Eur J Cancer Clin Oncol, Vol. 22, No. 7, pp. 787–791, 1986.
Printed in Great Britain.

0277–5379/86$3.00+0.00
Pergamon Journals Ltd.

Peptichemio, Vincristine and Prednisone versus Melphalan and Prednisone as Induction Therapy in Multiple Myeloma*

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Abstract—*Seventy-five patients with previously untreated multiple myeloma were randomly treated with the association of Peptichemio, Vincristine and prednisone (PTC–VCR–P) or of melphalan and P (MPH–P) for first induction therapy. After induction, all responsive patients received MPH and P until relapse, while unresponsive patients received it until unequivocal evidence of disease progression was observed. A second induction therapy with PTC–VCR–P was then administered, except to patients resistant to this association at first induction (who received combination chemotherapy which included cyclophosphamide and adriamycin).*

The response rate was 58% *in the PTC-VCR-P and* 41% *in the MPH-P group* ($P > 0.05$). *The PTC-VCR-P responsive patients experienced a median duration of response shorter than MPH–P responsive patients* (20.3 *vs* 39.7, $P = 0.041$). *Median survival from the start of treatment was* 26.2 *months in the PTC–VCR–P and* 54.1 *months in the MPH–P group of patients* ($P = 0.039$).

Stage I *and* II *myelomas had the same response rate to PTC–VCR–P and to MPH–P, but their survival was shorter on PTC-VCR-P than on MPH–P* ($P = 0.014$). *Stage* III *myelomas responded more frequently to PTC–VCR–P than to MPH–P* ($P < 0.02$) *and there was a trend to survive longer on PTC–VCR–P than on MPH–P* (22.0 *vs* 12.5 *months*, $P > 0.05$).

INTRODUCTION

AN UNSETTLED question [1] in multiple myeloma is whether intensive chemotherapy, when compared with traditional melphalan (MPH) and prednisone (P) treatment, increases the response rate, which in turn should prolong survival.

Peptichemio (PTC) is a derivative of sarcolysin, m-{di-(2-chloroethyl)-amino}-L-phenylalanine, covalently bound to six peptides thus combining an alkylating and an antimetabolic effect [2]. Used alone [3,4] or in association with Vincristine (VCR) [5], it induces a rapid response in over 50% of patients with untreated plasma cell tumors.

The purpose of this investigation was to evaluate the clinical course of myeloma patients when treated for induction with the association of PTC, VCR and P (which we consider an aggressive therapy) or of MPH and P. Therapy following induction was basically the same in the two groups of patients studied.

Accepted 25 November 1985.
*Research supported by C.N.R. (Consiglio Nazionale delle Ricerche, Roma, Progetto Finalizzato Oncologia, grant no. 84.00761.44) and A.I.R.C. (Associazione Italiana per la Ricerca sul Cancro).
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MATERIALS AND METHODS

From January 1977 till October 1984, 80 patients with untreated multiple myeloma were randomly treated with the association of Peptichemio (PTC, Istituto Sieroterapico Milanese, Milan, Italy), VCR, and P or of MPH and P as the first induction therapy. Diagnosis of multiple myeloma was made according to the criteria of the Chronic Leukemia and Myeloma Task Force [6]. Patients with light chain (LC) disease had a Bence Jones protein excretion in excess of 1.5 g/day (range: 1.5–60.5 g/day). Before treatment, patients were staged according to Merlini *et al.* [7] independently of randomization.

Five patients are excluded from the analysis due either to their refusal of continuing therapy shortly after starting induction (4 pts, 3 of which in the PTC–VCR–P group) or not returning for follow up after induction (1 pt). The general characteristics

of the remaining 75 studied patients are summarized in Table 1. Their median follow up is now 58 months (range 7–101 months).

First induction treatment

As the first induction, 36 of the 75 evaluable patients received three courses of PTC–VCR–P according to the schedule reported in Fig. 1. Vincristine (0.025 mg/kg) was administered on day 1, PTC (0.8 mg/kg in saline free isotonic solution in 30–60 min) was given on days 1, 3 and 5 and P was given at a dosage of 0.8 and 0.4 mg/kg/day in 'good' and 'poor' risk patients [8]. Three courses were administered with a 9-day therapy-free interval between courses.

