Combination Chemotherapy for Terminal-Phase Chronic Granulocytic Leukemia: Cancer and Leukemia Group B Studies


A 34% response was obtained in 202 evaluable patients in the terminal phase of chronic granulocytic leukemia using combinations of hydroxyurea, 6-mercaptopurine, and corticosteroids. Twelve percent of responses were complete and 22% partial. Overall median survival was 12 wk. A 30 wk median survival for responding patients was statistically superior to the 7-wk survival for nonresponders (p < 0.001). Response was inversely correlated with toxicity. No responses were obtained in patients sustaining both severe infectious and bleeding complications. No benefit could be demonstrated from the addition of vincristine in induction and daunorubicin for consolidation. Although the response frequency and duration of survival with this combination chemotherapy were generally superior to those previously reported by our group, the terminal phase of chronic granulocytic leukemia still remains a formidable and generally refractory disease.

SURVIVAL in chronic granulocytic leukemia (CGL) has not changed appreciably since the original description of its treatment by Minot more than 50 yr ago. The disease, belying the term chronic, has a median survival of approximately 3 yr, irrespective of the therapy employed. The disease terminates in an aggressive fashion, characterized by an accelerated or, frequently, a blast phase. Regardless of the term used, this aggressive, terminal, accelerated, and/or blastic phase is generally resistant to therapy and probably represents the most refractory leukemia. Death usually occurs within 2–3 mo.

For the past 13 yr, the Cancer and Leukemia Group B (CALGB) has been conducting chemotherapy studies of the terminal phase of CGL as a distinct and separate entity from acute myeloid leukemia. Results have generally been disappointing. Tanzer and associates, however, reported to the CALGB encouraging pilot results using daunorubicin and a combination of hydroxyurea (HU), 6-mercaptopurine (6-MP), and corticosteroids. In addition, Canellos and others have obtained a frequency response of approximately 30% using a combination of vincristine (VCR) and prednisone (PRED).

This article reports the results of 2 CALGB trials in 202 evaluable patients with terminal-phase CGL. The initial trial tested the efficacy and toxicity of a combination of HU, 6-MP, and corticosteroid. Since toxicity was minimal, a second trial was undertaken consisting of doubled starting doses of chemotherapy and a randomized evaluation of the efficacy of VCR in induction and daunorubicin (DNR) for consolidation.

MATERIALS AND METHODS

Patient Selection

Patients from participating institutions were admitted to study of the terminal phase on the basis of criteria described by Karanas and Silver, which have been adopted by the CALGB. These criteria are illustrated in Table 1 and have been shown repeatedly to predict a median survival of 2–3 mo. Almost every patient was placed on treatment within 1 wk of diagnosis of the terminal phase. All patients had a previously determined diagnosis of CGL on the basis of established histologic, biochemical and usually chromosome findings.

Treatment Programs

Study I (7131)

In the initial phase-I study, the following regimen was used:

**Induction:** hydroxyurea (HU) 15 mg/kg daily, orally; 6-mercaptopurine (6-MP) 1.5 mg/kg daily, orally; dexamethasone (DXM) 0.05 mg/kg daily, orally.

Doses of hydroxyurea and 6-MP were doubled every 2 wk if patients did not respond, which was defined as a stationary or rising leukocyte count and/or peripheral blood or marrow blast count. Drugs were continued so as to produce marrow hypoplasia. If no response occurred by day 56 or if progressive disease supervened, the patient was removed from study. Responding patients were placed on a maintenance regimen as follows:

**Maintenance:** hydroxyurea (HU) 7 mg/kg daily, orally, usually rounded to 500 mg; 6-mercaptopurine (6-MP) 0.7 mg/kg daily, orally, usually rounded to 50 mg; dexamethasone (DXM) 0.025 mg/kg daily, orally.

