Improved Survival of Increased-Risk Myeloma Patients on Combined Triple-Alkylating-Agent Therapy: A Study of the CALGB

By John B. Harley, Thomas F. Pajak, O. Ross McIntyre, Shaul Kochwa, M. Robert Cooper, Morton Coleman, and Janet Cuttner

Two hundred fifty-two previously untreated evaluable patients with multiple myeloma were entered into a study testing a regimen of three intravenous alkylating agents, melphalan, cyclophosphamide, and carmustine (BCNU), given in combination (BCMP) against a regimen employing oral melphalan (MP). Both regimens included a tapering course of prednisone. Objective responses based on the Myeloma Task Force criteria were significantly more frequent in the group receiving BCMP. Survival for the entire group of BCMP-treated patients was not significantly better than that for MP-treated patients (p = 0.62). However, when the survival of the poor-risk (high tumor cell load) group of patients treated with BCMP was compared with the survival of the poor-risk (high tumor cell load) group of patients treated with MP, an improvement in survival attributable to BCMP therapy was seen (p = 0.049 and 0.02, respectively). In the good-risk (low and intermediate tumor cell load) group, BCMP treatment resulted in a trend toward poorer survival, but this did not achieve statistical significance (p = 0.080 and 0.23, respectively). These results indicate that optimal therapy in myeloma may be dependent on the extent of disease at the time of first treatment. Additional studies to explore the effects of treatment intensity and duration are needed in order to design improved myeloma treatment based on the patient’s extent of disease.

Several trials have shown that melphalan (L-phenylalanine mustard, L-PAM) and cyclophosphamide (CTX) are effective treatments for multiple myeloma. Combining L-PAM with prednisone results in improved responses, and various combinations of these two drugs now represent standard initial therapy for multiple myeloma. Carmustine (BCNU) and prednisone also have activity in this disease. Thus, three well-studied alkylating agents are available for the treatment of multiple myeloma. On the basis of reports indicating that patients failing on one of the previously mentioned drugs may still respond to an alternative agent, it may be concluded that cross-resistance to these drugs in myeloma does not invariably occur. This has been supported by work performed with the mouse myeloma model, where Ogawa et al. have demonstrated sensitivity to CTX in MOPC 460D but relative resistance to melphalan.

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With this background, pilot studies of a combination of drugs (BCMP) consisting of L-PAM, CTX, and BCNU were initiated in 1970 at four member institutions of Cancer and Leukemia Group B (CALGB). Varying doses of the three alkylating agents with and without prednisone were employed in these studies. In view of the promising results obtained, a phase III trial was initiated. We present here our observations on response and survival for patients in this phase III trial.

MATERIALS AND METHODS

Patient Selection

All patients with unequivocal diagnoses of multiple myeloma were eligible for study except those patients who had previously received any one of the alkylating agents used in this study. Patients who had received prior corticosteroid therapy or radiation therapy were eligible. Protocol therapy was to be initiated immediately after diagnosis, except when dehydration, infection, or local symptoms necessitated specific therapy, but it was not to be withheld for more than 48 hr for such supportive therapy.

Patients were randomly assigned to melphalan and prednisone (MP) or to the combination of BCNU, cyclophosphamide, melphalan, and prednisone (BCMP). A Latin square randomization scheme was used to balance entries within and across institutions. Patients were not stratified before randomization.

Patients assigned to MP were initially given oral melphalan at 150 μg/kg/day for 7 days, with oral prednisone at an initial dosage of 1.2 mg/kg/day. The daily dose of prednisone was not to exceed 100 mg. After seven daily doses, melphalan was discontinued, and the patient was followed with weekly blood counts until the nadir of bone marrow depression was reached. When peripheral counts were clearly rising, the patient was placed on a daily maintenance dose of oral L-PAM of 50 μg/kg/day p.o. (2 mg/sq m). The prednisone was continued for 10 wk, with reductions as indicated in Fig. 1.

Patients assigned to BCMP were initially given BCNU at 100 mg/sq m, cyclophosphamide at 300 mg/sq m, and melphalan at 8 mg/sq m intravenously. The combination was repeated every 6 wk. Prednisone was given for the first 10 wk in the same fashion as in the MP regimen. For patients with severe azotemia, the three alkylating agents were started at 50% dosage. The two treatment schedules are summarized graphically in Fig. 1.

Further dosage modifications of all alkylating agents were made on the basis of leukopenia and

![Fig. 1. Study design for CALGB protocol 7261.](image-url)
thrombocytopenia. Local radiotherapy was allowed, if indicated. Patients who did not respond or who showed evidence of progressive disease before the 23rd wk were removed from the protocol. The patients who were shown to have responded by the 23rd wk were continued on therapy until relapse.

