A Randomized Study of the Efficacy of Consolidation Therapy in Adult Acute Nonlymphocytic Leukemia

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The Eastern Cooperative Oncology Group conducted a randomized study to determine the efficacy of consolidation therapy in prolonging the duration of complete remission (CR) in adults with acute nonlymphocytic leukemia (ANLL). Induction chemotherapy with daunorubicin, cytosine arabinoside, and 6-thioguanine (DAT) yielded CR in 65% of 283 patients with ANLL, aged 16–69. For patients aged 60–69, the CR rate was 58%. Of 184 patients in CR, 146 patients were then randomized to receive either maintenance therapy with weekly cytosine arabinoside and 6-thioguanine alone (69 patients) or two courses of reduced doses of DAT 1 mo apart, before commencing the same maintenance program (77 patients). Consolidation therapy resulted in hematologic toxicity, but was not lethal in any of the eligible patients. Patients receiving consolidation plus maintenance therapy experienced a longer CR duration (40 wk) and disease-free survival at 2 yr (28%) than did those patients receiving maintenance therapy alone (34 wk and 14%, respectively). These differences are not statistically significant. These results suggest that approaches to consolidation therapy employing reduced doses of the induction therapy regimen can have, at best, only a small benefit. For consolidation therapy to provide substantial improvement in CR duration, intensive regimens with non-cross-resistant drugs will be required.

TREATMENT OF ADULTS with acute nonlymphocytic leukemia (ANLL), utilizing varying doses of daunomycin, cytosine arabinoside, and 6-thioguanine, has produced complete remission (CR) rates ranging from 70% to 80%.1–3 Despite this success in achieving initial remission, the median duration of remission remains in the range of 10–14 mo,4 regardless of whether patients subsequently receive either no further therapy,5 consolidation therapy with no maintenance,6 maintenance therapy with no consolidation,7–9 or consolidation and maintenance therapy.1–3,10,11 Thus, it is not clear whether any therapy is of value after induction of CR. In 1980, the Eastern Cooperative Oncology Group (ECOG) initiated a randomized study (EST 1479) to test the efficacy of consolidation therapy in prolonging the duration of complete remission.

MATERIALS AND METHODS

All ECOG member institutions and their affiliates were eligible to participate in the study. Adult patients, less than 70 yr old, with de novo acute nonlymphocytic leukemia were eligible for the study providing they satisfied the following eligibility criteria: morphologic proof of ANLL, FAB types M1 through M6, as determined by repository center review of morphology and histochemistry by Dr. John Bennett; no previous treatment with chemotherapy or radiation therapy; greater than 30% marrow blasts; no prior hematologic disorders; no significant cardiac disease; adequate hepatic and renal function; and documentation of informed consent.

Induction therapy consisted of one or two courses of: daunomycin, 60 mg/sq m/day i.v. push on days 1, 2, and 3; cytosine arabinoside, 25 mg/sq m i.v. push followed by continuous i.v. infusion of 200 mg/sq m/day on days 1 through 5; and 6-thioguanine, 100 mg/sq m orally every 12 hr on days 1 through 5 (DAT). Patients with acute promyelocytic leukemia (FAB type M3) received heparin therapy during early induction treatment.

Patients who achieved complete remission were then randomized (not later than 4 wk after complete remission) either to receive two courses of consolidation therapy 1 mo apart followed by maintenance or to begin maintenance therapy immediately. A consolidation course consisted of: daunomycin, 45 mg/sq m i.v. push on days 1 and 2; cytosine arabinoside, 100 mg/sq m i.v. push; and 6-thioguanine, 100 mg/sq m orally each given every 12 hr on days 1 through 5. Maintenance therapy consisted of 6-thioguanine, 40 mg/sq m orally every 12 hr for 4 days of the week, followed by cytosine arabinoside, 60 mg/sq m subcutaneously on the 5th day of each week. Maintenance therapy was continued for 2 yr. Patients were eligible for randomization if they had a performance status of 2 or better (ECOG scale), no persisting infection, and adequate hepatic and renal function. Prophylactic therapy of the central nervous system was not employed.