Doses of HU and 6-MP were adjusted every 2 wk during maintenance for changes in the peripheral leukocyte and platelet counts. The adjustments are shown in Table 2. Steroids were discontinued for uncontrolled diabetes, hypertension, psychosis, or gastrointestinal bleeding.

Study II (7331)

Patients were randomly assigned to one of two treatment regimens by the sealed envelope technique. Random assignment was determined by a latin square arrangement, such that treatment...
Table 1. Requirements for Admission to the Study

<table>
<thead>
<tr>
<th>Requirement</th>
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<tbody>
<tr>
<td>(1) Peripheral blood blasts and promyelocytes 30% at any time, or</td>
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<tr>
<td>(2) Either (A) or (B)—whichever came first—plus one of the conditions listed under (3)</td>
</tr>
<tr>
<td>(A) Completion of 2 courses of &quot;conventional&quot; treatment</td>
</tr>
<tr>
<td>(B) Survival of at least 12 mo after diagnosis</td>
</tr>
<tr>
<td>(3) At least one of the following conditions in the absence of hemorrhage or toxicity:</td>
</tr>
<tr>
<td>(A) Peripheral blood blasts and promyelocytes 20%</td>
</tr>
<tr>
<td>(B) Hemoglobin value 9.0 g/100 ml</td>
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<tr>
<td>(C) Platelet count decreased from above 100,000/cu mm to below 100,000/cu mm during a conventional course of treatment</td>
</tr>
<tr>
<td>(D) An increase of the WBC after a conventional course of treatment to either 50,000 cells/cu mm or more than twice the count at the start of the course of treatment</td>
</tr>
<tr>
<td>(4) No chemotherapy for 2 wk preceding experimental therapy</td>
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<td>(5) No exposure to drugs used within 3 wk prior to study</td>
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</table>

assignments were balanced within and across institutions. These two regimens are displayed in Fig. 1 and are as follows:

Induction: Regimen A—hydroxyurea (HU) 30 mg/kg daily, orally; 6-mercaptopurine (6-MP) 3 mg/kg daily, orally; prednisone (PRED) 0.75 mg/kg daily, orally. Regimen B—induction as in regimen A plus VCR 2.0 mg weekly, intravenously for 4 doses. VCR was decreased by 50% or omitted for moderately severe neurotoxicity, consisting of paresthesia and muscle weakness interfering with normal function.

Table 2. Downward Modification of Drug Dose—Maintenance Phase

For Patients on Maintenance Therapy, the Dose of Hydroxyurea and 6-MP was Modified as Follows:

<table>
<thead>
<tr>
<th>Leukocyte Count</th>
<th>Platelets</th>
<th>Drug Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>5,000 or more</td>
<td>150,000 or more</td>
<td>Full dose</td>
</tr>
<tr>
<td>3,000-5,000</td>
<td>100,000-150,000</td>
<td>50% dose*</td>
</tr>
<tr>
<td>2,000-3,000</td>
<td>75,000-100,000</td>
<td>25% dose*</td>
</tr>
<tr>
<td>2,000 or less</td>
<td>75,000 or less</td>
<td>No drug</td>
</tr>
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*For fractions of available drug dosage, medication used on alternate days.

Regimens were also randomized as to whether or not to receive DNR consolidation 60 mg/sq m intravenously for 2 daily doses before maintenance. The randomization scheme was again based on a Latin square arrangement in an attempt to achieve balance of treatment assignment with respect to induction therapy and submitting institutions.

Maintenance: The maintenance regimens were as follows. Regimen A—patients initially randomized to regimen A were placed on the following maintenance: hydroxyurea (HU) 7 mg/kg daily, orally, usually rounded to 500 mg; 6-mercaptopurine (6-MP) 0.7 mg/kg daily, orally, usually rounded to 50 mg; prednisone (PRED) 0.25 mg/kg daily, orally. Regimen B—maintenance as in regimen A plus VCR 2.0 mg intravenously once monthly.

Doses of HU and 6-MP were adjusted every 2 wk for changes in the leukocyte and platelet counts.

