Combination Chemotherapy With Intermittent 1-3-Bis(2-Chloroethyl)1-Nitrosourea (BCNU), Cyclophosphamide, and Prednisone for Multiple Myeloma

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In order to study the effectiveness of the drug combination BCNU, cyclophosphamide, and prednisone (BCP) in myeloma, the Southeastern Cancer Study Group entered 126 previously untreated and 33 previously treated patients in this study. Patients received cyclophosphamide, 400 mg/sq m, BCNU, 75 mg/sq m, and prednisone, 80 mg/sq m, for 7 days, every 4 wk, and were evaluated for response after 6 mo of therapy. Responding patients were continued on therapy and followed for evaluation of survival. Previously untreated patients were evaluated for good and poor
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risk status as well as clinical stage by calculation of tumor cell mass. These calculated values, as well as the individual components such as blood urea nitrogen (BUN), immunoglobulin (Ig) type, and hemoglobin (Hb), were evaluated for correlation with response and survival. The response rate was approximately 50% for all untreated patients regardless of cell mass or risk status. Toxicity was not excessive, and no case of acute leukemia was seen. Median survival for untreated patients was 27.8 mo; good risk patients, 44 mo; and poor risk, 12 mo. Though cell mass status did not correlate well with survival, individual factors of BUN, IgA, and IgG protein types had strong predictive value. Using these factors, a model for survival prediction was created that had high predictive value in this group of patients. The study indicates that this treatment regimen is effective and could be used as an alternative to standard chemotherapy or in sequential combinations. Since it does not contain melphalan, it might be attractive if melphalan-containing regimens prove to be particularly leukemogenic. The survival-predictive model may be useful in assessment of patient prognosis and will be further evaluated in subsequent group studies.

CHEMOTHERAPY of multiple myeloma with melphalan and prednisone or other combinations that build upon that now standard regimen have generally produced response rates of approximately 50% and overall median survivals of approximately 2 yr.1 3 This is clearly an improvement over the median survival of patients prior to such treatment,4 5 but there has been little further improvement in these statistics in recent years. Thus, studies to determine the effectiveness of other agents in combinations have been undertaken. Preliminary studies indicated that 1-3-bis(2-chloroethyl)-1-nitrosourea (BCNU) had antitumor activity in multiple myeloma6 7 and that the agent was active in mouse myeloma tumor models.6 Cyclophosphamide has also been shown to possess antmyeloma activity5 8 equal to that of melphalan in untreated patients9 10 and considerably less in those previously treated with alkylating agents.11

In 1970, the Southeastern Cancer Study Group initiated a study to test the effectiveness of combining BCNU and cyclophosphamide with prednisone, an agent that appears to act synergistically with cytotoxic drugs in multiple myeloma.4 Though at doses <60 mg/sq m every 3 wk administration can be achieved, a 28-day schedule was devised to take advantage of the time course of peak myelosuppression by BCNU (approximately day 21) and cyclophosphamide (approximately day 10) to allow maximum antitumor effect with minimal additive toxicity. Data were collected that would allow the division of patients into potentially useful prognostic groups, both according to the criteria of good and poor risk, as previously reported by the Southeastern Cancer Study Group12 and according to the calculated cell mass and “myeloma staging system” employed by Durie and Salmon.13 Though reported in preliminary form,14 15 this represents the first full report of the results of the initial treatment responses and survival data with this regimen. The prognostic usefulness of the individual prognostic factor analysis in this well categorized group of patients who had long-term follow-up is also presented.

MATERIALS AND METHODS

Patients with the diagnosis of multiple myeloma, established according to the criteria of the Chronic Leukemia-Myeloma Task Force guidelines,16 were entered into this study. All were required to have measurable serum or urine monoclonal protein and/or a measurable plasmacytoma. The study was initiated in 1970 and closed to accession in 1972. As shown in Table 1, a total of 126 previously untreated patients were entered with an 81.5% evaluable rate. The inevaluability of the 24 patients was
Table 1. Response to Treatment for All Patients