The Myeloma Task Force's criteria for objective response were used in the evaluation. Briefly, a patient was considered an objective responder if there was a decrease of more than 50% in serum M-protein concentration or urinary M-protein excretion or a decrease of more than 50% in measured cross-sectional area of a plasmacytoma or recalcification of bone lesions.

**Statistical Methods**

Differences in pretreatment characteristics and response frequencies were evaluated using the Pearson $\chi^2$ test for differences in percentages and the Wilcoxon test for differences in continuous variables. Differences in survival were evaluated by the Breslow modification of the Kruskal-Wallis test, and the survival curves were plotted by the life-table method. Since 15 patients (7 on BCMP and 8 on MP) were lost to survival follow-up, all the survival comparisons were done two ways. In the first of these, patients were censored at the time of loss. In the second method, patients were judged as failures at the time of loss. With either approach, the significance levels were very close for all survival comparisons, and for this reason the data reported here are based on the first method. Screening of pretreatment characteristics that might influence survival was done with the Cox regression model.

**RESULTS**

Two hundred sixty-nine patients were entered on this protocol, and 252 were considered evaluable for this analysis. Of the disqualified, 6 patients lacked criteria for diagnosis of myeloma, 2 patients received the wrong drug, 2 patients received drug doses higher than the protocol prescribed, 1 patient was entered without control of infection, and no records were received on 9 patients. One patient on each regimen did not have sufficient data recorded to evaluate response, but each is included in the survival analysis.

Comparison of the two randomized treatment groups did not reveal significant differences between the two with respect to 16 presenting characteristics (Table 1). The objective response frequency for BCMP was significantly higher than for MP ($p = 0.047$). The frequency of 50% or more reduction in abnormal serum protein was again significantly higher for BCMP ($p < 0.001$). A similar trend in favor of BCMP that did not achieve statistical significance was noted for urinary M-protein response ($p = 0.07$). The time to best response in the serum protein was longer for

<table>
<thead>
<tr>
<th>Table 1. Pretreatment Presenting Characteristics Examined</th>
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<tbody>
<tr>
<td>1. Sex</td>
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<tr>
<td>2. Age</td>
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<td>3. Hemoglobin</td>
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<tr>
<td>4. Serum M-protein type</td>
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<tr>
<td>5. Serum M-protein concentration</td>
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<td>6. Urinary M-protein type</td>
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<td>7. Urinary M-protein concentration</td>
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<tr>
<td>8. Percentage marrow plasma cells</td>
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<td>9. Serum calcium</td>
</tr>
<tr>
<td>10. Performance score</td>
</tr>
<tr>
<td>11. Leukocyte count</td>
</tr>
<tr>
<td>12. Platelet count</td>
</tr>
<tr>
<td>13. Presence of infection</td>
</tr>
<tr>
<td>14. Blood urea nitrogen</td>
</tr>
<tr>
<td>15. Pain score</td>
</tr>
<tr>
<td>16. Staging system described by Durie</td>
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</table>
BCMP than MP (median 11 wk versus 75 wk, with \( p = 0.038 \)). The attainment of the best serum M-protein response was observed after 12 mo in 9 BCMP-treated patients and 4 MP-treated patients. A similar delay in achieving best urinary protein response was also observed for BCMP-treated patients (median 17.5 wk versus 8.0 wk, \( p = 0.011 \)). Further urinary M-protein responses were observed after 12 mo for 2 BCMP-treated patients and 3 MP-treated patients.

Although a higher frequency of serum M-protein responses was noted in the group of patients receiving BCMP, the magnitude of response in these patients (mean reduction of 65%) was not different than that seen in responding patients receiving MP (mean reduction of 66%).

From the 16 pretreatment characteristics listed in Table 1, a step-up procedure using the Cox regression model identified three factors influencing survival significantly. These were the grouped hemoglobin values (under 8.5 versus 8.5–10.4 versus 10.5+ g/dl) at \( p < 0.001 \), the logarithm of blood urea nitrogen (BUN) at \( p < 0.004 \), and the grouped performance score (PS: 0,1,2 versus 3,4) at \( p = 0.004 \).

