A Two-Step Timed Sequential Treatment for Acute Myelocytic Leukemia


Since 1980, adults with acute myelocytic leukemia (AML) have been treated on two clinical studies using intensive timed sequential therapy. All patients ages 16 to 80, including those with secondary AML (SAML) and those with AML preceded by a hematologic disorder (AHD), were treated, regardless of medical complications at the time of diagnosis. The first study combined high doses of cytarabine (ara-C, AC) and daunorubicin (DRN, D) in sequence (A_C2-D-Ac) and resulted in a complete remission rate of 55%. A group of these patients selected by functional status was able to receive a second course of therapy in remission, which resulted in a disease-free survival (DFS) of >40% at 7 years. Because of toxicity in that study, 114 patients were entered on a second trial initiated 4 years ago, using a less aggressive first course, with amsacrine, to achieve a stable remission (A_C2-D-Amsa). This first treatment was followed by a more intensive second course (A_C2-D-Ac). With this two-step approach, a higher complete remission (CR) rate (76% for de novo AML and 54% for SAML-AHD) was achieved, and more patients were able to receive the second course of therapy. At the current median follow-up of 26 months, the median duration of DFS and overall survival are 11 and 14 months for patients with de novo AML. Age ≤55 is the most significant prognostic factor for both prolonged DFS and overall survival, with median durations of 17 and 18 months, respectively, for these younger patients. Patients with SAML-AHD remain relatively refractory to treatment despite aggressive chemotherapy, with median durations of DFS and overall survival of 9 months and 5 months, respectively.

Sequential clinical studies based on principles developed in the laboratory and a rat model have been conducted to define concepts pertinent to the curability of leukemia with chemotherapy. Applied pharmacologic and cell kinetic data have produced durable disease-free survival (DFS) in adults with acute myelocytic leukemia (AML). In a study (8004) begun 8 years ago, which approximated two courses of a timed sequence of high-dose cytarabine (ara-C, AC) and daunorubicin (DRN, D, A_C2-D-Ac), an impressive cure rate was associated with significant toxicity. Because of cumulative morbidity in older patients, the investigational drug amsacrine (Amsa) was substituted for the second infusion of ara-C in the subsequent study (A_C2-D-Amsa). After obtaining tumor reduction and a stable clinical status with this first step, patients received a second course of timed therapy with ara-C in sequence, now at an initial dose three times higher than that given in the previous trial (A_C2-D-Ac), to ablate residual leukemia. This study (8410), begun 4 years ago, included two courses of timed sequential therapy (TST), a potentially less intensive induction, followed by a more aggressive second course—was designed to increase the remission rate and duration of remission, particularly in the elderly patient.

In addition, since study 8004 demonstrated a plateau of the disease-free survival (DFS) curve at 40% at >7 years, a second goal relevant to the more aggressive second treatment course was to decrease the early relapse rate. Results at >2 years in study 8410, aimed at enhancing the therapeutic advantage without compromising antitumor effect, were encouraging. These intensive treatment studies also highlighted thesubset of patients that remains relatively refractory to intensive chemotherapy.

Materials and methods

Patient population. All patients in the age range 16 to 80 years with AML who had not been previously treated for leukemia were eligible for treatment at the Adult Leukemia Service of the Johns Hopkins Oncology Center. Study 8004 was begun in January 1980, and 75 patients were enrolled through June 1982 when accrual was completed. The preliminary results of that trial have been reported. From July 1982 through May 1984 patients were accrued to an ara-C dose-escalation trial. Between June 1984 and June 1988, 114 patients were entered in protocol 8410. In total, 189 patients with AML received TST on two treatment protocols, either 8004 (1980 to 1982) or 8410 (1984 to 1987), each scheme consisting of two courses of intensive therapy (Table I). Patients were not excluded because of poor medical condition, infection at the time of presentation, a history of previous exposure to chemotherapy and/or radiation (secondary AML [SAML]), or a history of prolonged pancytopenia of more than 3 months, or myelodysplastic syndrome (MDS). Since it is common practice in the leukemia literature to exclude patients with either SAML or AML preceded by a hematologic disorder (AHD) from analysis, we have stratified them for easier comparison with other published studies.