<table>
<thead>
<tr>
<th>Group</th>
<th>Entered and Completed</th>
<th>Evaluable</th>
<th>Responders</th>
<th>Total Responses</th>
<th>Non-responders</th>
<th>Died</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previously untreated</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A Good risk</td>
<td>59</td>
<td>49(83%)</td>
<td>4</td>
<td>18</td>
<td>5</td>
<td>27(55%)</td>
</tr>
<tr>
<td>B Poor risk</td>
<td>67</td>
<td>53(79%)</td>
<td>0</td>
<td>21</td>
<td>6</td>
<td>27(51%)</td>
</tr>
<tr>
<td>Previously treated</td>
<td>126</td>
<td>102(81%)</td>
<td>4</td>
<td>39</td>
<td>11</td>
<td>27(51%)</td>
</tr>
<tr>
<td>C Good risk*</td>
<td>19</td>
<td>17(89%)</td>
<td>0</td>
<td>4</td>
<td>3</td>
<td>7(41%)</td>
</tr>
<tr>
<td>D Regimen containing</td>
<td>14</td>
<td>12(86%)</td>
<td>0</td>
<td>4</td>
<td>1</td>
<td>5(42%)</td>
</tr>
<tr>
<td>cyclophosphamide</td>
<td>33</td>
<td>29(88%)</td>
<td>0</td>
<td>8</td>
<td>4</td>
<td>12(41%)</td>
</tr>
<tr>
<td>Total</td>
<td>159</td>
<td>131(82%)</td>
<td>4</td>
<td>47</td>
<td>15</td>
<td>66(50%)</td>
</tr>
</tbody>
</table>

Shown here are all patients entered into this study. The criteria for response are given in Materials and Methods, as are the criteria for placing patients in each risk group.

*No prior cyclophosphamide.

due to major protocol violations (6 patients) and inadequate trial (18 patients; 13 lost to follow-up or no data available before completion of 6-mo trial). In addition, 19 patients who were previously treated with melphalan and prednisone but still considered good risk though relapsing were entered. Of these 19 patients, 17 had had some response to their previous therapy and had been followed on treatment from 2 to 54 mo (median 14.5 months) prior to relapse. All patients had actively progressing disease at entry into this study, and treatment was started from 1 to 3 mo following cessation of previous therapy (14 patients at 1 mo). Finally, 14 patients who had previously been treated with regimens containing cyclophosphamide were entered. Of these patients, all but 2 had had a previous response to therapy (including cyclophosphamide alone, cyclophosphamide and melphalan, or cyclophosphamide and irradiation). They had been treated from 1 to 84 mo (median 11.5), and all were in active relapse at the time of entry on study, predominantly 1–2 mo from the diagnosis of relapse. Initial studies included hemoglobin, hematocrit, white blood count, differential, bone marrow aspirate and biopsy if necessary, BUN, creatinine, uric acid, serum calcium, immunoelectrophoresis for determination of class of monoclonal component, 24-hr urine protein (when present), and skeletal x-rays. Blood and serum studies were repeated monthly, including total protein and serum electrophoresis. After 6 mo, all studies were repeated for evaluation of initial response. All responding patients were continued on the same regimens (BCP) until relapse or death. Nonresponders were not treated in any specified manner, and only survival data were collected. Subsequently, studies were repeated, at least every 6 mo, during the maintenance period for responding patients. At the beginning of the study, patients were divided into good- and poor-risk groups according to previously described Southeastern Cancer Study Group (SECSG) criteria. Good-risk patients had a hemoglobin equal to or greater than 9.0 g/dl, a BUN less than 30 mg/dl, a serum calcium less than 12 mg/dl, and a performance status equal to or greater than 60%; poor-risk patients failed to meet those criteria.

Retrospectively, the initial clinical and laboratory data were utilized to categorize the patients according to the Myeloma Staging System into stage I, II, or III corresponding to low, intermediate, and high tumor cell mass. These criteria involve the use of hemoglobin level, serum calcium level, presence or absence of bone lesions, and quantitation of the abnormal protein components. Subclassification on the basis of renal function (A, normal; B, abnormal, ≥ 30 mg/dl) was also assessed. In addition, to test the prognostic value of the individual components of the good–poor risk and staging systems as well as other factors, in the untreated group of patients, the relationship between individual factors as independent variables and duration of survival was assessed for the following: myeloma protein type (lgGα, lgGλ, lgAα, lgAλ, Bence-Jones protein), age, sex, race, hemoglobin, serum calcium, bone involvement, BUN, good or poor risk, and cell mass.