Patients were allocated to treatment at the consolidation phase using randomly permuted blocks with strata, the strata being age (<30, 30–59, 60–69), and number of induction cycles (1 or 2) to achieve complete remission. Institutions obtained the randomization assignment by telephoning the ECOG Operations Office in Madison, WI.

A total of 318 patients were registered for induction therapy between January 1980 and February 1982. The median age of patients entered on study was 51 yr (range 16–69), with an equal distribution of men (52%) and women (48%). Thirty-five patients have been excluded from subsequent analysis. Twenty of these patients were ineligible: 11 because subsequent histology review documented acute lymphocytic leukemia; 6 because they were...
withdrawn prior to treatment; and 1 each for an elevated creatinine, initial blast percentage in marrow less than 30%, and prior chemotherapy. Four additional patients lack follow-up data and 11 others were excluded because of patient refusal of treatment (4), inadequate drug dosage (3), improper supportive care (2), no follow-up bone marrow examination (1), and premature administration of a second course of therapy (1).

Thirty-eight eligible cases achieved a complete response but were not randomized and subsequently were treated off-study. Eighteen of these were ineligible for randomization because of organ dysfunction and persisting infection or side effects of induction therapy; seven others underwent bone marrow transplantation prior to randomization; eight patients refused randomization; three relapsed before randomization; and two patients were removed from study by their physicians despite eligibility.

Each investigator was asked to identify the morphological subtype of ANLL, according to FAB criteria. Routine cytochemistry, including peroxidase, nonspecific esterase (alpha-naphthyl acetate esterase), specific esterase (chloroacetate esterase), and naphthol ASD acetate esterase (with and without sodium fluoride), were done by the repository center on air-dried bone marrow smears. Only 3% of cases were reclassified as acute lymphocytic leukemia. Concordance between investigator and repository diagnoses was excellent in three FAB cell types (M3: 90%, M5: 83%, and M6: 100%), fair in M1 (79%), and poor in M2 (55%) and M4 (51%). The distribution of ANLL FAB subtypes was: M1: 19%, M2: 29%, M3: 9%, M4: 28%, M5: 10% (M5a: 4% and M5b: 6%), and M6: 5%.

Complete remission was defined as an M1 marrow status (<5% blasts, >15% erythroid elements, >25% normal granulocytes, in a nonhypocellular marrow), with normal physical (P1) status (normal liver, spleen, lymph nodes) and H1 peripheral blood (hemoglobin >11 g/dl, neutrophils >1,500/cu mm, no blasts, platelets >100,000/cu mm). Relapse was defined as the appearance of circulating leukemic cells or >5% blasts in the bone marrow. Bone marrow aspiration to detect relapse was routinely performed every 2 mo for the first 2 yr of follow-up.

Remission duration distributions were computed using the Kaplan-Meier technique. The log-rank test was used to compare curves of remission duration.

RESULTS

Induction Therapy

There were 283 cases evaluable for analysis of induction therapy. The overall complete remission (CR) rate was 65% (184/283). There was no significant difference in CR rate based on the percentage of marrow blasts or absolute numbers of circulating blast forms at presentation. Patients ≥60 yr old had a slightly lower CR rate than younger patients, and the M4 subtype (acute myelomonocytic leukemia) had a somewhat better CR rate than the other histologic subtypes, as shown in Table 1. However, a test of heterogeneity of patient groups by histology or age showed no significant differences. Of patients who achieved CR, 71% (131/184) did so after a single cycle of induction therapy. The frequency of obtaining CR on a single cycle was not influenced by age, circulating blast counts, or percent marrow blasts at presentation. Among histologic subtypes, M4 and M5 subtypes were more likely to gain CR after a single course of induction therapy than the other subtypes (p = 0.04). The median time to complete remission was 32 days (28 days if accomplished after one course, and 51 days if two courses were required to achieve CR). Of 109 patients who received two courses of induction therapy, 53 (40%) achieved CR. We defined deaths due to induction therapy as patients who died within 14 days after completing one or two induction cycles. Using this criterion, 17% (47/283) of patients died in induction therapy: 19% of those less than 30 yr old, 10% of those 30–59, and 27% of those 60–69.