The diagnosis of AML was established by review of Wright-stained smears of bone marrow aspirates and biopsies. Histochemical stains were performed on peripheral blood and bone marrow, and morphologic classification was made according to the American–British (FAB) criteria. Cell-surface marker phenotype was determined and chromosome analysis was routinely performed after January 1984. To substantiate the diagnosis of M7 and M1, electron microscopy and platelet-specific monoclonal antibody affinity were included in the analysis. Seventy-one of the 75 patients entered in study 8004 could be classified into FAB subsets by retrospective analysis: 4 with M1, 11

From the Adult Leukemia Program of the Johns Hopkins Oncology Center, Baltimore.

Submitted October 13, 1988; accepted June 12, 1989.

Supported by US Public Health Service Grants Nos. CA06973, CA33348, and CA40187, and by the Lloyd Watter Fund.

Dr Geller is a Leukemia Society Fellow.

Address reprint requests to Philip J. Burke, MD, Johns Hopkins Oncology Center, Rm 3-109, 600 N Wolfe St, Baltimore, MD 21205.

The publication costs of this article were defrayed in part by page charge payment. This article must therefore be hereby marked "advertisement" in accordance with 18 U.S.C. section 1734 solely to indicate this fact.

© 1989 by Grune & Stratton, Inc.

0006-4971/89/7405-0047$3.00/0
Table 1: Characteristics of Patients in Two Studies

<table>
<thead>
<tr>
<th></th>
<th>Study 8004</th>
<th>Study 8410</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%)</td>
<td>No. (%)</td>
</tr>
<tr>
<td>Total patients</td>
<td>75</td>
<td>114</td>
</tr>
<tr>
<td>Median age, range</td>
<td>44, 16-74</td>
<td>55, 19-79</td>
</tr>
<tr>
<td>De novo AML</td>
<td>61 (81)</td>
<td>75 (66)</td>
</tr>
<tr>
<td>AHD-SAML</td>
<td>14 (19)</td>
<td>39 (34)</td>
</tr>
<tr>
<td>One course only</td>
<td>48 (64)</td>
<td>35 (31)</td>
</tr>
<tr>
<td>Median age, range</td>
<td>52, 19-72</td>
<td>63, 19-79</td>
</tr>
<tr>
<td>Two courses</td>
<td>27 (38)</td>
<td>79 (69)</td>
</tr>
<tr>
<td>Median age, range</td>
<td>36, 16-74</td>
<td>48, 18-76</td>
</tr>
</tbody>
</table>

One patient with M2, 9 with M3, 26 with M4, 13 with M5, 3 with M6, and five with M7 (megakaryocytic) leukemia. In total, 9 patients in study 8410 were classified as M1, 21 as M2, 8 as M3, 33 as M4, 23 as M5, 9 as M6, 7 as M7, and 4 as biphenotypic.

Treatment protocols. The details of study 8004 have been previously published. Briefly, each course consisted of DRN at a dose of 45 mg/m² given daily on days 1, 2, and 3 and a total dose of 2 g/m² of ara-C as a 72-hour continuous infusion (CI) beginning on day 1 and again on day 10 (Ac2-D-Amsa). Entrants in protocol 8410 received DRN at a dose of 45 mg/m² given daily on days 1, 2, and 3 and a total dose of 2 g/m² of ara-C given as a 72-hour CI beginning on day 1, as in study 8004. However, on days 8, 9, and 10 of this first course, instead of ara-C, a daily bolus of Amsa at a dose of 200 mg/m² was given (Ac2-D-Amsa). Response to this therapy was first evaluated by bone marrow aspirate and biopsy on day 14 and then weekly thereafter. Absence of leukemia in the bone marrow aspirate on day 14 defined patients with complete tumor clearance (CTC), while patients with leukemia present were classified as nonresponsive (NR). Marrows of patients who died before day 14 could not be evaluated for tumor response and were designated too early to evaluate (TETE), but these patients were included as NR in all analyses of data. Any who had CTC on day 14 but died before recovery of hematopoiesis were considered to have died in aplasia (DIA). In contrast to the first study (8004), those with NR leukemia who tolerated the first course of therapy were candidates to receive the second course, as were patients in complete remission (CR). This timed sequence, started on day 63 ± 7 (mean ± SD) following Ac-D-Amsa, included DRN 45 mg/m² given daily on days 1, 2, and 3. Ara-C, 6 g/m², at a total dose three times higher than that used in study 8004, was given as a 72-hour CI beginning on day 1. A 72-hour CI of 2 g/m² of ara-C was then begun on day 10 (Ac2-D-Ac). Because of toxicity encountered in older patients with this increased dose of ara-C given on days 1 to 3 of the second course, after January 1987, all 12 patients >55 years of age received 2 g/m² of ara-C by CI of Ac-D-AMSA.

