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Short communication

Melphalan-resistant multiple myeloma: Results of treatment according to the M-2 protocol

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Summary. *A group of 46 patients with melphalan-resistant multiple myeloma was treated according to the M-2 protocol with melphalan, prednisolone, BCNU, cyclophosphamide, and vincristine. According to the Salmon and Durie classification, four patients had stage II A; 36, stage III A; and six, stage III B disease. Treatment resulted in five patients (11%) entering remission, while 21 (46%) had stable and 20 (43%) had progressive disease. The median survival for all patients was 12.5 months, patients in remission surviving longer (median 46 months) than those with stable disease (median 15.4 months) or progressive disease (median 6.9 months). Compared with other treatment regimens used in melphalan-resistant myeloma, the remission rate is low but the median survival exceeds that reported by most other authors.*

Introduction

Intermittent chemotherapy with melphalan/prednisone is widely accepted as standard treatment of multiple myeloma [4, 6]. For those patients, who do not respond to melphalan/prednisone or who develop secondary resistance, however, no optimum second-line treatment has been agreed upon [13, 18]. Case et al. have been reporting encouraging results of second-line combination chemotherapy with melphalan, cyclophosphamide, BCNU, vincristine, and prednisone (M-2 protocol [11]). Since the criteria of remission and survival are not absolutely precise, these results have not been unequivocally accepted by other authors [13]. So far only one other group of researchers has published similarly positive experience of second-line treatment according to the M-2 protocol [10]. In our hands, 46 patients with melphalan-resistant multiple myeloma have been treated with the M-2 combination chemotherapy program and we now report our results with this treatment regimen.

Patients and methods

After treatment with intermittent melphalan/prednisolone 46 patients – 24 male and 22 female – received chemotherapy according to the M-2 protocol either because of primary resistance to melphalan/prednisolone (14 patients) or because they had progressive disease after an initial phase of remission (19 patients) or stable disease (13 patients). The median age at the initiation of chemotherapy was 55 (37–76) years. Monoclonal IgG-K-type immunoglobulin was present in the sera of 20 patients, while IgG-L, IgA-K-, and IgA-L-type immunoglobulins were equally distributed among 18 patients. Bence-Jones myeloma was present in five patients and non-secretory multiple myeloma in two; one patient with monoclonal IgM fulfilled the diagnostic criteria for multiple myeloma and was included on our study.

At the time of switch to the M-2 protocol four patients had stage II A, 36 stage III A, and six stage III B disease according to the classification of Salmon and Durie [12]. The treatment regimen consisted of melphalan 0.1 mg/kg PO on days 1–7, prednisolone 1 mg/kg PO on days 1–7, BCNU 1 mg/kg IV on day 1, cyclophosphamide 10 mg/kg IV on day 1, vincristine 0.03 mg/kg IV on day 21, to be repeated every 5 weeks. All patients were regularly seen in our clinic at 5- to 6-weeks intervals for complete clinical and laboratory evaluation. Roentgenograms of skull, spine, pelvis, humeri, and femora were repeated every 6 months. Local checks were performed at shorter intervals if known osteolytic lesions had led to the initiation of second-line treatment or in the case of bone pain. Response was evaluated according to the SWOG criteria [5]. As few patients entered complete remission, those with complete and partial remissions were pooled. Criteria for partial remission were $> 50\%$ reduction of serum levels of monoclonal immunoglobulin, Hb > 10 g/dl, normal serum calcium, all sustained for at least 6 weeks, and lack of progression of osteolytic bone lesions. Stable disease was defined as $< 50\%$ reduction or $< 25\%$ increase of serum monoclonal immunoglobulin, Hb > 8 g/dl, normal serum calcium, and stable lytic lesions on bone roentgenograms. These criteria had to be met for at least 3 months. Statistical analyses were performed according to the chi-square test, and survival data were computed using the life-table method [17].

Results

Treatment according to the M-2 protocol resulted in five (11%) patients entering remission, while 21 (46%) had stable and 20 (43%) progressive disease. Stage distribution at the initiation of second-line therapy was five patients in stage III A for responders; for patients with stable disease three in stage II A, 15 in III A, three III in B; and for those with progressive disease one in stage II A, 16 in III A, and three in III B. The outcome of second-line chemotherapy was independent of response to primary treatment. Patient survival after initiation of M-2 therapy is shown in Fig. 1. The median survival for all