Grouped hemoglobin value proved to be a more important factor in survival than either the three-part staging system\(^7\) or a modified staging system (high tumor burden versus others combined). When either the original or the modified staging system is substituted for grouped hemoglobin in the preceding model, the maximum likelihood values fall from \((-769)\) to \((-773)\) and \((-773)\), respectively. Thus, this maximum likelihood value associated with the grouped hemoglobin in the Cox model with BUN and performance status is significantly higher than the maximum likelihood associated with either substitution (\( p < 0.01 \)). Because of this finding, we have placed certain patients into a poor-risk group on the basis of hemoglobin of 8.5 g/dl or less, BUN of 30 mg/dl or greater, or performance score of 3 or 4; the remaining patients are considered good risks.

The survival comparisons between BCMP and MP were then repeated for patients in each risk status. The poor-risk patients survived longer if they received BCMP (\( p = 0.05 \)) (Fig. 2). However, the good-risk patients receiving BCMP had a trend toward decreased survival when compared with those receiving MP (\( p = 0.08 \)) (Fig. 3). When responses were reexamined according to risk status, BCMP produced a higher percentage of objective responses in each risk group than MP.
The frequency of serum M-protein response was again significantly higher for BCMP in each risk group (Table 3). These striking survival differences between MP and BCMP with respect to survival were duplicated when the patients were divided by tumor load as defined by Durie and Salmon. Patients with high tumor load survived significantly longer if they received BCMP ($p = 0.02$) (Fig. 4), whereas patients with low or intermediate tumor cell load did not benefit from BCMP ($p = 0.23$).

**TOXICITY**

Severe leukopenia (WBC 1000/cu mm) was more common in patients receiving BCMP (20% as compared with 10%) ($p = 0.01$) (Table 4). When patients were divided by risk group, severe leukopenia due to BCMP was also significantly more frequent in the poor-risk group ($p < 0.01$). Thrombopenia was not significantly different for the two drug regimens. Likewise, severe infection was not significantly different for the two drug regimens. There were 11 deaths (8.9%) that were possibly treatment-related in the BCMP group and 5 deaths (4.0%) in the MP

<table>
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<th>Table 2: Objective Response Frequency</th>
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<tr>
<td>Patient Group</td>
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<tr>
<td>Total</td>
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<tr>
<td>Poor risk</td>
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<tr>
<td>Good risk</td>
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<tr>
<td>Combined</td>
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<th>Table 3: Frequency of Serum M-Protein Response</th>
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<td>Patient Group</td>
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group ($p = 0.19$); In the poor-risk group, the treatment-related death frequencies were similar (7.8% for MP and 11.3% for BCMP). However, in the good-risk group, 5 such deaths (7.0%) occurred with BCMP, whereas none was observed with MP ($p = 0.09$).

BCMP was less well tolerated than MP. Thirteen BCMP patients and 3 MP patients either refused further therapy or had chemotherapy stopped because of toxicity ($p = 0.019$). Severe nausea and vomiting associated with BCMP was the most common reason for abandonment of this treatment. The patient tolerances were similar for the two regimens in each risk group. The median time to the 13 discontinuations of BCMP was 13.3 mo (range 1.5–28.3 mo). Nine of the discontinuations occurred after 10.5 mo. The times to three discontinuations of MP were 1.4, 2.1, and 5.6 mo.

**DISCUSSION**

A significant improvement in objective response frequency, especially in serum M-protein values, was observed in the BCMP patients, without a corresponding

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#### Table 4. Toxicity Ratings in Evaluable Patients

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Regimen</th>
<th>Good Risk</th>
<th>Poor Risk</th>
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<tr>
<td></td>
<td></td>
<td>Toxicity Grade* (%)</td>
<td>Toxicity Grade* (%)</td>
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<tr>
<td></td>
<td>Evaluable Patients</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>L-PAM</td>
<td>62</td>
<td>13</td>
</tr>
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<td>Combination</td>
<td>71</td>
<td>14</td>
</tr>
<tr>
<td>Platelets</td>
<td>L-PAM</td>
<td>62</td>
<td>43</td>
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<tr>
<td></td>
<td>Combination</td>
<td>71</td>
<td>37</td>
</tr>
<tr>
<td>Infection</td>
<td>L-PAM</td>
<td>62</td>
<td>92</td>
</tr>
<tr>
<td></td>
<td>Combination</td>
<td>71</td>
<td>83</td>
</tr>
</tbody>
</table>

*Grade 0  > 4000  > 100 x 10^3  None
1  > 3000  > 75 x 10^3  Mild
2  > 2000  > 50 x 10^3  Moderate
3  > 1000  > 30 x 10^3  Severe
4  > 0  > 0  Life-threatening

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![Survival of high-tumor-load patients on treatment with MP (solid line) and BCMP (dash line).](image-url)
increase in survival. This experience is in contrast with the findings in other studies in myeloma, where response was related to survival. When survival was analyzed on the basis of the initial risk factors or tumor load, the explanation for this paradox became apparent. The poor-risk patients or high-tumor-load patients benefited from BCMP, whereas the low-risk patients and the low-or-intermediate-risk patients did not. In fact, a trend toward decreased survival was noted in the good-risk patients receiving BCMP.