The dose of 6-MP in all regimens, both in induction and maintenance, was reduced by two-thirds if concomitant allopurinol was used.

Patient Characteristics

Study I (7131)

Eighty-three patients were admitted to study of whom 78 were evaluable. Five were disqualified for ineligibility (3), major protocol violation (1), or inadequate data (1). Table 3 shows the characteristics of the patients at presentation for treatment with respect to sex and the median and mean for age, white blood count, platelet count, percentage of marrow blasts and promyelocytes, and the onset of the terminal phase from the original diagnosis of CGL. The median and mean percentage of combined blasts and promyelocytes in the marrow were 48% and 50%, respectively.

Study II (7331)

One-hundred-forty patients were entered into study; of these, 70 were randomly allocated to regimen A without vincristine, and 70 to regimen B containing vincristine. Ten patients were disqualified from study in regimen A and six from regimen B. Of these 16 patients, 5 were disqualified for ineligibility, 7 for major protocol violations, 2 for inadequate data, and 2 declined further protocol study. Patients were essentially comparable in each regimen with respect to pretreatment characteristics.
Table 3. Characteristics of Patients at Presentation for Treatment

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimen A</th>
<th>Regimen B</th>
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<tbody>
<tr>
<td>I (7131)</td>
<td>Number entered 83</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td>Number evaluable 78</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>Percent male 58</td>
<td>78</td>
</tr>
<tr>
<td></td>
<td>Age (yr)</td>
<td>Median 43</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean 46</td>
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<tr>
<td></td>
<td>WBC × 1000/cu mm</td>
<td>Median 45</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean 82</td>
</tr>
<tr>
<td></td>
<td>PLT × 1000/cu mm</td>
<td>Median 50</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean 106</td>
</tr>
<tr>
<td></td>
<td>Percent blasts + promyelocytes in marrow</td>
<td>Median 48</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean 50</td>
</tr>
<tr>
<td></td>
<td>Initial diagnosis to terminal phase (mo)</td>
<td>Median 28.5</td>
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<td></td>
<td></td>
<td>Mean 34.0</td>
</tr>
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</table>

The patient population in study I was essentially comparable to the overall patient population in study II. There were no statistically significant differences.

Criteria for Response

Complete response (CR) consisted of complete clearing of blast cells from the peripheral blood and return of peripheral blood counts and marrow cellularity to normal with less than 5% of the marrow cells being myeloblasts.

Partial response (PR) constituted a return of peripheral blood and marrow to a chronic state of CGL. Peripheral blood and marrow blasts and promyelocytes could not exceed 20%.

Improvement (IMP) consisted of improvement in performance status, organomegaly, peripheral blood, and bone marrow but not to the objective degree observed in complete and partial response. For purposes of analysis, improvement did not constitute a response.

Patients who did not meet the criteria of these three categories were considered nonresponders (NR).

Statistical Methods

Differences in pretreatment characteristics and response frequencies were evaluated using the contingency corrected \( \chi^2 \) test for differences in percentages\(^\text{11} \) and the Kruskal-Wallis test for differences in quantitative variables.\(^\text{12} \) Differences in survival were evaluated by the Breslow's modification of the Kruskal-Wallis test.\(^\text{13} \) and the survival curves were plotted by the life-table method.\(^\text{14} \)

RESULTS

Treatment Effect

Study I

Response frequency. The response frequency is shown in Table 4. Of the 78 patients evaluable, 11 had a complete remission, 19 a partial remission, 14 patients improved, and 34 either died or did not respond during induction therapy. In summary, of the 78 patients, 30 patients (38%) were responders for they had either a complete (14%) or partial (24%) remission.