In the following presentation, all proportions were compared by use of the chi-square statistic or Fishers exact test, where appropriate. Survival curves were plotted using the Kaplan Meier technique, and p values were derived by the generalized Wilcoxon procedure. The nonlinear regression model for survival was derived using the technique of Cox. With regard to the latter technique, the exact values of the following variables were loaded into the model: hemoglobin, serum calcium, BUN, age, and performance status. Stage was categorized as 1, 2, or 3. The variables coded as 0 (not present) and 1
(present) were IgGx, IgAλ, IgAκ, IgAλ, Bence Jones only, and bone lesions. Thus, none of the laboratory values were categorized.

**Treatment Regimen**

Each course of treatment consisted of: (A) cyclophosphamide, 400 mg/sq m i.v. push, (B) BCNU, 75 mg/sq m i.v. over a 10-30-min period, and (C) prednisone, 80 mg/day for 7 days, discontinuing by a rapid taper over the next 3 days. Courses were repeated every 4 wk. Treatment could be deferred for 1 or 2 wk if toxicity was excessive. Initially, the protocol included the potential for escalating the doses on the second course by 30% for BCNU and 50% for cyclophosphamide. Because sufficient cytopenia was obtained with the initial dosage regimens, escalation was generally not possible. An evaluation of response was made at 6 mo, following the guidelines of the Chronic Leukemia-Myeloma Task Force and previous SECSG criteria: "Excellent" response signifies disappearance of all manifestations of disease; "good" response is greater than 50% improvement in all abnormal parameters (abnormal serum protein, urine protein, marrow plasmacytosis, hemoglobin, tissue plasmacytomas, performance status, bone pain), and a "fair" response is greater than 25% improvement in all parameters. A "questionable" response was noted as improvement in some but not all parameters of disease. Nonresponders were those patients rated as "no change," "worse," or "dead" at the end of the initial phase of the study. Relapse was established when abnormal parameters reappeared or increased. Survival statistics represent all deaths, regardless of cause, including those who succumbed during the early weeks of their therapy.

**RESULTS**

**Initial Response**

Table 1 shows the initial response (at 6 mo) of the untreated patients. It can be seen that the overall response (fair or better) for the patient group was 54/102 evaluable patients or 53%, with equal response rates of 27/49 (55%) and 27/53 (51%) for good- and poor-risk patients, respectively. It should be noted, however, that among the nonresponding patients in the poor-risk group, the majority died during induction, while most nonresponding patients in the good-risk group were still living at the end of the 6 mo. Among the smaller, separate group of patients who had previously been treated and relapsed from alkylating agent therapy but qualified as good-risk patients, there were 7 of 17 (41%) fair or better responses. Even among 12 patients who had progressive disease on regimens containing cyclophosphamide, 5 (42%) had a fair or better response.

Adequate data for calculation of cell mass were available for 99 of 102 of the previously untreated patients. Calculations were made using the clinical criteria to determine a low, intermediate, or high cell mass corresponding to stage I, II, or III of the Clinical Myeloma Staging System. Table 2 shows the distribution of the categories among the SEG good- and poor-risk groups, indicating that the majority of patients were in the low cell mass category.

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**Table 2. Good- and Poor-Risk Patients Within Cell Mass Category**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Cell Mass</th>
<th>Good Risk</th>
<th></th>
<th>Poor Risk</th>
<th></th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>n (%)</td>
<td></td>
<td>n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>Low</td>
<td>21 (75%)</td>
<td></td>
<td>7 (25%)</td>
<td></td>
<td>28</td>
</tr>
<tr>
<td>II</td>
<td>Intermediate</td>
<td>16 (76%)</td>
<td></td>
<td>5 (24%)</td>
<td></td>
<td>21</td>
</tr>
<tr>
<td>III</td>
<td>High</td>
<td>8 (16%)</td>
<td></td>
<td>42 (84%)</td>
<td></td>
<td>50</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>45</td>
<td></td>
<td>54</td>
<td></td>
<td>99</td>
</tr>
</tbody>
</table>

Shown here are the 99 previously untreated patients for whom sufficient data were available to calculate stage.

