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Dose Intensity Analysis of Melphalan and Prednisone in Multiple Myeloma[1,2]

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The average relative dose intensity (DI) of conventional oral melphalan and prednisone therapy received by 93 newly diagnosed multiple myeloma patients was correlated with survival and with percent reduction in M-protein. A survival advantage was shown with increasing average relative DI of melphalan and prednisone. Multivariate analysis showed survival to correlate with increasing DI of prednisone ($P = .05$) but not with the DI of melphalan ($P = .93$) nor with the percent decrement in M-protein ($P = .10$). These results suggest that the initial management of myeloma should be reassessed, with particular emphasis on more intensive therapy employing high-dose steroids. [J Natl Cancer Inst 1988;80:414-418]

Oral melphalan and prednisone therapy, together with local irradiation for bone pain, has continued to be the reference treatment for human multiple myeloma since this therapy was introduced in the early 1960s (*1*). There have been many clinical trials of multidrug combinations, but it remains controversial as to whether they have shown improved survival over that obtained with melphalan and prednisone alone. Those trials claiming to have shown a survival advantage for combination chemotherapy (*2,3*) have

Abbreviation used: DI = dose intensity.

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suffered from significant methodologic difficulties that have cast doubt on this conclusion. Others have failed to demonstrate a survival advantage for combination chemotherapy (*4,5*), and at present the consensus appears to be that combination chemotherapy has not been convincingly shown to have improved survival in myeloma (*6,7*).

Preliminary data from several groups have produced a renewed interest in the implementation of more aggressive therapy for this cancer, such as high-dose iv melphalan in conjunction with other multiple-drug therapies and/or autologous bone marrow transplantation (*8-10*). The reaction to the use of aggressive therapy in this disorder has been mixed, due to the significantly increased toxicity produced and the belief that the conventional oral melphalan/prednisone therapy is effective, although not curative, in managing this cancer.

There has been much recent interest in the concept that DI may be a significant factor in chemotherapeutic outcome (*11-15*). We have, therefore, carried out a retrospective study of the average relative DI of oral melphalan and prednisone received in a large series of myeloma patients treated at our institution in an attempt to characterize further the effectiveness of this conventional therapy.

Methods

Patient selection. This study is a retrospective analysis of 161 patients who were diagnosed to have multiple myeloma at our institution between September 1977 and September 1985. We have a population-based cancer registry and are the main referral center for 1 million. Furthermore, our universal health care system essentially eliminates economic constraints as to when symptomatic patients first present to a physician. Consequently, the vast majority of multiple myeloma patients are seen in consultation and entered on protocols managed from our center. These protocols included the MY-2 and MY-4 programs of the National Cancer Institute of Canada. The minimum follow-up time for any patient in this study was 18 months.

The diagnosis of multiple myeloma was based on the standard criteria of a patient exhibiting two of the following findings: (*a*) either bone marrow plasmacytosis >10% or plasmacytosis in a biopsy of a bone or soft tissue lesion, (*b*) detection of a serum and/or urine M-protein, and (*c*) osteolytic lesions. Treatment was initiated at the time of diagnosis with oral melphalan (9 mg/m^2 per day) and prednisone (50 mg twice a day) for 4 days each 28 days. The fixed received dose of prednisone was subsequently converted in retrospect to milligrams per square meter for the purposes of this study. If the treatment-day wbc count was $<2.0 \times 10^9$/L or the platelet count was $<50 \times 10^9$/L, treatment was delayed until counts were above these levels. Radiation therapy was used as indicated for the treatment of painful osteolytic lesions and spinal cord compression. Supportive care for pain, infection, anemia, hypercalcemia, and renal failure was also given when indicated.