Survival. The survival for the patients is shown in Fig 2. Median survival for this group of patients was 13.8 wk. As demonstrated in Fig. 3, responding patients lived longer than nonresponders, for the median survival for the former was 30 wk contrasted to a median survival of 6.5 wk for the latter. The differences is highly significant at \( p < 0.001. \)

Study II

Response frequency. Of the 124 evaluable patients entered into study, 15 achieved a complete

![Graph showing survival rates]

(\( PR + CR \) response frequency A versus B: \( p = 0.26. \)
remission, 23 a partial remission, 16 improved, and 70 showed no response. Overall, responders comprised 31% of patients, a response rate slightly less than that of 38% seen in Study I. As shown in Table 4, there was no statistically significant difference between either regimen A or B with respect to partial or complete remission frequency (25% for regimen A and 36% for regimen B with $p = 0.26$).

**Survival.** The survival for patients is depicted in Fig. 2. The median survival for patients was 10.8 wk, slightly less but similar to that achieved in study I. Median survival in both regimen A and B was identical. Again, responders fared better than nonresponders. As illustrated in Fig. 4, the median survival for responding patients was 30.8 wk and for nonresponders 7.2 wk ($p < 0.001$).

**Daunorubicin (DNR) consolidation.** No prolongation of response duration or survival could be demonstrated in 13 patients receiving DNR consolidation as compared with the 23 patients who did not receive consolidation.

**Treatment Toxicity**

The toxicity observed in both studies during induction phase is depicted in Table 5. Only adequately reported toxicity data were used in the evaluation.

**Infectious Complications**

Severe or life-threatening infections were considerably higher in both regimens of study II compared to study I. In study II no significant difference could be detected in the frequency of either mild or severe infections between regimen A and B. The frequency of

<table>
<thead>
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<th>Table 5. Toxicity</th>
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<tr>
<td><strong>Graded infectious complications</strong></td>
</tr>
<tr>
<td>I</td>
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<tr>
<td>I</td>
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<tr>
<td>II</td>
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<tr>
<td>II</td>
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<tr>
<td><strong>Graded gastrointestinal complications</strong></td>
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<tr>
<td>I</td>
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<tr>
<td>I</td>
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<tr>
<td>II</td>
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<tr>
<td>II</td>
</tr>
<tr>
<td><strong>Graded bleeding complications</strong></td>
</tr>
<tr>
<td>II</td>
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<tr>
<td>II</td>
</tr>
<tr>
<td><strong>Graded steroid-related toxicities</strong></td>
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<tr>
<td>II</td>
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<tr>
<td>II</td>
</tr>
<tr>
<td><strong>Graded neurotoxicity</strong></td>
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<td>II</td>
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severe or life-threatening infections in both regimens of study II combined was observed in 47% of patients and was statistically higher than the 7% observed in study I ($p < 0.001$).

**Gastrointestinal Complications**

Gastrointestinal complications, primarily nausea and vomiting, were also greater in study II compared to study I. The frequency of severe or life-threatening complications in study II was statistically greater than in study I ($p < 0.01$). In study II, there was no significant additive gastrointestinal intolerance accompanying the use of vincristine in regimen B.

**Bleeding Complications**

Severe hemorrhagic complications occurred in approximately one-quarter of the patients treated in study II, even with the availability of platelet supplementation.

**Other Complications**

Only occasional severe endocrine or neurologic toxicity was encountered.

**Interrelation of Response and Induction Toxicity in Study II Response and Infectious Complications**

As shown in Table 6 the degree of infection graded 0 (none), 1 (mild), 2 (moderate), 3 (severe), and 4 (life-threatening) generally correlated inversely with response. Although patients demonstrating no complications had a slightly reduced response compared to those displaying modest graded infection (1, 2), the groups combined demonstrated a 48% response frequency compared to a 11% response for those severely infected (3, 4) ($p < 0.001$).

**Response and Bleeding Complications**

The severity of bleeding complications (Table 7) was also inversely correlated with the response frequency. Those patients displaying less severe graded complications (0, 1, 2) demonstrated a 37% response compared to a 13% response for those sustaining a severe or life-threatening hemmorhage ($p < 0.05$).

