Autologous Stem Cell Transplantation for Acute Myeloid Leukemia in First Remission

Charles A. Linker,[1] Curt A. Ries,[1] Lloyd E. Damon,[1] Peter Sayre,[1] Willis Navarro,[1] Hope S. Rugo,[1] Arnold Rubin,[2] Delvyn Case,[3] Pamela Crilley,[4] David Topolsky,[4] Isadore Brodsky,[4] Ken Zamkoff,[5] Jeffrey L. Wolf[6]

[1]University of California, San Francisco, California; [2]St. Joseph's Medical Center, Patterson, New Jersey; [3]Maine Medical Center, Portland, Maine; [4]Hahnemann University, Philadelphia, Pennsylvania; [5]State University of New York, Syracuse, New York; [6]Alta Bates Medical Center, Berkeley, California

Address correspondence to: Charles Linker, MD, A502 400 Parnassus Ave, San Francisco, CA 94143; email: linkerc@medicine.ucsf.edu

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ABSTRACT

We studied the feasibility, toxicity, and efficacy of a 2-step approach to autologous stem cell transplantation for patients with acute myeloid leukemia in first remission. Step 1 consisted of consolidation chemotherapy including cytarabine 2000 mg/m^2 twice daily for 4 days concurrent with etoposide 40 mg/kg by continuous infusion over 4 days. During the recovery from this chemotherapy, peripheral blood stem cells were collected under granulocyte colony-stimulating factor stimulation. Step 2, autologous stem cell transplantation, involved the preparative regimen of busulfan 16 mg/kg followed by etoposide 60 mg/kg and reinfusion of unpurged peripheral blood stem cells. A total of 128 patients were treated. During step 1, there was 1 treatment-related death. A median CD34$^+$ cell dose of 14 ($\times 10^6$/kg) was collected in 3 aphereses. Ten patients suffered relapse before transplantation, and 117 patients (91%) proceeded to transplantation. During step 2, there were 2 treatment-related deaths, and 35 patients subsequently suffered relapse. With median follow-up of 30 months, 5-year disease-free survival for all patients entered in the study is projected to be 55%. By cytogenetic risk group, 5-year disease-free survival is 73% for favorable-risk patients, 51% for intermediate-risk patients, and 0% for poor-risk patients. We conclude that this 2-step approach to autologous transplantation produces excellent stem cell yields and allows a high percentage of patients to receive the intended therapy. Preliminary efficacy analysis is very encouraging, with outcomes that appear superior to those of conventional chemotherapy.

KEY WORDS

Autologous transplantation • Acute myeloid leukemia • First remission treatment strategy

INTRODUCTION

The optimal strategy for autologous bone marrow transplantation (ABMT) for patients with acute myeloid leukemia (AML) in first remission is not well defined. Because ABMT relies primarily on the efficacy of the preparative regimen in the absence of a graft-versus-leukemia effect, we studied an intensive regimen for autologous transplantation combining busulfan with high-dose etoposide. Long-term follow-up of a small, primarily single-center experience using this intensive regimen combined with 4-hydroperoxycyclophosphamide (4HC)-purged bone marrow rescue suggested that the intensive regimen may improve results, with long-term disease-free survival (DFS) of 70% in 50 first-remission patients [1,2]. However, although the treatment-related mortality rate was low (4%), delayed engraftment, prolonged hospitalization, and severe nonhematologic toxicity limited the broad application of this treatment approach.

We modified our approach to autologous transplantation to allow the more widespread use of the intensive busulfan-etoposide preparative regimen. We used peripheral blood stem cells rather than bone marrow, basing the decision on the hypothesis that more rapid engraftment would reduce the overall toxicity of the transplantation regimen. Previous data have suggested that ABMT using unpurged bone marrow directly after induction chemotherapy led to an unacceptably high rate of relapse [3]. We therefore gave a single course of moderately intensive postremission therapy to achieve further cytoreduction of the leukemia and to take advantage of a possible in vivo purging effect, collecting peripheral blood stem cells during the recovery phase from this chemotherapy [4]. Because

our goal was to maximize the percentage of patients able to proceed to transplantation, the consolidation chemotherapy was developed as a compromise between giving intensive enough treatment to avoid a large number of early relapses and avoiding excessive toxicity that would result in dropouts from the treatment program.