Supportive care. All patients were treated in single rooms. Patients with fever >38.3°C and granulocytopenia (<500 granulocytes/µL) were treated with broad-spectrum antibiotics, including an antipseudomonal penicillin and an aminoglycoside, or with trimethoprimsulfamethoxazole. Fever with granulocytopenia not responding to one of the above regimens after three to seven days was treated empirically with amphotericin-B. Random or HLA-matched platelets were given to maintain a platelet count greater than

Fig 1. Schema of studies 8004 and 8410. In study 8004, DRN was given by a daily bolus of 45 mg/m² on days 1, 2, and 3, and ara-C as a 72-hour infusion of 2 g/m² starting on days 1 and 10. A similar second course of TST was given in early remission (circa day 63). In study 8410, Amsa 200 mg/m², administered on days 8, 9, and 10 as a daily injection, was substituted for ara-C in the initial course (Ac2-D-AMSA). The second course of TST was given in early remission (circa day 63) and consisted of DRN 45 mg/m² on days 1, 2, and 3 and ara-C 6 g/m² as a 72-hour infusion starting on day 1 and 2 g/m² as a 72-hour infusion starting on day 10 (Ac2-D-AC).
20,000/µL, and packed red blood cells were transfused to maintain the hematocrit >30%.

The toxicity of Ac-D-Acm relates to compounding toxicities associated with combined GI mucosa destruction and the adult respiratory disease syndrome (ARDS) when high-dose ara-C is given in sequence. This untoward effect probably relates to the situation at presentation, with bone marrow suppression and ongoing infection, tumor load and lysis, and overall poor functional status. By using AMSA on days 8 to 10, the difficult management of tumor probody excretion and concomitant diuresis in preparation for the second ara-C57 was mitigated. The first step of this trial was designed to interdict the untoward effects seen in study 8004 by using the lower dose of ara-C (2 g/m²) sequenced with AMSA at presentation, preserving the ablative step with the maximal tolerated dose of ara-C, 6 g/m²,7 for the controlled, clinically stable period early in remission. To further reduce GI toxicity, all patients received nothing by mouth and hyperalimentation through day 21 of treatment.

**Results**

Comparison by age of patients in the two studies who received one or two courses of TST. The patients in each study who received either one or two courses of TST are compared by age (Table 1). The median age of the 114 patients in study 8410 was higher than that in study 8004 (P = .013), and the number of patients with de novo AML was significantly different between the two studies (P = .011) (Table 1). The median age of patients with de novo AML was 44 years (range, 16 to 74) in the first protocol and 51 years (range, 19 to 74) in the second protocol (P = .158). This difference in distribution of patients with SAML, AHD, and de novo AML can be accounted for by referral-pattern change and a possible increase in the incidence of MDS and treatment-related leukemia. The number of patients treated in study 8410 who were able to receive both courses was greater (P < .001), and those who received both courses were older (P < .003) than those given two courses in study 8004.

Clinical response after one or two courses of TST. Treatment with Ac-D-Amsa achieved remission in 63 percent of patients (Table 2). All patients clinically able to tolerate a second course of therapy were candidates for Ac-D-Acm, irrespective of remission status following Ac-D-Amsa. Seventy-nine (69%) of the 114 patients were given the second course.