The criteria for designating patients as poor or good risk, and for calculation of clinical stage (cell mass), are given in Materials and Methods.
Table 3. Response Rates of Good- and Poor-Risk Patients Within Cell Mass Category

<table>
<thead>
<tr>
<th>Stage</th>
<th>Cell Mass</th>
<th>Good Risk (% Responding)</th>
<th>Poor Risk (% Responding)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>I</td>
<td>Low</td>
<td>13/21 (62)</td>
<td>5/7 (71)</td>
<td>18/28 (64)</td>
</tr>
<tr>
<td>II</td>
<td>Intermediate</td>
<td>8/16 (50)</td>
<td>3/5 (60)</td>
<td>11/21 (52)</td>
</tr>
<tr>
<td>III</td>
<td>High</td>
<td>4/8 (50)</td>
<td>20/42 (47)</td>
<td>24/50 (48)</td>
</tr>
</tbody>
</table>

Shown here are the 99 previously untreated patients for whom sufficient data were available to calculate stage. For each category, the number of responding patients/number of evaluable patients in that category is shown. Response includes patients considered fair, good, or excellent, as defined in Materials and Methods, at the 6-mo evaluation.

Of the good-risk patients were of low or intermediate cell mass, while most poor-risk patients were in the high cell mass group. However, there were poor-risk patients in the low cell mass and good-risk patients in the high cell mass categories. Table 3 shows the response rate for patients in the three cell mass categories compared with their risk status. There is a slight, but not statistically significant, trend toward better responses among the lower cell mass patients, especially in the poor-risk group, although the number of patients in these individual groups is small. Thus, none of the criteria, including BUN, predict very well for extent of initial response. A total of 10 patients in this group (7.6%) had plasmacytomas, but they also had other features of myeloma, not solitary plasmacytomas. There was no significant difference in response of these patients from the overall group.

Following the initial 6-mo evaluation, though patients were continued on BCP therapy, the protocol called only for survival evaluation, so no specific reassessment of level of response was made. Retrospective analysis permitted only a general assessment. There were no improvements from good to excellent, and patients tended to remain in the good and fair categories, though stable in each situation, until relapse.

Survival

Previously Untreated

The median survival for the entire group of untreated patients is 27.8 mo (see Fig. 1). Figure 1 demonstrates that increased survival is dependent on response to
treatment, since patients with fair or better responses had a median survival of 44 mo, while those with no change or disease progression had a median survival of 12 mo. It should be noted that all patients are included in the analysis, regardless of “early” death soon after entry into protocol. There were a significant number of deaths in the early months of the study, reflecting a group of rather sick patients, often from large city hospitals, having rather severe renal failure or infections. Patients having a fair response appear to be true responders, since an increase in survival was associated with this type of response. Thus, the median survival for nonresponding patients (no change or worse) (Fig. 1) is 12 mo. This is increased to 19 mo by the addition of the patients who achieved a fair response. Questionable improvements—improvement in a single parameter (hemoglobin, performance status, plasmacytosis)—were included in the nonresponse category. Their poor survival indicates the lack of significance of such isolated changes.

Duration of survival was dependent on both good- and poor-risk status as well as the clinical stage to some extent. Figure 2 shows the survival of the good- and poor-risk groups, with a median of 42 mo for the former and 21 mo for the latter. The largest number of early deaths occurred within the poor-risk group, and the longer survivals occurred among the good-risk patients. However, even among the poor-risk group, there are some long-term survivors. Survival according to stage is shown in Fig. 3. The overall median survival for stage I patients is 27 mo and stage
III 20 mo (Fig. 3). However, these curves are not significantly different ($p = 0.131$) at the 0.05 level, and for this group of patients, the good/poor risk criteria appear to be a better overall predictor of survival than the cell mass.

Among the low cell mass patients (stage I), both good- and poor-risk patients seem to have a good survival, though there were few poor-risk patients in this group (i.e., good risk: 21 patients, median survival 36 mo; poor risk: 7 patients, median survival 32 mo). Among stage III patients (high cell mass) (Fig. 4), however, the median survival of the poor-risk patients was 16.5 mo, while there was a small group of good-risk patients who, despite having a high body burden of tumor, had a better prognosis, i.e., 32-mo median survival in 8 patients. In assessing the role of BUN in this survival differential, the stage I and stage III patients with relatively normal renal function—BUN $<30$ (A) and those with BUN $>30$ (B)—were evaluated. There were too few stage IB to make any valid comparisons, but as shown in Fig. 5, stage 3B patients clearly had poorer survival than stage 3A. On the other hand, patients with normal renal function (3A and 1A) had equivalent survival despite considerably different tumor loads, again suggesting the overriding importance of this variable.

