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Oral Dosage of Melphalan and Response to Treatment in Multiple Myeloma

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Abstract—*Forty-nine consecutive patients with multiple myeloma were analysed for treatment response in relation to dose of orally administered melphalan (induction therapy). All patients were given at least six courses of melphalan-prednisone. Treatment response, defined as a reduction of the myeloma protein of* >50%, *was seen in* 26 *patients while* 23 *were non-responders. When treatment response was related to the dosage of melphalan given by* mg/kg of body weight, *the numbers of responding and non-responding patients were similar in the group of patients without dose reduction as well as in that with dose reduction. Drug-induced suppression of white blood cell and platelet count was similar in the responding as well as in the non-responding group indicating that the reason for non-response is not simply explained by deficient drug absorption. When the* cumulative dose *of melphalan given during the induction therapy was analysed, however, a positive correlation* ($r = 0.47$, $P < 0.001$) *was seen between the cumulative dose and the degree of response. Thus, the cumulative dose of melphalan given during induction therapy seems to be of importance for the response, but other factors as intrinsic differences in cell sensitivity may also explain the individual responsiveness.*

INTRODUCTION

INTERMITTENT melphalan-prednisone therapy [1] is considered the primary standard treatment for multiple myeloma. About 50% of the patients respond to this therapy regimen [2]. Factors predicting sensitivity and resistance to treatment are poorly understood. One reason for the different sensitivity to therapy of the patients might be variations in the dosage of cytostatics given to the patients. Differences in dosage between patients might be due to drug toxicity, especially bone marrow depression resulting in dose reduction. Moreover, the uptake and bioavailability of melphalan vary between individuals [3]. The aim of the present study was to analyse whether the dose of melphalan is important for the antitumour effect. To evaluate this the antitumour effect in patients receiving 'full dose' was compared to that in patients receiving a reduced dose of melphalan. Further, the importance of melphalan dose calculated as cumulative dose after six therapy courses was evaluated.

MATERIALS AND METHODS

Forty-nine consecutive patients treated for multiple myeloma at the Department of Oncology, Radiumhemmet, Karolinska Hospital between 1974 and 1983 were analysed. The diagnosis of multiple myeloma was established when at least two of the following criteria were met: (1) a monoclonal immunoglobulin peak revealed at electrophoresis of serum and/or urine with a subnormal concentration of at least one non-monoclonal immunoglobulin class (IgG, IgM, IgA) in serum; (2) more than 10% plasma cells in the bone marrow; (3) osteolytic and/or osteoporotic bone lesions compatible with multiple myeloma [4]. The majority of patients were in stage II and III according to the system proposed by Durie and Salmon [5]. All patients received a minimum of six courses of intermittent melphalan-prednisone (MP) treatment: 0.25 mg melphalan/kg body wt/day and 2 mg prednisone/kg body wt for 4 consecutive days, usually without tapering of prednisone. The course was repeated every 6th week. The dosage schedule was reduced if the white blood count was $<2 \times 10^9$/l and/or platelet count $<100 \times 10^9$/l. The prednisone was reduced only if side-effects could be attributed to the steroid component. For each patient the total dosage of melphalan given during six consecutive courses of induction therapy (cumulative dose) was calculated. Response to therapy was defined as a reduction of the M-component concentration with > 50% of the pretreatment value after six treatment courses. No patient was withdrawn from therapy during the observation time.

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Statistical significances were evaluated by Student's t test, linear regression analysis and Pearson's correlation test.

RESULTS

To give patients a similar amount of a drug the drug dosage is determined by body weight [6]. It is, however, apparent from previous studies [2] as well as from the present that this dosage principle will result in different treatment responses among the patients. Twenty-six of 49 patients were classified as responders and 23 as non-responders.

A poor response to therapy could be related to a reduced dosage. To analyse this possibility the patients were separated into two groups; those with and those without a dose reduction of melphalan as defined by dose intensity during the 'induction period' (Table 1). As can be seen, a similar relation between responders and non-responders was found in the two groups. Among other factors that may explain response to therapy is a variable bioavailability of the drug, e.g. drug absorption from the gut. The level of white cells and platelet counts in the blood of treated patients may give an indication of drug availability. We analysed the numbers of white blood cells and platelets before and after six courses of treatment. A significant ($P < 0.0005$) decrease in the white blood cell count was found in the non-responding patient group as well as in the responding group (Table 2). Moreover, there was no difference between responders and non-responders with regard to percentage reduction of the white blood cell count as well as of the platelet count (Table 3). The cumulative dose of melphalan given to the patients during the induction therapy period varied from 125 to 600 mg. To analyse whether the total dose given to the patients during the induction period might relate to the treatment effect, the cumulative dose was plotted against the percentage reduction of the M-protein concentration (Fig. 1) after six courses of induction therapy. A significant positive correlation ($r = 0.47$, $P < 0.001$) was found between the cumulative dose and the decrease in the M-protein concentration. This was shown by multivariate analysis to be the strongest and only independent predictor of response.

DISCUSSION

The importance of dose and dose intensity in cancer chemotherapy has been discussed with increasing interest during recent years [7]. The aim of this study was to analyse whether the dose of oral melphalan during the induction therapy of multiple myeloma is of importance for the clinical response.