**Response and Combined Complications**

When complications of infection and bleeding were combined, the inverse correlation with response, as before was even more evident (Table 8). With the exception of the somewhat lower response for patients demonstrating no complications compared to those with modest complications, those patients sustaining severe combined complications fared so poorly that there was no response in any patient who sustained combined life-threatening infection and bleeding.

**Survival Comparison With Prior Studies**

The median survivals for previous CALGB protocols in 1964, 1965, 1968, and 1969 shown in Fig. 5 were 4.9 wk, 3.7 wk, 5.2 wk, and 8.6 wk, respectively. Median survival for protocol study I (7131) was 13.8 wk, for protocol study II (7331), 10.8 wk, and both protocols combined, 12 wk. Some modest improvement is apparent in the survival curves. The statistical
100
75
50
25
0

Weeks from onset of protocol

Fig. 5. Survival of patients on CALGB protocols since 1964. The initial two numerals of the protocol designate the year of study initiation, i.e., 7131 and 7331 were begun in 1971 and 1973, respectively.

Fig. 6. Survival of patients in study I (7131), study II (7331), and the previous protocol in 1969 (6932). Survival superiority of study I over study 6932 was statistically significant (p = 0.02) but was not statistically significant compared to study II (7331) (p = 0.41).

difference in survival between the last prior protocol in 1969 and study I (7131) was p = 0.02, study II (7331) p = 0.07, and combined p = 0.03 (Fig. 6). There was no statistically significant difference in survival between study I (7131) and study II (p = 0.41).

DISCUSSION

The treatment of the terminal phase of CGL has been disappointing and associated with brief remissions. CALGB has tested a series of drug regimens including "high" and "low" dose 6-MP, thioguanine with azacytidine in high and low doses, and cytosine arabinoside-bischloronitrosourea in varying doses with and without VCR-PRED. In none of these regimens was a response of 20% achieved. Similarly, Foley et al. were able to produce a response in only 3 of 13 patients using PRED, 6-MP, methotrexate, and VCR. 

The 34% response achieved with all the HU, 6-MP, and steroid combinations appears superior to previous regimens; however, the modest improvement in response was not translated into any major impact on survival compared to prior studies by the group as a whole. This is not surprising since the majority of patients still do not respond to therapy. While survival of the responding patients was clearly superior, being over 4 times longer than that of nonresponders, the overall median duration of remission of approximately 7 mo, similar to that reported by others, remains brief, thus precluding any significant improvement on overall survival.

No statistical benefit could be demonstrated from the addition of VCR. While the VCR-PRED combination is especially useful in lymphatic malignancies, the relative marrow-sparing quality of this combination prompted its use by Canellos et al. in blastic CGL. Responses were obtained in 30% of 30 patients, a frequency similar to that achieved here with HU, 6-MP, and steroids alone. The results with VCR-PRED have been buttressed by reports that approximately one-third of patients with blastic CGL may demonstrate terminal deoxynucleotidyl transferase activity, an enzymatic activity thought to be specific for thymus tissue and thymus-derived (T) lymphocytes. Further, those patients with blastic CGL responding to VCR-PRED were more likely to display blast morphology characteristics of lymphoblasts, although not all terminal deoxynucleotidyl transferase positive CGL blasts necessarily display lymphoblastic morphology. Nevertheless, any blastic CGL responding to VCR-PRED in the series of Marks et al., regardless of morphology, was terminal deoxynucleotidyl transferase positive.

The similarity in response frequency between the VCR-PRED regimen and the HU, 6-MP, steroid regimens, and the lack of additional benefit from
CHEMOTHERAPY OF TERMINAL PHASE CGL

combining the regimens, suggests that those patients most apt to respond will do so regardless of the therapy, and that once this optimal group of patients has been culled, the majority still remains resistant despite the increasing number and combinations of drugs. Indeed, responders may simply reflect a group of patients with an intrinsically better prognosis who regardless would have survived longer.