Because these results indicate that both risk and cell mass could contribute different survival information, analysis of the individual factors utilized in the
Table 4. BUN and Immunoglobulin Type Within Cell Mass Category

<table>
<thead>
<tr>
<th>BUN &lt; 24</th>
<th>No. of Patients</th>
<th>Percent of Patients</th>
<th>BUN &gt; 24</th>
<th>No. of Patients</th>
<th>Percent of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgGx</td>
<td>20</td>
<td>69</td>
<td>Non-IgGx</td>
<td>9</td>
<td>31</td>
</tr>
<tr>
<td>Non-IgGx</td>
<td>9</td>
<td>31</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The number and percentage of patients with BUN > 24 and < 24 and immunoglobulin types of IgGx or others are shown for the low and high cell mass group. The total group includes 41 IgGx, 21 IgGk, 15 IgAx, 6 IgAl, and 7 Bence Jones only.

Construction of the good- and poor-risk and cell mass categories was performed by a step-wise procedure using the Cox regression model. In this analysis, BUN (<24 favorable, \( p < 0.001 \)) and performance status (≥70% favorable, \( p = 0.001 \)) had the strongest correlations, and only IgAα (unfavorable, \( p < 0.007 \)) and IgGx (favorable, \( p = 0.037 \)) added to the model. Surprisingly, neither risk nor cell mass, as previously defined, entered the survival model as significant variables. Though there was a greater percentage of patients with BUN >24 and non-IgGx protein in the high cell mass than low cell mass group (Table 4), this was apparently not sufficient to create a statistically significant difference in median survival between stage III and I, though the trend was certainly in that direction (Fig. 3). The survival curves of patients with these protein types are shown in Fig. 6. The survival of patients with IgGx myeloma is significantly superior to that of those with other types combined (\( p = 0.013 \)). IgGx patients had longer survival than IgGk (\( p = 0.027 \)) as well, with no significant difference in Bence Jones protein excretors between the two groups. There are too few patients with IgAα (6) for valid statistical comparison, though this group had the shortest median survival of all (6 mo). This trend for IgGx patients to survive longer is consistent within all mass categories (plots not shown) and independent of other variables. With respect to BUN, the median survival of patients with BUN <24 was 30 mo, while that of patients with BUN >24 was 13 mo (\( p = 0.031 \)).

Utilizing the major individual factors predictive of survival and the Cox
Table 5. The Fit of the Probability Model

<table>
<thead>
<tr>
<th>Months</th>
<th>Predicted survival</th>
<th>Observed survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>.919</td>
<td>.895</td>
</tr>
<tr>
<td>20</td>
<td>.630</td>
<td>.605</td>
</tr>
<tr>
<td>30</td>
<td>.476</td>
<td>.457</td>
</tr>
<tr>
<td>40</td>
<td>.382</td>
<td>.376</td>
</tr>
<tr>
<td>50</td>
<td>.278</td>
<td>.294</td>
</tr>
<tr>
<td>60</td>
<td>.255</td>
<td>.276</td>
</tr>
<tr>
<td>70</td>
<td>.255</td>
<td>.276</td>
</tr>
<tr>
<td>77</td>
<td>.255</td>
<td>.276</td>
</tr>
</tbody>
</table>

The probability model, derived as described in Materials and Methods, was used to calculate the probability of survival of these patients to each time point shown. This is compared to the actual fraction of these patients surviving to those same times.

Regression model, a model for survival prediction based on this group of patients was created as follows:

$$\frac{\lambda(t)}{\lambda_0(t)} = \exp \left[ 0.02909(\text{BUN} - 24.0) + 1.223(\text{IgA} - 0.057) - 0.66127(\text{IgG} - 0.443) \right]$$

where $\lambda(t)$ is the hazard rate for survival at time $t$ and $\lambda_0(t)$ is the hazard computed at the average values of the factors in the model.

The ability of this model to predict survival compared to actual observed survival in this group of patients is shown in Table 5. It can be seen that the fit is quite good at each time point, with a maximum discrepancy of 0.025 occurring at 20 mo. In initially loading the preliminary regression equations, performance status had a positive correlation with survival (performance status $\geq 70$ favorable, $0.3819$, $p < 0.001$), but had a negative correlation with BUN, i.e., $-0.27645$ ($p = 0.011$). However, when the predicted survival curve using the model containing performance status was plotted against observed survival there was a discrepancy of 0.07 over most of the time axis, compared with the maximum of 0.025 noted above utilizing BUN. Thus, we have proposed the equation using BUN for our final model, since it is more predictive of survival and BUN is not crosseliminated by performance status, which may be a more subjective measurement. The survival data for the previously treated patients (plot not shown) were calculated from the time BCP therapy was begun. Survivals are shorter (median, 25 mo) than for the previously untreated good-risk group, but a few did achieve a prolonged response. This represents a highly select group of patients, however, since they were still “good” risk at the time they failed previous therapy.