The 93 patients eligible for this DI study met the following criteria: (*a*) They had received no prior therapy, (*b*) they system (*16*), (*c*) they had received only oral melphalan and prednisone therapy, and (*d*) they had survived for 9 months after the initiation of the oral melphalan/prednisone therapy. The ineligible patients consisted of (*a*) 26 patients with stage I disease, (*b*) 30 patients who had survived <9 months, and (*c*) 12 patients who had been treated with other drugs because of disease progression during the initial 9 months of treatment. Stage I patients were omitted in this retrospective study because many such patients have smoldering disease and our policy is to initiate therapy only when they become symptomatic. An analysis of prognostic variables in those patients excluded because they received other cytotoxic drugs within the first 9 months following diagnosis and treatment initiation or because they failed to survive 9 months from diagnosis did not demonstrate any significant difference compared to patients included in the analysis. The eligible patients consisted of 37 patients with stage 2A disease, 4 patients with stage 2B disease, 42 patients with stage 3A disease, and 10 patients with stage 3B disease. The overall response rate by the Chronic Leukemia-Myeloma Task Force criteria (*17*) was 71%.

Dose intensity. The individual DIs for oral melphalan and for oral prednisone that were actually received by each patient were determined over the first 9 months of treatment and were expressed as milligrams per square meter per week. The average DIs for the combination of melphalan and prednisone for each patient were calculated relative to the stated protocol dosage, as described by Hryniuk and Bush (*13*).

The selection of 9 months as the time over which DI was calculated was based on information already in the clinical myeloma literature. A recent large clinical trial has shown that the median time for a clinical response after initiation of oral melphalan and prednisone therapy was 89 days and the median time to disease response and stabilization was 10.1 months (*18*). This same study concluded that maintenance therapy, after response and stabilization, did not improve overall survival. Consequently, it may be concluded that any benefit in overall survival derived from existing therapy is the result of some, as yet undefined, duration of initial therapy. On the basis of these aforementioned data, 9 months appeared to be an appropriate time period over which to calculate the DIs of oral melphalan and prednisone therapy.

Statistical methods. Actuarial survival curves were generated using the life-table method of Kaplan and Meier (*19*). Survival analysis was performed using the log-rank test (*20*) and Cox's proportional hazards model (*21*). Regression analysis and Pearson correlations were performed using the SPSS^X statistical software package (*22*).

Results

The median survival for the 93 eligible patients in this study was 39 months. There was no significant difference between the median survival of responders (42 mo) and nonresponders (29 mo), as defined by the Chronic Leukemia-Myeloma Task Force criteria ($P = .08$).

The DIs received over the first 9 months of treatment for this series of myeloma patients ranged from 2.3 to 9.1

week for prednisone. The variation in melphalan DI was the result of cumulative hematologic toxicity. When melphalan administration was delayed, prednisone was also withheld until it was again appropriate to administer melphalan. Further variation in prednisone DI resulted from giving patients a fixed dosage of this drug irrespective of their body surface area. Prednisone therapy was not initiated in one patient due to previous peptic ulcer disease; it was discontinued in one patient due to difficulty with diabetic control and in another patient due to gastrointestinal bleeding. The average relative combined DIs for the melphalan/prednisone combination, as calculated by the method of Hryniuk and Bush (*13*), ranged from 0.33 to 1.02.

Patients were stratified into the following three groups according to the average relative DIs of melphalan and prednisone received: low (DI < 0.69; $n = 32$), intermediate ($0.69 < DI < 0.84$; $n = 29$), and high (DI > 0.84; $n = 32$). The actuarial survival curves for these three groups are shown in figure 1. While the median survivals for the low, intermediate, and high DI groups were 33.0, 40.5, and 46.0, respectively, statistical significance was not achieved ($P = .07$) when these three curves were simultaneously compared by the log-rank test. However, trend analysis of the ratios of the actual to the predicted death rates (i.e., relative death rate) for these three groups demonstrated a statistically significant trend ($P = .03$), with the patient group that received the highest DI of melphalan and prednisone showing the lowest relative death rate. There was no significant difference in the distribution of MY-2 and MY-4 protocol patients among the three DI levels.