Of the 55 patients with de novo AML who were in CR after the first course, 48 received a second course, 42 completed therapy in CR, and six died during treatment. Of the 14 patients with de novo AML who did not respond after the first course, 11 received a second course; two achieved CR after the second course, six remained NR, and three died during treatment. Three patients refused the additional therapy. Therefore, the total number of patients with de novo AML who achieved CR with either one or two courses of treatment was 57 (76%). Of the 59 patients with de novo AML who received the second course, 44 patients (75%)

### Table 2. Clinical Outcome of One or Two Courses of Therapy in Study 8410

<table>
<thead>
<tr>
<th>Course 1</th>
<th>Course 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>De Novo AML</td>
</tr>
<tr>
<td>CR*</td>
<td>CR</td>
</tr>
<tr>
<td>No. of patients</td>
<td>75 (73)</td>
</tr>
<tr>
<td>Complete response</td>
<td>55 (73)</td>
</tr>
<tr>
<td>No response</td>
<td>14 (19)</td>
</tr>
<tr>
<td>Died too early to evaluate</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Died in aplasia</td>
<td>5 (7)</td>
</tr>
</tbody>
</table>

*Complete response at start of second course.
†No response with first course.
completed the therapy in CR, six (10%) remained NR despite the more aggressive second therapy, and nine (15%) died of toxicity.

Thirteen of 17 patients with SAML or AHD who achieved CR after the first course received Ac-D-Ac, with nine (15%) completing the therapy in CR, six (10%) remaining NR (P<0.005), and one died during aplasia. In total, 18 (46%) of patients with SAML-AHD achieved CR with one or two courses of therapy.

Factors determined by chi-square analysis that predicted for CR were age ≤55 (P=.004), absence of leukemia in the day 14 bone marrow aspirate (P=.005), and de novo AML (P<.001). Poor response was predicted for FAB M6 and M7 (P=.018). Although not predicted as a continuous variable, WBC when stratified (<200 μL) was a significant variable for obtaining CR (P=.062). With the logistic-regression model, de novo AML (P<.001) and WBC <2,000 (P=.035) predicted for CR, and with inclusion of the day 14 bone marrow results, absence of tumor on day 14 (P=.011) and age ≤55 (P=.030) were also predictive. For patients with de novo AML, 83% (39/47) ≤55 years achieved CR, while 64% (18/28) >55 years responded to therapy.

Toxicity. Toxicities experienced during induction therapy in study 8410 included 12 episodes of ≥ grade 3 (ECOG)31 hemorrhage, resulting in 3 deaths (2 CNS and 1 GI) and 2 episodes of hepatitis, which ultimately resolved. Cardiac arrhythmias related to Amsa, which developed in 7 patients, were treated appropriately with medications and resolved once the Amsa was completed (4 patients) or when discontinued (3 patients). The major toxicity during the second course of study 8410 was adult respiratory distress syndrome, manifested by hypoxemia (PO2 <60 mm Hg on room air) or infiltrates seen in the chest radiograph, which occurred in 26 patients (34%) following the final infusion of 2 g/m2 of ara-C and resulted in two deaths.35

Myelosuppression with both courses in study 8410 was of long duration, with the time until granulocyte recovery of >500/μL for the first course 32 ± 7 days (mean ± SD) and 40 ± 10 days for the second course. Fungal infections, predominantly aspergillosis, fusariosis, and candidiasis, were responsible for ten deaths during both courses of treatment. Gram-negative sepsis occurred in 18 patients, with six deaths.

Disease-free survival of all patients in trial 8410. The median duration of DFS for the 57 patients with de novo AML who entered CR was 11 months; for the 18 patients with either SAML or AHD, the median duration was 9 months (Fig 2). Using the Cox proportional-hazards model, only age ≤55 predicted for prolonged disease-free survival (P=.007), with patients ≤55 years having a median duration of DFS of 17 months, compared with 7 months for older patients. There was no significant difference in the DFS between patients >55 who received either 2 g/m2 or 6 g/m2 of ara-C in the second course of treatment. Disease category, results of the day 14 bone marrow aspirate, and WBC were not significant factors.

Postremission therapy. When all patients studied in study 8410 who received a second course of treatment in remission are considered, the median DFS is 14 months (Fig 3), and 22 months for those ≤55 years (Fig 4). This latter result compares favorably with the long-term DFS in study 8004 for a similar subset of patients, although the period of observation is shorter.