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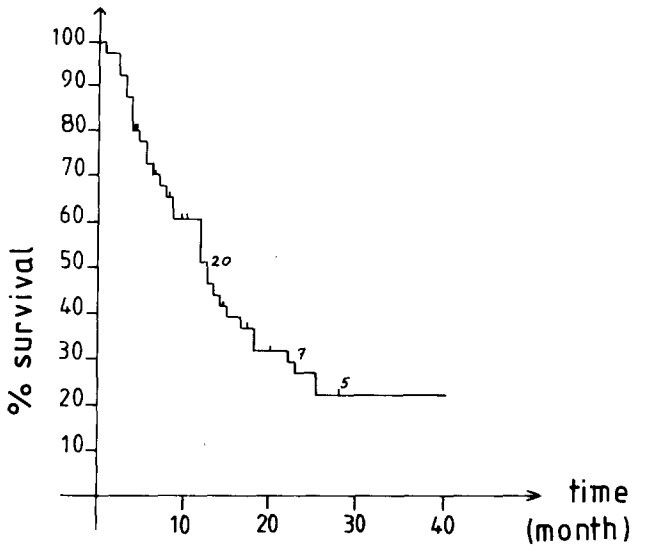

Fig. 1. Survival of 46 patients with melphalan-resistant myeloma treated according to the M-2 protocol

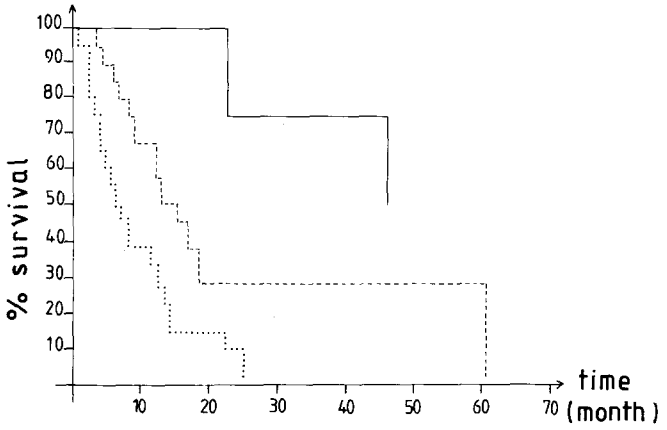

Fig. 2. Survival according to response to treatment: (———), five patients entering remission; (- - -), 21 patients with stable disease; (· · · · ·), 20 patients with progression

patients was 12.5 months. Survival broken down by quality of response to therapy is shown in Fig. 2. Patients in remission had improved survival (median 46 months) compared with those who had stable (15.4 months) or progressive (6.9 months) disease. Side-effects of therapy were mainly hematologic: 22 patients had leukopenia with less than 2,000/μl, 10 additional patients had combined leuko- and thrombocytopenia (< 80,000 platelets/μl). Dose reductions were necessary in single courses for 13 patients and in more than one treatment for six. In 10 patients dose reductions and extended treatment intervals were necessar. In addition to systemic polychemotherapy, local irradiation was administered in 24 patients because of pain or impending skeletal instability caused by osteolytic bone lesions. The outcome of treatment was not influenced by these modifications.

Discussion

Treatment of melphalan-resistant myeloma with other alkylating agents, especially cyclophosphamide, resulting in remission rates of less than 10% [7, 8, 13], has been rather disappointing. After single-agent chemotherapy with adriamycin or vincristine had shown some promise [1, 3, 8], these agents were included in polychemotherapy regimens, resulting in remission rates of approximately 25% and a median survival of 8–9 months for all patients [2, 9, 14, 15]. In the hands of Alexanian single-agent high-dose prednisone seemed to be equally effective [6].

Case et al. [11] have reported very favorable results with the M-2 treatment regimen, with remission rates of 50% and a median survival of 22 months. In their study, however, the criteria of remission included recalcification of lytic lesions and > 50% reduction in the size of solitary plasmocytomas which might have positively influenced remission rates. The results obtained by Buonanno et al. [10] with an identical chemotherapy regimen were less impressive, with remissions in three of 12 melphalan-resistant patients and a median survival of 12 months. However, in their report, the number of patients is small and the observation time is short.

In our hands, outcome of treatment according to the M-2 protocol has been considerably less favorable than originally reported by Case et al. [11]. In particular, the remission rate of only 11% is low compared with those yielded by other treatment protocols [2, 9, 14, 15]. It has to be taken into account, however, that criteria of remission vary considerably among different authors. Median survival of our patients, though not as good as in the series of Case et al. [11], is still better than reported by most other investigators: 46 months for responders and 15.4 months for patients with stable disease. The latter is within the range of survival reported for 'responders' in other series [9, 14, 15], suggesting the possibility that owing to different criteria of remission some patients classified as having stable disease in our series might have been 'responders' elsewhere.

As regards overall survival, our experience proves that treatment of melphalan-resistant myeloma according to the M-2 protocol may be superior to other second-line chemotherapy regimens.

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