The patients were next stratified into stage II and stage III, and the survival curves were generated for the same low, intermediate, and high DI levels. Again log-rank analysis of these overall survival curves showed no statistical significance ($P = .07$), while the trend analysis was again statistically significant ($P = .03$). If the patients were stratified into groups of stage 2A, stage 3A, and stage 2B + 3B to take into account the bias of impaired renal function, the trend analysis of the relative death rates was not significant ($P = .08$). This suggests that poor renal function is a more important factor in survival than is the benefit derived from drug therapy in this group of patients.

In light of the statistically significant trends in the ratios of actual to expected death rates, using Cox's proportional hazards model, we carried out a multivariate analysis of survival versus age, percent decrement in the M-protein, DI of melphalan, and DI of prednisone. Prior to this analysis, patients were stratified into three groups, namely, 2A, 3A, and 2B + 3B. The two-sided *P*-values were $P = .99$ for age, $P = .93$ for DI of melphalan, $P = .10$ for percent decrement of M-protein, and $P = .05$ for DI of prednisone. This analysis revealed that the most significant factor contributing to survival was the DI of prednisone, not the DI of melphalan.

Figure 2 shows that there was no significant correlation between the average relative DI of the melphalan/prednisone combination and the percent decrement of M-protein ($r = .09$; $P = .21$). A multivariate regression analysis of percent decrement of M-protein versus the individual DIs of melphalan and prednisone again failed to show a significant correlation for either variable ($P = .35$).

Discussion

Hryniuk and Bush (*13*) have proposed a method that has facilitated the determination of the average relative DI of cytotoxic drugs given in multidrug protocols. They have recently presented evidence relating DI to disease-free survival in stage II breast cancer (*23*) and to response in advanced breast cancer (*13*) and ovarian cancer (*24*). The major as-

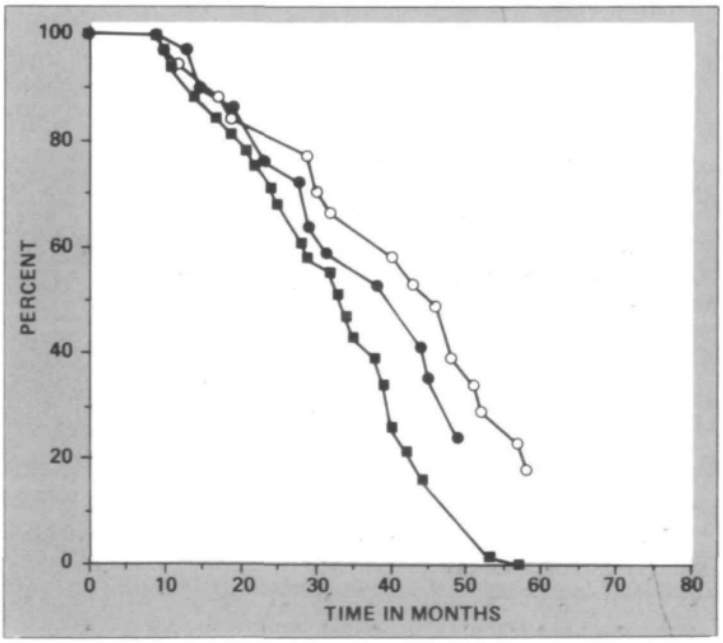

Figure 1. Kaplan-Meier actuarial survival curves for myeloma patients receiving low (■), intermediate (●), and high (○) average relative DIs of the melphalan/prednisone combination ($P = .07$). The ranges of values and number of patients for these groups were the following: low, DI < 0.69, *n*

