plasma cell leukemia (PCL): a report on 15 patients. Blood 52: 839

Received December 5, 1980/Accepted September 21, 1981