We report the success of this strategy in achieving excellent peripheral blood stem cell mobilization with rapid engraftment and decreased toxicity and enabling a high percentage of patients to undergo transplantation. The preliminary outcome results suggest that this treatment strategy may be efficacious as well as feasible.

METHODS

Patient Selection

Patients entered this study from 6 centers from May 1993 to November 1998. All patients gave written informed consent in accord with each institution's committee on human research. Eligible patients were over age 16 and, initially, up to age 60. In June 1994, based on the acceptable toxicity profile of the treatment, patients up to age 70 were eligible to be in the study. All patients were required to be in first remission of de novo AML. Patients with prior myelodysplasia, myeloproliferative disease, or chemotherapy-related leukemia were excluded.

Complete remission was defined as normal bone marrow morphology with fewer than 5% blasts, resolution of previously abnormal cytogenetics, no evidence of extramedullary leukemia, absolute neutrophil count (ANC) ≥1500/μL, and platelets ≥140,000/μL. Before entry into the study, patients must have been in complete remission for at least 30 days but less than 6 months. We required adequate organ function, with bilirubin <1.5 mg/dL, alkaline phosphates and aspartate transaminase less than twice the upper limit of normal, creatinine <2.0 mg/dL, cardiac ejection fraction ≥0.40, and diffusion capacity of carbon monoxide ≥50%. Patients receiving previous postremission high-dose cytarabine (ara-C), defined as more than 4 doses of ara-C 2000 mg/m^2, were ineligible, but patients may have received less intensive postremission therapy before study entry.

Patients were classified by cytogenetics as "favorable" if they had t(15,17), t(8,21), or inv16q. Patients with unequivocal French-American-British (FAB) M3 morphology, without cytogenetics performed, were also classified as favorable. Patients were classified as poor risk if they had monosomy of chromosomes 5 or 7, abnormal 7q, or complex abnormalities. Other patients were classified as intermediate risk, including those with normal cytogenetics, +8, 11q23 abnormalities, miscellaneous abnormalities, and unknown cytogenetics.

Step 1: Consolidation Chemotherapy

Patients were treated with ara-C 2000 mg/m^2 intravenously over 2 hours, every 12 hours × 8 doses on days 1-4 plus etoposide 40 mg/kg by continuous intravenous (IV) infusion over 96 hours on days 1-4. All chemotherapy calculations were based on corrected weight, defined as ideal weight plus 25% of the difference between actual and ideal weight. Granulocyte colony-stimulating factor (G-CSF) 5 mg/kg subcutaneously daily was started on day 14 of therapy and continued until peripheral blood stem cell collection was completed. The dose of G-CSF could be escalated to 10 mg/kg if stem cell collection was proceeding slowly.

Stem Cell Collection

Initially, stem cell collection was begun when the white blood cell (WBC) counts were >5000/μL. This procedure was modified in August 1994 to begin collection at WBC counts >10,000/μL because of inefficient collections at lower WBC counts. At the beginning of this study, not all centers had the capability of measuring CD34$^+$ cells. Therefore, the target for stem cell collection was initially either a CD34$^+$ cell dose ≥10 × 10^6/kg or a mononuclear cell count (MNC) ≥15 × 10^8/kg. By June 1995, the MNC target was reduced to 12 × 10^8/kg. By November 1995, all centers had the capability of measuring CD34$^+$ cells, and the collection target was a CD34$^+$ cell dose ≥10 × 10^6/kg. In November 1996, the CD34$^+$ cell dose target was reduced to ≥5 × 10^6/kg.

Leukopheresis was performed according to institutional criteria, with processing of 12-18 L of blood daily. A buffy coat was prepared by centrifugation and mixed in M199 media with 5% autologous plasma and 10% dimethyl sulfoxide to achieve a final cell concentration of 2.5 × 10^8 cells/mL. The stem cell product was frozen in a controlled-rate freezer and stored in the liquid phase of liquid nitrogen.