Response Duration and Survival

Of the 184 patients achieving CR, 146 patients were randomized within 4 wk of CR, with 77 patients assigned to 2 cycles of consolidation followed by maintenance and 69 patients assigned to maintenance therapy alone. All of these patients are included in the analysis of outcome. The two groups of patients did not differ significantly by age, histology, percent marrow blasts and numbers of circulating blasts at presentation, or median time to CR.

Of the 77 patients randomized to consolidation, 8 patients received only 1 of the 2 intended cycles. The second cycle was not administered as scheduled in these 8 patients because of bleeding due to severe thrombocytopenia with first cycle (2 patients), surgery for ovarian abscess (1 patient), persisting abnormal liver function tests after first cycle (3 patients), and relapse occurring before second course (2 patients). All of these patients are included in the subsequent analysis of data.

As shown in Table 2, the median duration of CR for all randomized patients was 37 wk, with no significant difference in outcome between patients who received (40 wk) or did not receive (34 wk) consolidation. However, the curves of remission duration show differing plateaus at 2 yr at 28% for patients receiving
consolidation and maintenance and at 14% for patients receiving maintenance alone (Fig. 1). Nine of 77 (12%) consolidated patients currently remain in remission for more than 2 yr, compared to 2 of 69 (3%) patients who did not receive consolidation. There was no significant difference in CR duration based on age, percent blasts in the marrow or platelet count at presentation, number of courses (one or two) of induction therapy received, or histologic subtype, although the M5 (monocytic) subtype tended to have a short CR duration and the M6 (erythroleukemia) subtype a long CR duration. Patients presenting with circulating blasts >20,000/cu mm had a shorter CR duration than those whose presenting blast counts were lower (p = 0.02). However, this did not contribute to a longer survival (p = 0.73).

**Toxicity of Consolidation Therapy**

Using ECOG toxicity criteria, 36 of 77 patients experienced life-threatening myelosuppression (<500 granulocytes/cu mm; platelets <25,000/cu mm) as expected; and in 12 others, myelosuppression was severe (<1,000 granulocytes/cu mm; platelets <50,000/cu mm). Six patients experienced severe hepatic dysfunction, and one patient each had bleeding, neurologic toxicity, and fever graded as severe. However, there was only one instance of life-threatening infection, and only one patient died of bleeding and infection. This last patient was, in fact, ineligible for randomization because he was receiving antibiotics for persisting infection at the time of initiation of consolidation. Thus, there were no deaths among patients who received consolidation therapy according to protocol guidelines.

**Central Nervous System Leukemia**

Routine sampling of spinal fluid in asymptomatic patients was not required in this study. To date, overt central nervous system (CNS) leukemia has been detected in 5.3% (15/283) of the patients. Eleven of the 15 cases with CNS leukemia occurred in the M4/M5 (monocytic) subtypes, with the following frequency within FAB subtypes: M1 (4%), M2 (1%), M3 (4%), M4 (9%), M5a (25%), M5b (13%), and M6 (0%). All but 2 patients who developed CNS leukemia had presented with white blood cell counts >40,000/cu mm at diagnosis.