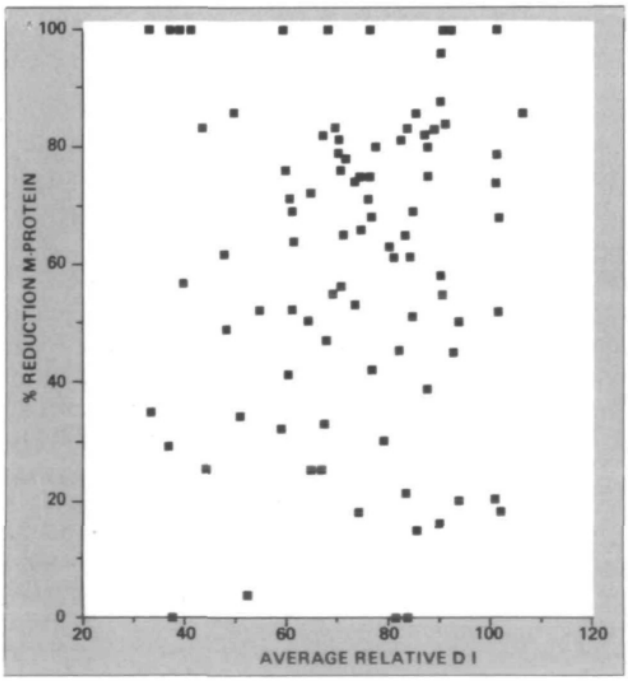

Figure 2. Percent reduction in M-protein as a function of the average

sumptions made by Hryniuk and Bush in their DI calculations are that all drugs in a multidrug therapy are equally effective, that the effects of the individual drugs are additive, and that drug scheduling is relatively unimportant. In this study no assumption need be made about scheduling, as all patients included were treated with the use of the same schedule. The multivariate analysis in which the relative DI of melphalan and that of prednisone are treated as separate variables avoids the other assumptions of each drug's having an additive effect and of equal efficacy of each drug. However, these latter two assumptions are made in the analyses involving the *average* relative DI of melphalan and prednisone. While these assumptions may certainly be questioned, this methodology provides a step in the assessment of the role of dose escalation in the treatment of human cancers.

We have used the method of Hryniuk and Bush to calculate the average relative DIs of melphalan and prednisone that were received by a large series of myeloma patients treated at our institution. The DI data were correlated with survival and percent decrement of the M-protein. Log-rank analysis showed a statistically significant trend in the relative death rates as the average relative DI of melphalan and prednisone increased. There was no significant correlation between the average relative DI of melphalan and prednisone and the percent decrement of the M-protein. The multivariate analysis gave the surprising result that it was the DI of prednisone, not the DI of melphalan, that correlated with survival.

This latter observation is clearly contrary to the currently held dogma that melphalan is the significant cytotoxic component in the melphalan/prednisone therapy of myeloma. There are three possible explanations for the observed lack of correlation between melphalan DI and survival. The first is that there is indeed no correlation over the DI range studied. This may occur if the DI range studied was in the plateau region of the dose-response curve or if the slope of the DI versus survival curve was extremely small. We believe it unlikely that the extremely low serum concentrations of melphalan attained with this conventional dosage would place the received DI in the plateau portion of the dose-response curve. The second possibility is that the oral absorption of melphalan is highly variable and that this variation is masking any DI effect that might exist at the tumor level. Few data are available on the absorption of oral melphalan at conventional dosages due to the difficulty of measuring the low concentrations attained in the blood. In one reported study of six patients, the mean bioavailability after a 10-mg dose of melphalan was 78.3% ± 6.3% (*25*). The melphalan dose reductions in our patients were the result of cumulative hematologic toxicity occurring toward the end of the 9-month interval over which the DI was calculated. Therefore, in our opinion, it is difficult to attribute the lack of correlation between the received melphalan DI and survival to variable oral absorption.

The third possible explanation for the lack of correlation between melphalan DI and survival is that melphalan therapy is not as effective as is generally believed. Examination of the myeloma literature shows that the effectiveness of melphalan in the treatment of myeloma is not as firmly established as is generally believed. Melphalan was first used in treating myeloma in 1958 (*26*) and was subsequently introduced for more general use in the early 1960s (*1,27*). The claim that melphalan treatment increases overall survival in myeloma patients resulted from comparisons of melphalan-treated patients with historical controls (*1*), as there has never been a randomized controlled trial of treatment with melphalan versus no cytotoxic agent.