CD34$^+$ and colony-forming unit granulocyte-macrophage (CFU-GM) assays were done according to institutional criteria. During the first 18 months of the study, patients had backup bone marrow collected after the completion of stem cell collection.

Step 2: Autologous Stem Cell Transplantation

Patients were eligible to proceed to step 2 when they had been out of the hospital for at least 4 weeks after completion of consolidation chemotherapy and were documented to be in continuous remission. This determination was made by bone marrow biopsies performed within 2 weeks of admission and by peripheral blood counts with ANC ≥500/μL and platelets ≥50,000/μL (either improving or stable).

The preparative regimen consisted of busulfan 1 mg/kg orally every 6 hours for 16 doses (total dose 16 mg/kg) on days –7 through –4, followed by intravenous etoposide 60 mg/kg over 10 hours on day –3. As in step 1, all chemotherapy doses were calculated according to corrected weight. Peripheral blood stem cells were infused on day 0. Administration of G-CSF 5 mg/kg subcutaneously daily was started on day 0 and continued until the ANC measured ≥1500/μL for 2 consecutive days or >5000/μL for 1 day.

Supportive Care

During consolidation chemotherapy, patients received fluorometholone ophthalmic solution 0.1% 2 drops 4 times daily on days 1-6. Amphotericin 0.3 mg/kg per day was started on day 5 and continued until ANC ≥500/μL.

During autologous stem cell transplantation, amphotericin 0.3 mg/kg per day was started when ANC <500/μL and continued until ANC ≥500/μL. Acyclovir 2 mg/kg intravenously every 12 hours was started on day –2 and continued until it could be switched to acyclovir 200 mg orally 3 times daily. This was continued for the first year

Table 1. *Patient Features**

	Median
Age (years)	39 (range 18-65)
WBC (10^3/μL)	9 (range 1-530)
Cytogenetics profile	
Favorable	38 (30%)
Intermediate	69 (54%)
Poor	7 (5%)
Not done	14 (11%)

**WBC indicates white blood cells.*

after transplantation. *Pneumocystis carinii* prophylaxis was maintained with trimethoprim-sulfamethoxazole 160 mg 2 times daily twice per week until at least 3 months after transplantation or until $CD4^+$ lymphocyte count ≥200/μL. Red blood cell (RBC) and platelet transfusions were administered according to institutional criteria.

Toxicity

Toxicity was graded according to the University of California, San Francisco BMT Toxicity Grading Scale. Mucositis was scored as grade 2 (moderate) if the patient required narcotic analgesics or was unable to eat because of mucositis and grade 3 (severe) if >25% of the mucosa was ulcerated. Skin toxicity was scored as grade 2 (moderate) if the patient required narcotic analgesia or local care (or both) and grade 3 (severe) if significant desquamation and breakdown occurred.

Statistical Evaluation

DFS was calculated from the date of the start of step 1 consolidation chemotherapy using Kaplan-Meier analysis on a Macintosh computer. Data were analyzed as of February 9, 1999.

RESULTS

A total of 128 patients were treated (Table 1). Patients were enrolled at the University of California, San Francisco (n = 65), St. Joseph's Medical Center (n = 20), Maine Medical Center (n = 18), Hahnemann Medical Center (n = 18), State University of New York, Syracuse (n = 8), and Alta Bates Medical Center (n = 3). Thirty-six patients (28%) were over 50 years of age, 5 patients (4%) were over 60 years, and median age was 39 years. The median WBC count at diagnosis was 9000/μL, and 15 patients (12%) had WBC counts greater than 100,000/μL. Eighty-eight patients (69%) received induction chemotherapy with high-dose ara-C (HDAC) and daunorubicin. Thirty-two patients received standard-dose ara-C plus anthracycline therapy, and 8 patients received all-*trans* retinoic acid (ATRA) plus idarubicin or daunorubicin. One hundred nineteen patients (93%) received no postremission therapy before study entry. Nine patients received some prior postremission therapy, 7 with a single course of standard-dose ara-C–based regimen and 2 with 2-day regimens of HDAC. The median interval between achieving remission and study entry was 42 days, and 9 patients were enrolled after intervals longer than 100 days.