A possible explanation for these results emerges from an examination of the survival curves for good-risk patients (Fig. 3). Here it may be seen that the main difference in survival between the two regimens emerges during the first 18 mo. The chance of dying during that interval for patients receiving BCMP was 34% (24 of 71), in contrast to 16% (10 of 62) for patients treated with MP (p = 0.020).

One explanation for this is that BCMP is more toxic than MP. The increased number of treatment-related deaths in BCMP-treated good-risk patients is one reason for the failure of this therapy to prolong survival in this group. Whereas the initial loading dose of oral melphalan and the initiation of therapy with daily melphalan are at least as toxic as the first course of BCMP, as revealed by the occurrence of treatment-related deaths during this interval, there is a later cumulative toxicity of BCMP as evidenced by late deaths, which causes the survival curves to diverge.

Another possible explanation for this observation in the good-risk patients is that such BCMP patients failing to respond or developing early drug resistance do not respond as well to subsequent treatment as similar MP patients. In the first 18 mo, 24 patients on MP and 20 patients on BCMP exited the study alive with progressive disease. Twenty-eight of the 30 patients failing on the protocol had a survival follow-up of 18 mo or more from the start of the study. Only 19% (4 of 21) of the MP patients died during that interval, as contrasted with 47% (9 of 19) of the BCMP patients (p = 0.12). Although the postprotocol therapy and subsequent response data are unavailable, this difference in survival suggests the possibility that for the nonresponsive good-risk patients sequential therapy with a series of ineffective agents is less harmful than initial therapy with a combination of ineffective agents.

It is also legitimate to ask whether or not the increase in response to BCMP was attributable to the intravenous route of administration for melphalan. Alberts and associates have reported that absorption of oral melphalan is highly variable; so the improved responses seen in the BCMP-treated patients could result from improved delivery of the melphalan in this regimen. Also, the effectiveness of BCMP for high-risk patients could be caused simply by more intensive total alkylating agent exposure. The significantly greater leukopenia in the group receiving BCMP is consistent with this possibility. The design of this study did not allow us to draw conclusions regarding the possible effect of the route of administration (oral versus intravenous) or schedule.

The toxic complications and deaths in the good-risk group subsequent to initial therapy suggest that modification or alternation of later treatment for this group could be beneficial. Alexanian et al. have advocated cessation of treatment for responding patients, and this viewpoint may be valid in the present context. However, there is a problem in recognizing when a patient has achieved a
maximum response. We have observed the best serum M-protein and urinary M-protein responses after 12 mo of therapy in this study. The question is whether or not the additional increment of improvement is worth the increased toxicity and other risks of continuous aggressive therapy.

These results should be considered in the context of other combination chemotherapy programs for myeloma. Although, in general, combination treatments have not shown clear advantages, such studies have not considered the possible differential effects of treatments on patient subgroups. There is growing evidence that combinations including alkylating agents and vincristine may improve survival. In the nonrandom study by Case et al., a combination of vincristine, BCNU, and cyclophosphamide intravenously with melphalan and prednisone given orally was employed. Patients receiving this combination did remarkably well compared with historical controls who received melphalan and prednisone. Although in most series about 25% of patients have failed to survive 12 mo after first treatment, only 5% of the patients reported by Case had succumbed in the first 15 mo, and a median survival of 50 mo is projected. Nonrandom investigations recently conducted by the Southwest Oncology Group have also shown survival advantages for alkylating-agent regimens that are supplemented by vincristine. The survival for the vincristine-containing alkylating-agent combinations was about 9 mo longer than those for patients on five previous combinations of alkylating agents and prednisone.

Further use of alkylating-agent combinations with and without the addition of cycle-active agents is indicated in myeloma. In these studies, analysis of response by patient risk group and tumor load may prove advantageous in the development of therapies particularly helpful to certain patient subsets.

REFERENCES

14. Breslow N: A generalized Kruskal-Wallis test for comparing K samples subject to unequal
IMPROVED SURVIVAL BY STAGING OF MYELOMA


APPENDIX

The following Principal Investigators or investigators represent institutions contributing cases to this study:

<table>
<thead>
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