In the present material the dose intensity (mg/kg/week) for the patients with dose reduction, mainly due to bone marrow toxicity, was generally 10–25% lower than in patients having no reduction of the melphalan dose. A similar number of responders and non-responders in the group of patients with dose reduction compared to the group without dose reduction contradicts the possibility that dose intensity was the main factor determining treatment response. Another possible explanation for the lack of treatment response may be a deficient uptake of melphalan from the gut [3]. Treatment-

Table 1. Treatment response in relation to dose intensity

Patients without dose reduction ($n = 37$)		Patients with dose reduction ($n = 12$)	
Responders	Non-responders	Responders	Non-responders
19	18	7	5

Patients who had no dose reduction received 0.17 mg/kg/week and those who were given a reduced dosage received 0.09–0.15 mg/kg/week.
Induction time: 36 weeks.

Table 2. White blood count and platelet count ($\times 10^9/l$) *(mean ± S.E.M.) before and after treatment in responding and non-responding patients respectively*

	Before treatment	After treatment	P-value
WBC			
Responders	6.86 ± 0.49	4.65 ± 0.31	<0.0005
Non-responders	5.85 ± 0.44	4.03 ± 0.44	<0.0005
Platelets			
Responders	236 ± 15.9	180 ± 14.4	<0.005
Non-responders	241 ± 32.5	195 ± 21.4	<0.05

Table 3. Percentage (mean ± S.E.M.) reduction of blood cell counts in relation to tumour response

	Responders	Non-responders	*P*-value
White blood cells	30.3 ± 3.9	32.5 ± 4.5	n.s. ($P = 0.72$)
Platelets	23.7 ± 4.2	18.4 ± 4.6	n.s. ($P = 0.40$)

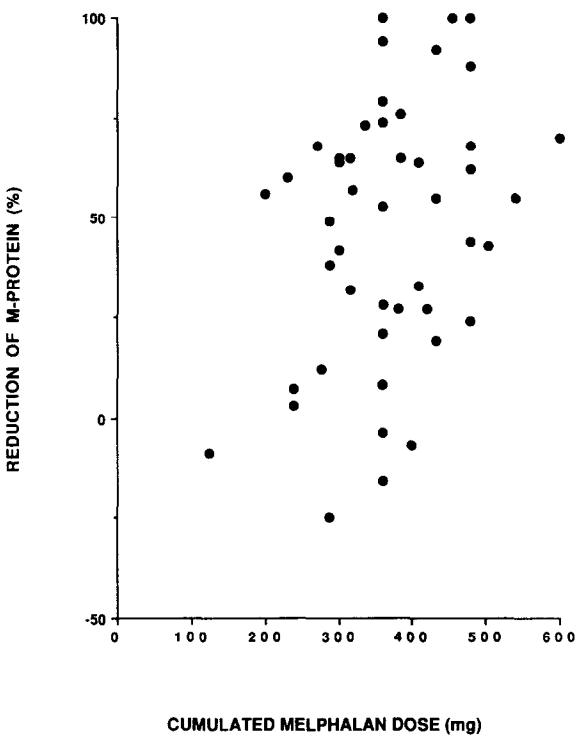

Fig. 1. Reduction of M-protein concentration in relation to the cumulative dose of melphalan. Negative values of the y-axis represent an increase in M-protein.

induced reduction of blood cell counts may be taken as a measure of bioavailability of the drug. A similar reduction of the white blood cell count and platelet count in the responding as well as in the non-responding group of patients is an indication of a roughly similar bioavailability of the drug in the two groups. Only three patients in the group of non-responders showed significant (> 10%) progression of M-protein which could otherwise be a factor other than melphalan reducing blood cell counts.

However, this should be interpreted with care as the endpoint, in this case the capability of normal marrow cells to regenerate after six courses of melphalan-prednisone treatment, might not disclose minor differences in bioavailability of the drug which might be of importance for the tumour response. In a recent publication by Palmer *et al.* [8] the authors failed to show a correlation between dose intensity of melphalan and neither reduction of M-protein nor survival for myeloma patients giving rise to questions about the effect of melphalan and more interest in prednisone for which the dose intensity correlated to survival. However, in that study the initial dose intensity was high and most patients had a dose redution which might indicate that maximum melphalan effect was at hand, giving a small room for dose–effect analysis. We calculated the cumulative dose since our lower initial dose intensity gave relatively few and small dose intensity differences in the material. Calculation of the cumulative dose given during the induction therapy disclosed a correlation between dose and treatment response. The correlation indicates that the dose of oral melphalan is of importance. The result suggests that an increased response rate may be expected with an increased dosage of melphalan. It has recently been shown by Selby *et al.* [9] that with high doses of melphalan intravenously, a higher response rate (78% CR + PR) can be achieved. It is, however, apparent from that study as well as from the present investigation that factors other than bioavailability might be of importance for the treatment response. Such a factor may be intrinsic tumour cell sensitivity/resistance. Thus, in an *in vitro* cloning system using human myeloma stem cells a correlation between the *in vitro* and *in vivo* sensitivity has been shown for individual patients [10].

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