Thirty-eight patients were classified as favorable; 22 patients had acute promyelocytic leukemia FAB M3. In 19 patients, t(15,17) was demonstrated. One patient did not have a cytogenetics assay, and in 2 patients cytogenetics assays were reportedly normal. Eight of the 22 patients had WBC counts >5000/μL, and 2 had WBC counts >100,000/μL. Eight patients had FAB M4Eo, and all of these had inv16q. One of these patients had a WBC count >100,000/μL. Eight patients had t(8,21). The median age for all favorable patients was 36 years.

Seven patients (median age 46) had poor-risk features: 1 patient had –7, 1 had –5, 1 patient had complex abnormalities including –7, 3 patients had both –7 and –5, and 1 patient had an abnormal 7q+.

Eighty three patients were classified as intermediate risk. Fifty-four patients had normal cytogenetics, 3 patients had 11q23 abnormalities including 2 patients with t(9,11), 4 patients had +8, 8 patients had miscellaneous abnormalities, and cytogenetics assays were not performed in 14 patients. The intermediate-risk patients included 3 patients with FAB M6 and 2 with FAB M0.

Step 1: Consolidation Chemotherapy

Consolidation chemotherapy was generally well tolerated. Hematologic toxicity was as expected, with a median of 13 days with ANC <500/μL (Table 2). Patients required a median of 4 (range 0-19) units of RBCs and 6 (range 1-34) platelet transfusions. There was little nonhematologic toxicity, with median 0 (range 0-22) days of parenteral nutrition and 0 (range 0-24) days of narcotic agents (Table 3). Fourteen patients (11%) required more than 14 days of parenteral nutrition, and 14 patients received more than 14 days of parenteral narcotics. The median number of days with mucositis ≥grade 2 was 0 (range 0-10), but 4 patients had mucositis ≥grade 2 lasting more than 7 days. No patient had significant skin toxicity. Two patients experienced transient central nervous system neurotoxicity related to HDAC, but recovered completely. There was little hepatotoxicity, with a median bilirubin of 1.0 mg/dL (range 0.5-6.6). Seven patients had a peak bilirubin >3 mg/dL, and the highest bilirubin was 6.6 mg/dL. The 1 treatment-related death was due to sepsis. Ten patients suffered relapse after completing consolidation and before transplantation.

Table 2. *Hematologic Recovery**

	Median Values (Range)	
	Step 1	Step 2
ANC/μL >100	20 (15-28)	+8 (5-15)
>500	21 (17-29)	+9 (7-15)
>1000	21 (17-32)	+9 (7-15)
Days ANC <500/μL	13 (7-27)	5 (3-14)
Platelets / μL >20,000	24 (16-27)	+13 (0-359)
>50,000	28 (18-72)	+19 (8-400 +)
>100,000	35 (18-400 +)	+28 (9-400 +)
Platelet Tx	6 (1-34)	3 (0-100)
RBC units	4 (0-19)	3 (0-20)

**ANC indicates absolute neutrophil count; RBC, red blood cell; Tx, transplantation.*

Table 3. *Nonhematologic Toxicity**

	Median Values (Range)	
	Step 1	Step 2
Days on TPN	0 (0-2)	6 (0-34)
Days on narcotic agents	0 (0-2)	7 (0-27)
Hospital discharge	25 (18-73)	+15 (9-59)
Peak bilirubin (mg/dL)	1.0 (0.5-6.6)	0.9 (0.4-3.6)

**TPN indicates total parenteral nutrition.*

Stem Cell Collection

The median day to first stem cell collection was day 25 (range 18-40) of treatment (Table 4). Patients underwent a median of 3 (range 1-11) collections. However, the target for stem cell collection evolved over time as institutions developed the capacity to measure $CD34^+$ cells. We initially set a very high $CD34^+$ target of 10×10^6/kg. This decision was based on previous ABMT data that demonstrated that engraftment in AML patients was slower than that in patients with other diseases. As we developed more experience with this regimen, the $CD34^+$ cell dose target was reduced to 5×10^6/kg.

If the stem cell collection results are analyzed based on a $CD34^+$ target cell dose of 5×10^6/kg, 57% (ie, 55/96 for whom $CD34^+$ data are available) achieved this goal in 1 collection. The mean number of collections to reach the target was 1.9 (range 1-9); collections were obtained from 89% of patients in ≤3 days, and only 2 patients required >5 days.

