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Perspectives and Commentaries

Is Aggressive Chemotherapy More Effective in the Treatment of Plasma Cell Myeloma?

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(A COMMENT ON: Peest D, Deicher H, Coldeway R, Schmoll, H-J, Schedel I. Induction and maintenance therapy in multiple myeloma: a multicenter trial of MP versus VCMP. *Eur J Cancer Clin Oncol* 1988, **24**, 1061–1067.)

THE PROGNOSIS for patients with plasma cell myeloma has improved remarkably during my lifetime. The median survival of patients has increased from 7 months in the 1950s [1] to about 30 months today (see Table 1). The major factors contributing to this improvement have been the introduction of alkylating agents (usually melphalan or cyclophosphamide) and prednisone to reduce the myeloma cell mass, and better supportive care, such as effective antibiotics for the prompt treatment of infections, and an emphasis on the importance of increased fluid intake (at least 3 l per day), in the management of the disease.

The current standard form of treatment with intermittent courses of melphalan and prednisone (MP) was introduced in the 1960s, and since then many attempts have been made to improve the effectiveness of treatment by using various drug combinations. The results of 10 prospective, randomized trials of MP versus a drug combination are summarized in Table 1. The recognition that mouse [2] and human [3] plasma cell neoplasms, which were resistant to melphalan, will still respond to another alkylating agent, stimulated clinical trials of combinations of alkylating agents [4–6]; none proved to be better than MP alone. Several trials of a combination of vincristine with three alkylating agents and prednisone (the M2 protocol) also failed to improve the response rate or survival of myeloma patients [5, 7, 8], although in one study the response rate, but not survival, was increased by the drug combination [9]. These trials clearly show that combinations of alkylating agents and prednisone are no more effective than MP in prolonging the survival of myeloma patients. The only study reporting an improvement in survival for myeloma patients treated with a drug combination used alternating combinations of vincristine, alkylating agents, doxorubicin and prednisone [10]. The improved response and survival was noted in patients with Stage III disease, rather than in those with Stages I and II. The results of this trial are weakened, however, by a separately reported study, following the same protocol, which failed to show any advantage for the drug combination; the survival of the MP group was actually better than for the drug combination in this study [11]. The GMTG used the VMCP portion of the SWOG alternating chemotherapy schedule to compare with MP [12]. In a large well-conducted trial, no differences in response rates were observed and there was a surprising, significantly improved survival for the MP group. The median survival of the patients treated with MP in this study cannot be determined yet, because 68% of this group are alive at 54 months, the time of reporting, and this is significantly better than the median survival of 42 months for the VMCP group ($P < 0.02$).

It is of interest that the median survival of myeloma patients treated with MP in 10 different studies ranges from 19 to more than 54 months. The fact that the median survival of myeloma patients treated with the same drugs in different studies can vary by more than 35 months demonstrates that other important variables such as the stage of the disease, the growth rate of the myeloma cell mass, and supportive care have an important influence on the survival of these patients. In fact,

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Table 1. Melphalan/prednisone versus drug combinations in the treatment of plasma cell myeloma

Group*/year (Ref.)	Drug combination†	Number MP/comb.	Percentage‡ response MP/comb.	Median survival (Mo) MP/comb.	Significance of difference (*P*) Response	Survival
ECOG/1982 [4]	BCP	92/96	43/50 (B)	19/25	NS	NS
Denmark/1985 [7]	VBCMP (M2)	31/33	45/58 (B)	21/21	NS	NS
Norway/1986 [8]	VBCMP (M2)	34/33	67/74 (B)	32/33	NS	NS
ECOG/1987 [9]	VBCMP (M2)	219/214	51/72 (B)	30/31	<0.0001 comb. > MP	NS
GATLA/1987 [5]	VCMeCMP	145/115	33/44 (B)	42/44	NS	NS
GATLA/1987 [5]	CMeCP	67/83	40/40 (B)	38/30	NS	NS
NCI-C/1979 [6]	BCMP	125/174	40/39 (A)	28/31	NS	NS
SWOG/1983 [10]	VMCP,VCAP + VBAP	79/160	32/53 (A)	24/40	0.002 comb. > MP	0.01 comb. > MP
Alexanian/1984 [1]	same as above	30/75	53/57 (A)	37/26	NS	NS
GMTG/1988 [12]	VMCP	170/150	33/33 (A)	>54/42	NS	<0.02 MP > comb.

*ECOG—Eastern Cooperative Oncology Group; GATLA—Grupo Argentino de Tratamiento de la Leucemia Aguda; NCI-C—National Cancer Institute of Canada; SWOG—South West Oncology Group; GMTG—German Myeloma Treatment Group.
†A—adriamycin (doxorubicin), B—BCNU (carmustine), C—cyclophosphamide, V—vincristine, M—melphalan, MeC—methyl CCNU (semustine), P—prednisone.
‡Response criteria: A—SWOG ≥ 75% reduction in M protein synthetic index; B—Myeloma Task Force ≥50% fall in M protein concentrations.

these other factors probably have a more important influence on the survival of groups of myeloma patients than variations of the antineoplastic therapy administered to them. Although the groups of patients randomized to MP versus one of the drug combinations appear to have been well matched, it is difficult to compare the groups because of the multitude of important prognostic factors. Recently, serum beta-2-microglobulin levels have proven to be such a strong prognostic factor that it may be possible to make better comparisons of treatment groups by adjusting for this variable [13].

These randomized studies do not clearly show that drug combinations are better than MP in the treatment of myeloma patients. Five of the studies [5–9] show less than a 3 month difference in the survival of the MP and drug combination groups, two show an improvement of 6 and 16 months [4, 10] in the median survival of the drug combination groups, while three show an improvement of 8, 11 and more than 12 months in the median survival of the MP groups [5, 11, 12].

The effect of adding doxorubicin to drug combinations is not clear from the studies reviewed here, since the results of two parts of the same study are not confirmatory. Doxorubicin is clearly active in the treatment of myeloma, but its role in drug combinations needs to be defined further. It is of interest that the ABCM drug combination tested in the fifth MRC myelomatosis trial does improve the survival of myeloma patients in comparison to melphalan alone, and the improved survival is significant, even after correction for serum beta-2-microglobulin levels [13].

Investigators at the Royal Marsden and St. Bartholomew's hospitals in London have tested the value of very high doses of intravenous melphalan (140 mg/m^2) in the treatment of plasma cell myeloma [14]. This treatment causes severe, life-threatening hematologic toxicity. The median duration of the remission was 7 months for patients who had been treated previously, and 18 months for previously untreated patients, with only one remission persisting beyond 4 years. It is of great interest that these large doses of intravenous melphalan can overcome the resistance developed to conventional doses of the drug, but the failure to cure is disappointing.

Intensive chemotherapy and total body irradiation, with marrow transplantation to facilitate marrow recovery, has been tested, usually on younger myeloma patients who had failed prior therapy. Marrow from an identical twin (syngeneic), an HLA compatible sibling (allogeneic), and from the patient (autologous), have been used. All of these studies have been disappointing in that this intensive chemotherapy and total body irradiation usually fails to eliminate the myeloma clone from the body [15–18].

There is a great need to discover new agents which are effective in the treatment of plasma cell myeloma. The agents which have been tested to date can control the growth of the myeloma cells for a time, and prolong life by preventing death from complications. However, these agents do not

eliminate the mycloma clone and cure the disease, or alter the progressive course of the disease. Plasma cell myeloma progresses, despite treatment, to become resistant to therapy, to grow at an increased rate, to enter the acute phase and to cause death. An agent capable of preventing progression would alter the course of the disease, and prolong life.

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