Toxicity

The most frequent toxicities noted were hematologic and gastrointestinal. Of the total 131 patients entered into the study, 16 (12%) had a decrease in hemoglobin; 52 (40%) became granulocytopenic, and 47 (36%) thrombocytopenic. Only two episodes of severe or life-threatening granulocytopenia and four of thrombocytopenia were noted (all among poor-risk patients). The remainder were mild or moderate cytopenia. There were four patients in whom drug toxicity (three thrombocytopenia, one granulocytopenia) was felt to contribute to their death. In four additional patients, therapy was stopped because of drug toxicity. Retrospective evaluation of total doses delivered revealed that in most other cases doses did not need to be reduced but that some delays in treatment were necessitated, so that
approximately 30% of individuals had not received full planned dose at 6 mo. Therapy was continued to full dose, however. Forty patients experienced moderate to severe nausea and vomiting attributable to the chemotherapy regimen. Possible central nervous system effects were noted in three patients: a psychotic episode in one, a grand mal seizure in a second, and a stroke in the third. All of these patients had preexisting conditions that could have been related to those events. Five patients, all with previous histories of cardiac disease, had congestive failure or acute myocardial infarction during treatment. It is not possible to assess the role of BCP in those events. There were no episodes of pulmonary toxicity observed in this patient group. In the previously untreated group, 8 patients are still living (5+ yr) with no evidence of acute leukemia; in all but 6 of the remaining patients, followed to death, the cause of death was known and included primary disease, disease-related causes (renal failure, infection), and disease unrelated (myocardial infarction), but no evidence of acute leukemia by peripheral blood, bone marrow, or autopsy examination.

DISCUSSION

Prior to the introduction of alkylating agent therapy and new antibiotics, the median survival for patients with multiple myeloma was in the range of 6–11 mo. Since a publication by Alexanian and the Southwest Oncology Group (SWOG) of the comparative study of daily melphalan versus intermittent melphalan with prednisone, the latter has become the most widely used regimen. This and other similar regimens all achieve approximately similar response rates of 50% and median survivals of approximately 2 yr from diagnosis, when all patients are included in the analysis. In the years since those studies, more has been learned about the biology and staging of the extent of disease and attempts have been made to find better initial treatment, since most patients continue to die of the disease or its complications. In addition, reports of the development of acute leukemia among long-term survivors whose myeloma was treated by an alkylating agent have spurred efforts to find alternative chemotherapy regimens.

At the time this study was initiated in 1970, the intermittent melphalan and prednisone regimen or other daily melphalan regimens were standard “first line” therapy. Cyclophosphamide was an alternative choice and was used by some to successfully treat some refractory and relapsing patients. BCNU had been shown to have activity in myeloma as a single agent in preliminary studies but had not yet been studied in combination. Since the study reported here was completed and preliminary reports published, a variety of chemotherapy combinations have been studied by other groups. The Southwest Oncology Group (SWOG), in particular, studied a variety of combinations, including melphalan-cyclophosphamide plus prednisone; melphalan-adriamycin plus prednisone; melphalan-vincristine-procarbazine plus prednisone; melphalan-cyclophosphamide-BCNU-prednisone; vincristine-cyclophosphamide-adriamycin plus prednisone; vincristine-melphalan-cyclophosphamide plus prednisone; cyclophosphamide-adriamycin plus prednisone, and others. In all of these studies, response rates and survival have differed little from that of the standard intermittent melphalan plus prednisone.
regimen as an historical control. There is a possibility that the addition of vincristine to some of the regimens may have resulted in a very slight survival advantage.

The combination reported here, BCNU, cyclophosphamide and prednisone (BCP), achieved a response rate of 50%–55%, which is about the same as recorded for other programs. In order to be classified as a response, our patients had to maintain improvement to at least the 6-mo evaluation time, so that transient responses of 1–2 mo, which might be counted by other investigators but not included here, could have increased the response rate slightly. A median survival for the entire group of patients of 28 mo is also equivalent to that reported for other regimens. The combination is clearly effective treatment, however, as shown by the increased survival in responding patients.