Patients with successful collections numbered 126 of 127. One patient who failed to mobilize during the period of sepsis subsequently had stem cells mobilized with G-CSF alone and then proceeded to transplantation.

Step 2: Autologous Stem Cell Transplantation

Of 128 patients, 117 (91%) proceeded to transplantation. No patient was precluded from proceeding to transplantation because of toxicity.

Engraftment after stem cell infusion was rapid, with ANC >500 by day +9 and with no patients reaching this landmark later than day +15 (Table 2). Median number of days spent with ANC <500 was 5 (range 3-14). Platelets recovered to >20,000/μL by day +13. Only 12 patients required more than 30 days to reach this landmark, and only 2 patients required more than 100 days. One of these patients never engrafted platelets and died of sepsis on day +359, probably because of his continued use of an indwelling catheter. The median number of transfusions required was 3 units of RBCs (range 0-20, mean 3.6) and 3 platelet transfusions (range 0-100, mean 5.2). No patient was infused with backup pelvic bone marrow.

The incidence of nonhematologic toxicity of the regimen was very acceptable (Table 3). Median number of days of parenteral nutrition were 6 (range 0-34), and median days of narcotic analgesia 7 (range 0-27). Some outliers included 8 patients (7%) receiving more than 3 weeks of parenteral nutrition and 2 patients receiving more than 3 weeks of narcotic agents. Median number of days with mucositis ≥grade 2 was 6 (range 0-16), and only 1 patient had this degree of mucositis for longer than 14 days. Skin toxicity was minimal with median 0 (range 0-16) days of grade 2 toxicity; only 1 patient had more than 14 days of grade 2 toxicity. No patient had more than 2 days of grade 3 skin toxicity.

There was little hepatotoxicity, with median peak bilirubin of 0.9 mg/dL (range 0.4-3.6). Patients were discharged from the hospital by median day +15 (range 9-59). Only 6 patients were hospitalized longer than 30 days and only 1 patient longer than 40 days after stem cell infusion.

There were 2 treatment-related deaths. One was an iatrogenic death related to perforation of the duodenum during endoscopy, with resulting acute respiratory distress syndrome. The other patient, who retained a central catheter (mentioned above) because of failure to engraft platelets, died of sepsis 1 year after transplantation.

Treatment Outcome

A total of 128 patients began the study therapy (Table 5). During consolidation chemotherapy, there was 1 death followed by 10 early relapses. One hundred seventeen patients proceeded to transplantation. During transplantation, 2 treatment-related deaths occurred, and 35 relapses occurred after transplantation. Median time to relapse was 9.0 months (range 5.5-35), and median time to relapse after transplantation was 7.0 months (range 3.0-32.5) for transplanted patients. With median follow-up of 30 months (range 2-66), 5-year DFS is 55% (95% confidence interval 45%-65%) (Figure 1). There was a nonsignificant trend toward improved outcome for patients aged <40 compared with those ≥40, with DFS 61% ± 7% versus 49% ± 7%, respectively. The small group of patients aged >60 tolerated therapy well, with 3 of 5 remaining in remission (relapse in 1 patient with FAB M6 and normal cytogenetics profile and in 1 patient with poor-risk cytogenetics). There was also a nonsignificant trend toward improved outcome for those who received HDAC induction compared with those who received standard-dose induction therapy (DFS 66% versus 50%).

For 38 favorable-risk patients, overall 5-year DFS is 73% (range 58%-88%) (Figure 2). Five-year DFS for the 22 patients with FAB M3 is 71% and is not significantly different for those with WBC counts above or below 5000/μL (71% versus 73%). However, both M3 patients with WBC counts >100,000/μL suffered relapses. Those 8 FAB M3 patients who received ATRA-containing induction therapy

Table 4. *Stem Cell Collection**

	Median Values (Range)
Start day	25 (18-40)
Collection (n)	3 (1-11)
Collection (n) to $CD34^+$ >5 ($\times 10^6$/kg)	1 (1-9)
MNC ($\times 10^8$/kg)	11 (0.5-57)
$CD34^+$ ($\times 10^6$/kg)	14.6 (1.8-230)
CFU-GM ($\times 10^4$/kg)	193 (1.5-2100)