In an effort to determine if responders represent a group of patients with an intrinsically better prognosis, presenting parameters at the onset of the terminal phase have been analyzed for prognostic significance. In an initial report of the 77 patients in study I, a positive correlation of response with the magnitude of the relative blast count and platelet count was noted.\(^{21}\) Whereas age was inversely correlated, the magnitude of the leukocyte count and duration of disease were of no predictive significance. All 223 patients are currently undergoing analysis and will be the subject of a future report.

While the correlation with platelets and the inverse correlation with age was not unanticipated, the positive influence of blasts was surprising. Conceivably, patients with blastic disease are more likely to respond because they are more prone to have “lymphoblastic” disease, whereas poorly responding patients enter the terminal phase under a different setting, i.e., severe myelofibrosis, thrombocytopenia, etc. Rosenthal and associates have shown that of the two morphological subgroups—lymphoblastic and myeloblastic—the lymphoblastic group in general had a greater number of blasts.\(^{22}\) Thrombocytopenia was more profound in this lymphoblastic group in contrast to our data. Myelofibrosis, while associated with a shorter median survival, did not statistically affect response.

Blastic disease may be more responsive to S-phase cycle-specific agents. Interestingly, T lymphocytes are also 20 times more sensitive to cytosine arabinoside than are B lymphocytes.\(^{23}\) Indeed, the positive influence of blasts on response in these studies may have represented, in large part, the response of T lymphoblasts to hydroxyurea which, similar to cytosine arabinoside, is uniquely S-phase-specific.\(^{24}\) HU was especially useful in our studies, since many of the patients in this study had already been exposed to prior cytosine arabinoside. HU is active in both the chronic and the terminal phases of CGL.\(^{25-27}\) Additionally, both HU and 6-MP have some platelet-sparing qualities, making them particularly useful in thrombocytopenic settings, such as terminal CGL.\(^{24}\)

Response frequency and median survival of 38% and 13.8 wk, respectively, were slightly superior in study I to the 31% and 10.8 wk achieved in study II. Whereas these data were not statistically significant, the differences may reflect the effects of the increased dosage of HU and 6-MP in study II. Since toxicity was minimal in the initial study, the doses of HU and 6-MP were increased in an effort to achieve further improvement in response and survival. These efforts were obviously futile and further support the concept that more is not necessarily better. Toxicity was inversely correlated with response.

It is possible that the increased infectious and bleeding complications may have reflected the characteristics of a poorly responding patient rather than the effects of drug toxicity. This is unlikely, however, since there were no obvious major differences in the patient selection or treatment to explain the differences in response between the two studies except for the increase in dosage.

One minor difference, however, was the use of different steroids. In the initial study, dexamethasone was employed, whereas prednisone was used in study II. Dexamethasone use was originally derived both from preliminary CALGB observations in childhood acute lymphatic leukemia, suggesting the superiority of this steroid over prednisone, and from experimental data suggesting prednisone, but not dexamethasone and prednisolone, reduced the potency of methotrexate by interference with cellular transport.\(^{28}\) Corticosteroids of varying chemical structure have been shown to have differing effects on host resistance.\(^{29}\) Glasser et al. found no impairment of neutrophil viability, chemotaxis, phagocytosis, fungicidal activity, and bactericidal activity following a single dose of dexamethasone.\(^{30}\)

In contrast to the experience here, Spiers and associates, using an aggressive combination of eight drugs administered simultaneously, termed TRAMPCOL, have reported a 42% response in 19 patients.\(^{31}\) The results obtained with this combination, however, may not be totally comparable to the data here, since differing criteria for response were employed. Indeed, response frequency in various treatment programs may be more indicative of differences in patient selection, the definition of the terminal phase and what constitutes a response than in the salutary effects of the agents employed. Clearly, there is a need for both a common language and innovative approaches to this formidable and generally refractory disease.

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