The 1960 paper of Osgood (*28*) is most often quoted as showing the poor survival of myeloma patients prior to the introduction of melphalan therapy. In this report Osgood summarized the survival data of nine studies conducted by other investigators that showed that the median survival time from first treatment was 7.1 months (although the median survival from the time of first symptoms was 17 mo). The current overall median survival of myeloma patients is 28–30 months (*6*). The use of such historical controls to prove drug effectiveness is no longer acceptable. In the case of myeloma, interpretation of such data is further complicated by a number of factors. Most clinicians treating myeloma will concede that diagnosis of this disease is made earlier now than in the 1950s because of better awareness of the presenting symptoms of the disease and the availability of routine serum protein electrophoresis and biochemical screening. It might also be argued that the time from first symptoms until the patient presents to a physician is also shorter as medical care becomes more accessible to the general public. While initiation of therapy for myeloma is now almost simultaneous with diagnosis of stage II or III disease, it is seen in the early myeloma literature that there was often a gap of a year or more between diagnosis and initiation of therapy (*27*). If survival is monitored from initiation of therapy, it is easily seen that all of the aforementioned factors will result in an increased survival of current myeloma patients over historical controls, irrespective of any contribution by the therapy. Lastly, improved supportive care, including better management of renal impairment and of infection in the immunocompromised host, has also clearly contributed to the increase in overall survival as compared to that seen in early historical controls.

The results presented in this article do not prove a cause-and-effect relationship between prednisone DI and survival, as they do not rule out any beneficial effect of melphalan. They do, however, strongly suggest that the first-line treatment of myeloma should be reassessed. There have been many multidrug combination therapies tested in myeloma. These therapies have included various alkylating agents, anthracyclines, and vinca alkaloids. While controversy still exists as to whether combination chemotherapy has improved survival over that achieved with oral melphalan and prednisone alone (*2–5*), the consensus appears to be that it has not (*6,7*). It is interesting that the common feature of essentially all of these combination therapies has been a steroid, usually either prednisone or dexamethasone. The clinical evidence to support the addition of prednisone to melphalan dates back to the 1960s (*29,30*). The question of whether conventional-dose oral prednisone contributes to plasma cell cytotoxicity or merely alters M-protein synthesis and/or turnover has been controversial, the clinical evidence available being consistent with either explanation (*31,32*).

The results obtained in this study again demonstrate the importance of impaired renal function in myeloma, an observation that has previously been made by ourselves and others (*33-36*). Impaired renal function overrides the effect of increased average relative DI of melphalan and prednisone on improved survival, as it does the impact of other prognostic variables recognized in the staging system of Durie and Salmon.

The observation that there was no correlation between the percent decrement of M-protein and either the individual melphalan and prednisone DIs or the average combined melphalan/prednisone DIs is very interesting. While therapy with conventional intermittent oral melphalan/prednisone does significantly reduce the serum concentration of the M-protein in ≈50% of myeloma patients, these results indicate that there is no linear relationship between this M-protein decrement and the drug DI. Consistent with this observation is our recent report describing the poor correlation between response and survival when myeloma patients were stratified by stage (*33*). Consequently, we conclude that the use of current response criteria that are largely defined by a given M-protein decrement, to imply a survival advantage, is not warranted. We have analyzed the relationship of M-protein decrement as a continuous variable to survival in more detail, and this analysis will be the subject of a separate publication.

The data presented suggest various directions that future clinical trials might take. In light of our results, we believe that future trials of higher dose steroid therapies, such as the vincristine, doxorubicin, and dexamethasone (VAD) regimen (*37*), as first-line therapies in newly diagnosed myeloma are warranted. The question of melphalan efficacy is complicated, but the questions we have raised by this study could be resolved with a prospective randomized trial of various DIs of melphalan administered iv.

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