**CFU-GM indicates colony-forming unit granulocyte-macrophage; MNC, mononuclear leukocytes.*

Table 5. *Outcome*

	All	Favorable	Intermediate	Poor
Step 1	128	38	83	7
Death	1	0	1	0
Early relapse	10	1	5	4
Step 2	117	37	77	3
Death	2	1	1	0
Relapse	35	7	25	3
Continuing remission	80	29	51	0

had a trend toward improved outcome, with DFS 88% versus 64%. The 5-year DFS for 8 patients with FAB M4Eo is 83%, with 1 death and no relapses. The 5-year DFS for 8 patients with t(8,21) is 69%, with 2 relapses. All 7 patients with poor-risk cytogenetics relapsed either before or within 1 year of transplantation.

For the 83 patients with intermediate-risk disease, overall 5-year DFS is 51% (range 38%-64%). No significant difference in outcome exists between patients with normal cytogenetics (DFS 48%) and those whose cytogenetics were not obtained (DFS 62%). There is no difference in outcome for intermediate-risk patients based on induction chemotherapy received. Of the 57 patients who received HDAC induction, 20 suffered relapse and DFS is 52%. Of the 26 patients who received standard induction, 13 suffered relapse and DFS is 48%. Among the intermediate-risk patients, there is a trend toward better outcome in those under age 40, with DFS 61% versus 40% for those over age 40. Two of 4 patients with +8 and 3 of 3 patients with 11q23 abnormalities remain well. One of 3 patients with FAB M6 and 0 of 2 patients with FAB M0 remain in remission. High WBC count by itself does not appear to be an adverse prognostic factor. Of the 12 intermediate-risk patients with WBC ≥100,000/μL, 1 death and 2 relapses occurred with 5-year DFS of 72%.

DISCUSSION

For any treatment strategy to be successful, patients should be able to receive all of the intended treatment. By this criterion, our 2-step approach to autologous stem cell transplantation for AML is highly effective, with 91% of the patients able to receive the intended therapy. Of the 128 patients, only 1 patient died during step 1, and no patient was prevented from proceeding to transplantation because of toxicity. Ten early relapses occurred; such relapses will be unavoidable if patients are enrolled in the study rapidly after achieving remission. Four of these 10 early relapses were in patients with high-risk cytogenetics. Of favorable-risk and intermediate-risk patients, 94% received the full intended therapy. Intensive-induction chemotherapy (HDAC plus daunorubicin) in the majority of these patients possibly contributed to their ability to remain in remission long enough to receive the planned treatment.

This consolidation-chemotherapy regimen of HDAC plus etoposide appears to be highly effective in mobilizing peripheral blood stem cells. Only 1 of 127 patients had an inadequate stem cell collection, and this appeared to be related to ongoing sepsis. The median number of collections to reach a $CD34^+$ cell dose target $\geq 5 \times 10^6$/kg is 1, with 93% reaching this target in ≤3 days. Engraftment of