Overall survival. Of the 75 patients with de novo AML, 59 (79%) were able to receive both courses of therapy (Table 3). There were 16 treatment-related deaths from both courses and 37 deaths related to refractory or relapsing leukemia. One patient died of lung cancer in remission and, at present, 21 patients are surviving 14 to 56 months after diagnosis. Twenty patients (51%) with either SAML or AHD were able to receive both courses of treatment. There were seven treatment-related deaths and 27 deaths related to
remission in years between de novo AML and the poor-prognosis AHD-SAML groups. This may relate in part to the success of intensive remission-induction therapy in a refractory population. With longer observation these groups may separate, although both

Table 3. Survival of 114 Patients After One or Two Courses of TST in Study 8410

<table>
<thead>
<tr>
<th></th>
<th>One Course Only</th>
<th>Two Courses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>De Novo AML</td>
<td>AHD-SAML</td>
</tr>
<tr>
<td>No. of patients</td>
<td>16</td>
<td>19</td>
</tr>
<tr>
<td>Deaths</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In aplasia</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>In remission</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>In relapse</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>Surviving</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Refractory or relapsing leukemia. Only five of this subset are alive 14 to 31 months after diagnosis. Using a Cox proportional-hazards model for overall survival, only age ≤55 (P = .001) and de novo AML (P = .055) predicted for prolonged survival.

The overall survival for patients with de novo AML and for those with either SAML or AHD treated in study 8410 was a median duration of 14 months and 5 months, respectively (Fig 5). The median duration of overall survival for patients with de novo AML, stratified by age (≤55 or >55), is 18 months for those ≤55 years and 7 months for those older (Fig 6). The first-year survival was improved in patients >55 years of age who received the lower dose of ara-C (2 g/m²) compared with those who received 6 g/m²; however, there was no significant difference in overall survival between the two groups (log-rank, P = .24).

There is no apparent difference in the duration of CR between de novo AML and the poor-prognosis AHD-SAML groups. This may relate in part to the success of intensive remission-induction therapy in a refractory population. With longer observation these groups may separate, although both
DISCUSSION

Brief but intensive treatments aimed at cure of leukemia\textsuperscript{21-25} generally include doses of active drugs given to host tolerance, some requiring bone marrow rescue.\textsuperscript{26,27} Most have in common initial tumor reduction, with a less intense regimen followed by a more aggressive tumor-ablative treatment in a medically stable patient with normal bone marrow function. In such a two-step program, we have added specific timing of drug to attempt to further reduce the amount of leukemia while preserving host recovery capability. In these trials, initial reduction of tumor with intensive chemotherapy results in leukemic regrowth forced by host-derived humoral stimulatory activities (HSA).\textsuperscript{28-30} which, with appropriate timing of a second drug, combine to produce a large tumor kill.\textsuperscript{1-5}

This premise, initially substantiated in the laboratory,\textsuperscript{5-11} forms the basis of our empiric clinical trials in humans. In study 8004,\textsuperscript{4} the probability of DFS of >40% of patients in CR who tolerated a second course of TST has been at a plateau for >7 years. Equally intensive treatments by other groups have produced comparable results.\textsuperscript{22-25} Each demonstrates that AML is curable with drugs, a result usually limited to younger patients who can tolerate the inherent toxicities necessary to eradicate responsive leukemia.

The first course of study 8004 produced a 55% CR rate but was associated with a high morbidity and mortality. Although this CR rate was comparable to that in other studies ongoing at that time,\textsuperscript{30} many patients were unable to...
TIMED SEQUENTIAL THERAPY

be treated with a second course. Nonetheless, of the 27 patients who received the second course, there were only two deaths before bone marrow recovery. Those who tolerated both courses had a good chance of long survival, but selection by toxicity was evident, as only 40% of the initial population, a younger group with predominantly de novo AML, was treated the second time.

The primary goal of study 8410 was to achieve a higher CR rate after the initial cycle of therapy without incurring the morbidity and mortality experienced with high-dose TST in study 8004. Amsa, substituted for the second infusion of ara-C in the first course, was given at the time of peak regrowth of residual tumor in the first of two courses (Ac-D-Amsa). The aim was to protect the host from the effects of prolonged bone marrow depression and the toxicity of ara-C given in a high-dose sequence, while at the same time to produce a large tumor kill.

Ac-D-Amsa produced a CR rate higher than Ac2-D-Ac by decreasing the number of patients who were TETE or who DIA (18% v 7%), even though the patients were older. Improved supportive care may have contributed to this result.