Thirty-nine patients were treated with 4 courses of MPH and P at a dose of 0.25 and 2.0 mg/kg, respectively, for 4 consecutive days every 6 weeks.

The standard intervals between courses (9 days for PTC–VCR–P and 38 days for MPH–P) were extended until white blood cells (WBC) and platelets reached 2.5 and 100×10^9, respectively, without reduction of drug dosage. Testosterone enanthate (250 mg/week) was administered i.m. over the course of both induction programs. Response was judged after treatment had been completed in all but three patients (two allocated in the PTC–VCR–P and one in the MPH–P group) who died within 6 weeks from starting therapy. These are considered as treatment failures.

Treatment after first induction

After induction all patients (responsive and unresponsive) received MPH and P at the above dosages. Responsive patients received this association until relapse and unresponsive patients until MC reached a value 25% higher than that before induction or until one or more of the following unequivocal signs of disease progression were evidenced: appearance or worsening of the bone pain, extension of bone lytic lesions, >20% increase in bone marrow plasma cell percentage, occurrence of renal insufficiency or of hypercalcemia, decrease of Hb to less than 10 g/dl, which was believed not to be related to chemotherapy.

When MPH–P was withdrawn, all patients (except those unresponsive to first PTC–VCR–P induction) received a second induction treatment with PTC–VCR–P. Only those patients who originally did not respond to PTC–VCR–P were treated with other drug combinations, including both adriamycin and cyclophosphamide.

Clinical evaluation

Prior to therapy and serially after its beginning, the following parameters were evaluated: serum and urine concentration of M component (MC) (as the scanning percentage of total serum and urine proteins), hemoglobin, serum calcium and creatinine. A sternal aspirate (for bone marrow plasma cell percentage) was repeated every 2–3 months

Table 1. Main clinical data of the patients studied (LC: light chain; staging was performed according to Merlini et al [7])

Parameter	Treatment groups PTC–VCR–P	MPH–P
No. of patients	36	39
Age (median)	62	61
Sex (M/F)	21/15	21/18
M component (IgG/IgA/LC)	23/7/6	25/8/6
Bence Jones (kappa/lambda)	20/16	22/17
Stage: I/II/III	10/9/17	18/12/9

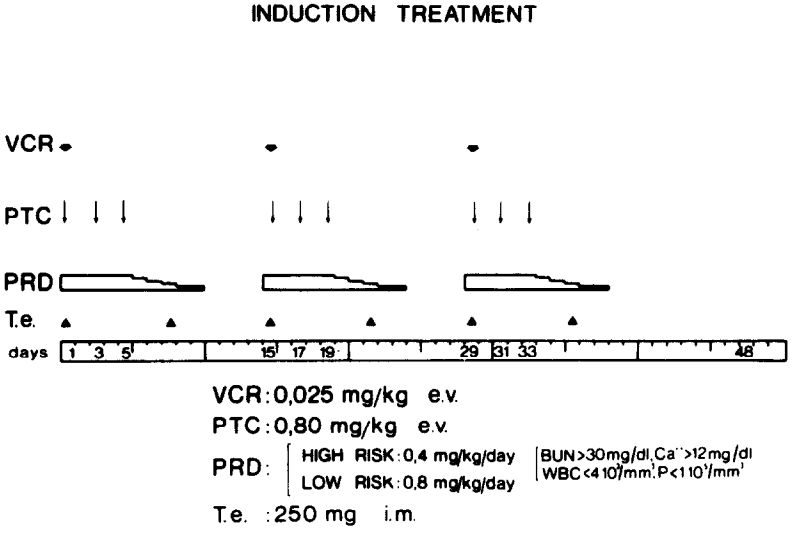

Fig. 1. Schedule of Peptichemio (PTC) – Vincristine (VCR) – prednisone (PRD) treatment. TE = testosterone enanthate.

and a skeletal radiogram (for bone lesions) every 3–6 months.

Response (CR) was defined according to the criteria of the Chronic Leukemia and Myeloma Task Force [6]. Patients were considered as responders when a decrease of more than 50% in serum MC concentration or in urinary MC excretion was documented following induction therapy. The half-time ($T1/2$) of MC decrease, as a measure of rapidity of response, was determined in responsive patients [9]. Duration of response is calculated from the start of response until relapse. Relapse was defined as an MC increase of 50% over the minimal level reached at response or following it (during maintenance). Survival is calculated from the start of therapy.