Of more interest are the results of our analysis and prognostic factors. This verified that poor-risk patients (on the basis of SECSG criteria) do much more poorly than good-risk patients with respect to survival, though their chance for a response is approximately the same. This may relate in part to a larger body burden of tumor so that a proportional tumor cell kill may be achieved with equal facility in each group, but the residual tumor is greater in the poor-risk group. In addition, however, this group has a large proportion of early deaths within the first 6 mo, apparently related mainly to a larger proportion of patients with renal failure, previously defined as the single most important negative prognostic factor.25,26 Many SECSG institutions draw patients from county, city, or Veterans Administration Medical Centers, where they often present for medical care late in the course of their disease and with renal failure already extant. Such a group of patients can seriously affect overall survival statistics for the total population under study. Thus, when assessing comparability of data, the number of patients with such poor-risk criteria must be taken into account along with those who have advanced disease as determined by tumor cell mass. Our data suggest that the individual factors—BUN, IgGx and IgAA protein type, and performance status—are the major predictors of survival and that a patient may be evaluated in this regard by the model derived from the Cox regression formula, as we have proposed, independent of other staging or risk criteria. This postulate will be tested in subsequent SECSG studies where the model will be applied to different groups of patients.

It is of interest that no instances of acute leukemia have been reported among this group of patients. It is difficult to say whether this represents a significant trend, since data from SWOG27 suggest that approximately 2% of patients on melphalan-containing regimens have developed acute leukemia. Thus, in our group of patients, the maximum expected number would have been up to 2 patients, and the study may have too few patients to detect a meaningful incidence. It is important, however, that this phenomenon be watched carefully in subsequent studies of patients on regimens not containing melphalan (such as this one) to determine whether the incidence of acute leukemia does in fact differ.

The only combination drug regimen that has been reported to achieve greater response and survival rates than those mentioned above is the “M2 protocol” from Sloan-Kettering Memorial Hospital,28,29 which includes melphalan-prednisone-cyclophosphamide-vincristine and BCNU. A response rate of up to 80% (though
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requiring maintenance of improvement for only 2 mo) with improved survival was reported. Analysis of the survival of the patients in that study shows a striking lack of early deaths during the entire first year, suggesting the possibility that there were few poor-risk patients. Though those patients were predominantly stage III, they had a mean BUN of 21, a serum creatinine of 1.1 among the previously untreated patients, and an 80% performance status supporting this contention. Thus, through some inadvertent selection factor(s), a larger proportion of good-risk patients, who might be expected to demonstrate a longer survival, may be included in that study. In fact, the survival curve reported in the “M2” study29 is similar to those demonstrated here, both for responding patients and the good-risk patient group.

We conclude, therefore, that the combination of BCNU-cyclophosphamide plus prednisone used in this study provides an effective alternative to programs containing melphalan for the treatment of myeloma and could be useful should an increased incidence of acute leukemia, as a result of melphalan therapy, become a significant factor for those patients who survive long enough. In addition, BCP provides a therapy that could be used in a plan of alternating sequences of drug combinations or as a subsequent program for patients relapsing from other drug treatment. In support of this, our current study shows that 40% of patients relapsing from melphalan-prednisone therapy respond to BCP. In addition, almost the same proportion of patients failing regimens containing cyclophosphamide, but not BCNU, respond to BCP, suggesting some specificity for different agents in myeloma, as has been suggested by Bergsagel.6 On the other hand, in the crossover portion of a more recent SECSG study, only 13% of the patients who failed initially with melphalan plus prednisone responded subsequently to BCP.30 This underscores again that patients who fail to achieve an initial response have a worse prognosis for subsequent response than those achieving response initially and then relapsing. These groups of patients must be considered separately in the evaluation of secondary treatment regimens. The studies to evaluate BCP in comparison directly with melphalan plus prednisone and its role in alternating therapy regimen are still under evaluation or in progress. However, it is clear that new approaches are still needed for both induction and maintenance regimens in order to increase response rates and survival in patients with multiple myeloma. The data presented here also indicate that analysis of such programs should consider the effect of BUN and myeloma protein type as the major variables having a significant impact on survival.

REFERENCES

Combination chemotherapy with intermittent 1-3-bis(2-chloroethyl)1-nitrosourea (BCNU), cyclophosphamide, and prednisone for multiple myeloma

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