All patients >18 and <80 were treated on the 8410 protocol without exclusion by a history of previous chemotherapy or complications of prolonged pancytopenia. While 20% of patients entered in study 8004 had either SAML or AHD, 35% of patients on 8410 had those poor-prognosis leukemias.

Because of changing referral patterns and the inclusion of all patients in the study, the average age of patients accrued to 8410 was 10 years higher than in the previous study. Nonetheless, the 70% receiving a second course contrasted with the 40% of the younger group given two cycles of Ac2-D-Ac in study 8004. In addition, the duration of aplasia with Ac-D-Amsa, shorter by 10 days than Ac2-D-Ac, allowed recovery of bone marrow function in some patients who probably would not have survived the longer aplasia. Since the incidence of fungal infection was high with this initial course, some of the infected patients probably would have died if the WBC recovery had been delayed. Persistence of these infections prevented offering a second course of therapy to some patients in both studies. There were also seven cases of cardiac arrhythmias with Amsa, which required monitoring and drug cessation.

Once the tumor mass was reduced, patients received another course, this time with ara-C as the second drug in the sequence. The 6 g/m²/72 h initial ara-C dose was 3 times higher than that in study 8004, resulting in a total dose of ara-C given during both courses of study 8410 2 g/m² greater than that given in the two courses of study 8004. This strategy was derived from evidence of a steep cytotoxic dose response for ara-C, good initial results with high-dose ara-C therapy at other centers, and the dose-related increase in the plasma levels of induced humoral stimulatory activities. The resultant effect was enhanced growth of residual tumor and drug uptake and retention. Whether this concept of brief two-step TST is more effective than other high-dose intensive therapies when given in this particular design remains to be tested in controlled large-group studies.

This second course of intensive TST, given at the time of hematologic reconstitution, diminished tumor burden and biologic balance and was designed to maximize tumor cytotoxicity. However, even with patients in CR after recovery of normal bone marrow and immune system function, Ac-D-Ac remained deleterious to normal tissues and produced a period of aplasia too long for some older patients to survive. This intolerance forced a dose modification to 2 g/m² of ara-C in patients >55 midway in the study. With reduced host toxicity, the immediate survival improved, but total overall survival was less than in the younger group. The reduction in dose in the older subset did not influence that outcome. However, a greater proportion of older patients in study 8410 completed the two-course treatment with less debility than in study 8004.

Since the previous trial of TST demonstrated a plateau of the DFS curve for those patients who were in CR at 18 months, a second goal of the 8410 design was to decrease the early relapse rate after remission induction and augmentation seen with study 8004. However, despite the differences in age and patient characteristics between the two studies, the early phases of the DFS probability curves are essentially identical because of similar overall treatment-related deaths and an early relapse rate. The reason for relapse may relate to a large tumor mass and to the older age of the patients with a high incidence of SAML-AHD. This lack of effect on the early relapse rate is disappointing, since short of new supportive measures such as leukokines, this chemotherapeutic approach, which combines maximal tolerated doses and brief schedules of active drugs, cannot be extended in drug content or in duration without further untoward effects. When discernible, this early-relapse group will receive alternate therapies or further therapies in remission with trials of biomodulators.

While the probability of DFS has reached a plateau for patients treated in remission in study 8004, a plateau for DFS has not yet been reached for study 8410, with a shorter period of follow-up. No prognostic factors were found to predict for duration of first remission. Both studies, however, have demonstrated a plateau in their overall survival curves at >40%. Younger age (≤55) was found to be the only significant prognostic factor for predicting longer survival.

ACKNOWLEDGMENT

The authors recognize the expert secretarial assistance of Lisa E. Nicholson and applaud the housestaff, nurses, and fellows of the Johns Hopkins Oncology Center for their outstanding care of the patients and their attention to protocol requirements.

REFERENCES

3. Vaughan WP, Karp JE, Burke PJ: Long chemotherapy-free
A two-step timed sequential treatment for acute myelocytic leukemia

RB Geller, PJ Burke, JE Karp, RL Humphrey, HG Braine, RW Tucker, MG Fox, M Zahurak, L Morrell and KL Hall