Statistical analysis

Differences in response rates were tested with the chi-square or the Fisher's exact probability test. Survival curves were estimated using the actuarial method of Berkson and Gage [10] and the procedure described by Hankey and Myers [11], which takes into account differences in distribution between two groups with respect to factors thought to be associated with survival. Chi-squares were calculated in order to detect any difference in survival, using the procedures of Lee and Desu [12] and of Mantel [13], respectively.

RESULTS

The obtained results are summarized in Table 2 and in Figs 2 and 3.

Overall analysis

The response rate was 58% in the PTC–VCR–P and 41% in the MPH-P group (Pns) (Table 2). Time to response (determined as the $T1/2$ of MC decrease) was shorter ($P = 0.018$) in the first (median = 55 days for serum spike and 27 days for

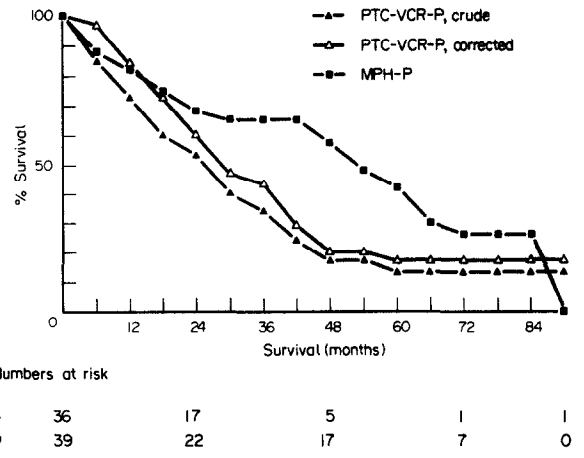

Fig. 2. Survival of Peptichemio–Vincristine–prednisone (PTC–VCR–P) and of melphalan–prednisone (MPH–P) treated patients. The corrected survival curve of the PTC–VCR–P group has been made comparable to the MPH–P group with respect to stage composition [7], according to Hankey and Myers [11].

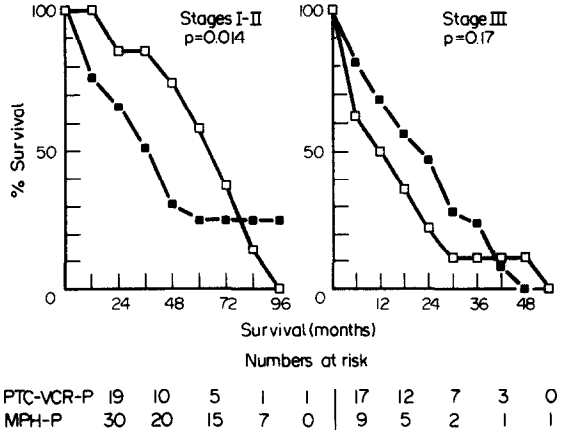

Fig. 3. Survival by stage and treatment (abbreviations as in Fig. 2).

Table 2. Clinical course of myeloma in patients treated with Peptichemio, Vincristine and prednisone (PTC–VCR–P) and with melphalan and prednisone (MPH–P) (R: response; CR: positive response [6]; NR: no response)

Treatment group	R	No.	%	P	Duration of 1°CR* mos	P	time to 2° induction	Survival from 2° induction* mos	P
PTC–VCR–P (36 pts.)	CR	21	58		20.3		23	8.0	
									n.s.
	NR	15	42		—		8.5	6.0	
				n.s.		.041			
MPH–P (39 pts.)	CR	16	41		39.7		41	12.5	
									n.s.
	NR	23	59		—		31	9	

* Median value.

LC myelomas) than in the second group (where the corresponding figures are 181 and 74 days).

Median response duration was 20.3 months in the PTC–VCR–P and 39.7 months in the MPH-P group ($P = 0.041$).

Relapsing patients who had been originally treated with PTC–VCR–P had very poor (5%) response rate to second induction therapy. The response rate to this association was higher (32%) in the patient group originally treated with MPH–P ($P < .05$). Survival from second induction treatment was somewhat shorter in the former than in the latter group of patients.