![Fig. 1. Kaplan-Meier plot of the probability of being in remission for patients receiving consolidation and maintenance therapy (solid line) and for patients receiving maintenance therapy alone (broken line). Vertical lines indicate patients still in remission.](image-url)
DISCUSSION

The complete remission rate of 65% in this study confirmed the effectiveness of the DAT regimen initially suggested by Arlin et al.16 and evaluated in a preceding ECOG pilot study.2 The frequency of CR and the CR duration for those aged 60–69 did not differ significantly from the results in younger patients. These data differ from those of the CALGB study17 of ANLL, which utilized 7 days of cytosine arabinoside with either of two different doses of daunorubicin given for 3 days. In patients aged 60–69, CALGB obtained a CR rate of 49% when the dose of daunorubicin was 30 mg/sq m/day, compared with 36% when the dose was 45 mg/sq m/day. CALGB attributed the better results with low versus high dose daunorubicin in this age group to a decreased death rate in induction. In contrast, the CR rate (58%) in patients aged 60–69 in our study was higher than that reported by CALGB using a higher dose of daunorubicin (60 mg/sq m/day) with only 5 days of cytosine arabinoside. Our results in this age group are consistent with reports from single institution studies.18–20

The DAT regimen used here required only one course of therapy to attain CR in most patients, thereby limiting the period of marrow aplasia and pancytopenia, with its attendant risks. A relatively short time to CR contributes to the outcome in older patients who have difficulty weathering the complications of prolonged myelosuppression.20,21 At least for older patients less than 70 yr old, aggressive therapy for ANLL is warranted and useful because the resulting CR durations are as long as in younger patients (Table 2).

Patients in this study with the monocytic subtypes of ANLL (M4 and M5) were at higher risk for overt CNS leukemia than those with other morphological subtypes, confirming the observations of others.22 Most of the patients with CNS leukemia (13/15) had markedly elevated white blood cell counts at diagnosis. The likelihood of CNS penetration seems to relate to the presence of large numbers of circulating blast cells and/or the capacity for tissue infiltration of monocytic blast forms. In either circumstance, spinal fluid sampling should be performed routinely to detect asymptomatic CNS leukemia.

The sample size in each of the randomized treatment arms of 77 and 69 patients provided an 80% chance of demonstrating a significant result (at the 0.05 level, one-sided) if the consolidation treatment arm actually improved the CR duration by 50% and only a 40% chance of documenting a significant improvement if CR duration actually improved by 25%. Each course of consolidation therapy provided 50% of the daunorubicin dose, 50% of the cytosine arabinoside dose (equal dosage but i.v. push versus continuous infusion), and 100% of the 6-thioguanine dose given in the induction regimen. Consolidation was thus moderately intensive. It yielded only a modest benefit to the treated patients, as shown in the tail of the CR duration curves (Fig. 1), which fails to achieve statistical significance because of the sample size.

Consolidation therapy is intended to reduce the residual leukemic burden that persists in most patients in complete remission. The number of persisting leukemic cells in CR can be substantial, but they are so diffusely distributed in bone marrow and other tissues as to be clinically undetectable. Subsequent regrowth of these cells is thought to cause relapse.23 The duration of CR is dependent on the numbers of residual leukemic cells and their repopulation kinetics. However, the leukemic cells persisting in CR are those that survived initial induction chemotherapy. This factor may explain why greater benefit did not accrue to those patients receiving consolidation therapy, which, in this study, consisted of reduced doses of the same drugs used in the induction therapy regimen. That is, more substantial leukemic cytoreduction did not occur because of the reduced doses employed and/or because induction therapy selected out resistant residual leukemic cells.

The results of this study suggest that consolidation may be useful in prolonging remission duration. It is also apparent that further improvement in outcome by consolidation regimens will require more intensive regimens than used here and/or the use of drugs not cross-resistant with DAT, such as AMSA24 or high-dose cytosine arabinoside25 alone or in combination.26 However, the potential morbidity and mortality of intensive consolidation regimens is a persistent concern. Recent pilot studies of intensive consolidation with drugs not used in induction therapy27,28 have demonstrated both the benefits and hazards of such therapy. Allogeneic bone marrow transplantation of patients ≤40 yr old with ANLL in first remission involves a 21% early mortality rate but appears to provide longer disease-free survival than does conventional chemotherapy.29 Use of potentially life-threatening consolidation therapy for patients ineligible for bone marrow transplantation may be necessary to achieve similar results.

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REFERENCES

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