Crude median survivals were 26.2 months for the PTC–VCR–P and 54.1 months for the MPH–P group ($P = .039$) (Fig. 2). However, the PTC–VCR–P group contained more stage III and less stage I myelomas than the MPH-P group. When the PTC–VCR–P group is made comparable with the MPH–P group with respect to stage composition (according to the method of Hankey and Myers), median survival increased to 29.3 months ($P = .059$) (Fig. 2).

Analysis by stage

Stage I and II myelomas had similar response rates to PTC–VCR–P (10/19 patients) and to MPH–P (14/30 patients). Stage III patients responded much more often to PTC–VCR–P (11/17 patients) than to MPH–P (2/9 patients) ($P < 0.02$). The $T1/2$ of MC decrease was independent of stage.

Stage I and II myelomas survived longer on MPH–P than on PTC–VCR–P (63.1 vs. 36.3 months, $P = .014$), while there was a trend for stage III myelomas to survive longer on PTC–VCR–P than on MPH–P (22.0 vs 12.5 months, $P = 0.17$) (Fig. 3).

Toxicity of PTC–VCR–P treatment

Before starting treatment, 31 of 36 PTC–VCR–P patients had a WBC count over 4.0×10^9/l and a platelet count over 100×10^9/l. A reduction in WBC count below 2.5×10^9/l occurred in 7 (19%) patients and lasted 2–9 days. No patient experienced severe granulocytopenia (granulocytes less than 1.0×10^9/l). A reduction in platelet number below 75×10^9/l occurred in 5 (14%) patients and lasted 3–9 days. Two patients experienced severe thrombocytopenia (platelets less than 50×10^9/l). The nadir of leukocytes and platelets occurred between the 9th and 14th days following the therapy course and in 9 patients the interval between courses had to be extended to 10–18 days. No relevant clinical problem due to cytopenia was observed.

The most frequent non-hematologic side-effect was phlebothrombosis at the vein site of the PTC injection, which occurred in 69% of patients. Nausea and/or vomiting ensued in a minority (32%) of patients and alopecia was uncommonly observed (12% of patients). Neuropathy, due to VCR, was constant but moderate. No cardiac, pulmonary or CNS toxicity was seen.

DISCUSSION

The purpose of this study was to ascertain whether an aggressive induction therapy with PTC associated with VCR and P increases the response rate and prolongs survival in myeloma patients with respect to the traditional therapy employing MPH and P. The postinduction program was basically the same in the two groups studied.

The data obtained confirm that the association of PTC–VCR–P is an active first induction therapy in multiple myeloma [5], with a response rate somewhat higher than MPH and P. However, survival was longer in MPH–P than in PTC–VCR–P treated patients. This finding is in keeping with those obtained from randomized studies [14–20] in which combination chemotherapies were compared with MPH and P. Some of these [14, 16–18] attained higher response rate with combination therapy. However, all except one study [18] failed to demonstrate a survival advantage.

The main reason for the poor survival of PTC–VCR–P treated patients is that patients responsive to PTC-VCR-P experience shorter responses than those responsive to MPH–P. Response to PTC has been shown to be rapid [9], as it is for PTC–VCR–P. Residual plasma cell recruitment ensues [21,22] and probably accounts for the rapidity of relapse on a cell-cycle aspecific maintenance such as MPH and P. A shorter response in patients treated with combination chemotherapy (BCNU–CTX–P) than in patients treated with MPH–P has been already reported [17].

The only patient group who seemed to gain benefit from both aggressive treatment and its response had advanced (stage III) myeloma. Renal and hematopoietic functions are often compromised in these patients [7]. As detailed in a preliminary report on PTC–VCR–P treatment [5], the rapid tumor reduction often restores these functions. One may speculate that this advantage exceeds the disadvantage of tumor cell recruitment. Prolongation of survival in advanced myelomas with aggressive combination chemotherapy has been reported in two other studies [14,18].

On the whole our study demonstrates that using aggressive chemotherapy and obtaining a response is not a prerequisite for prolonging survival in stage I and II multiple myeloma. However, patients

with advanced disease could gain some survival advantage from being treated aggressively, but a greater number of cases needs to be investigated to ascertain this point.

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