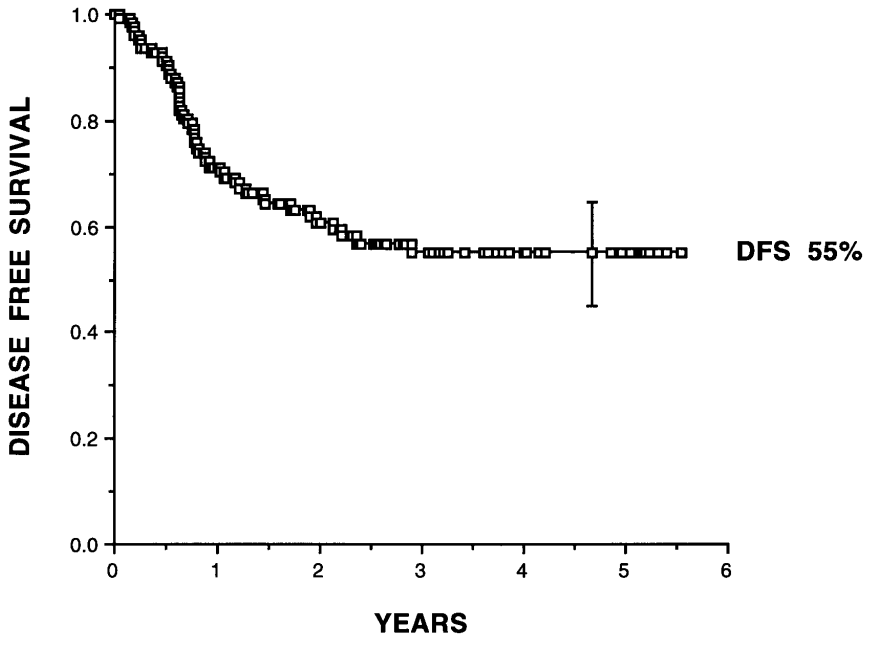

Figure 1. *Disease-free survival (DFS) of all 128 patients entered in study. Error bars indicate 95% confidence intervals.*

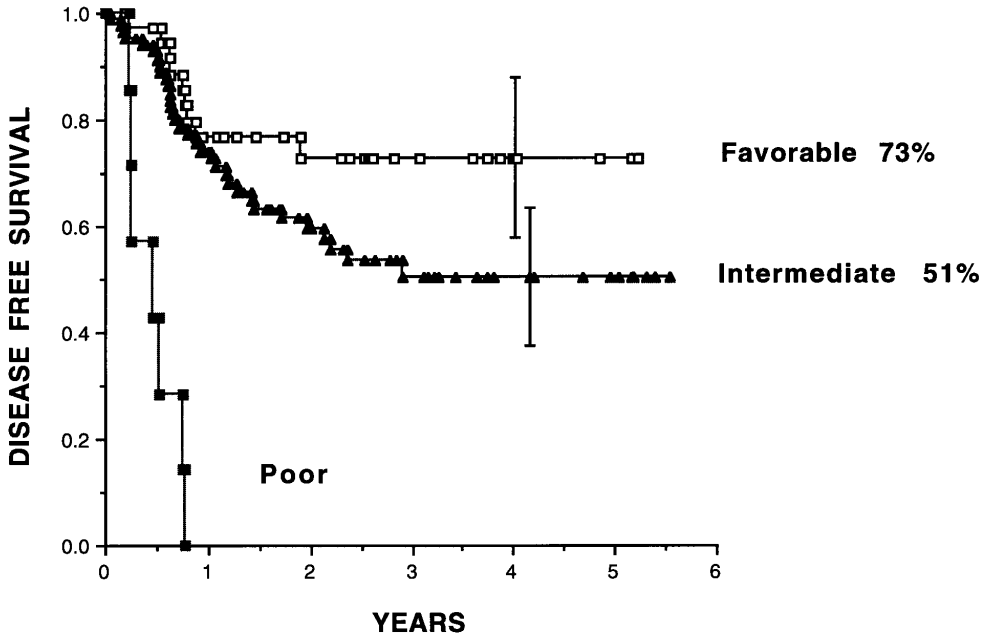

Figure 2. *Disease-free survival of all patients entered in study according to cytogenetic risk group: 38 favorable, 83 intermediate, and 7 poor. Error bars indicate 95% confidence intervals.*

these peripheral blood stem cells was extremely rapid. Neutrophils >500 were reached by day +9, and no patients engrafted neutrophils later than +15. The total number of days spent neutropenic (ANC <500) was 5. This short duration of neutropenia likely contributed to the low treatment-related mortality and low morbidity. Platelets recovered to >20,000/μL by day +13, and only 2 patients reached this point later than day +100. Transfusion requirements were low, with patients requiring a median of 3 units of RBCs and 3 platelet transfusions.

The toxicity level of the transplantation step was very acceptable and appeared markedly different from our experience with the identical regimen when 4HC-purged bone marrow was used. The median number of days requiring parenteral nutrition fell from 38 to 6, and the median number of days requiring parenteral narcotics fell from 19 to 7. Rapid neutrophil recovery likely contributed to reduced gastrointestinal toxicity. Less easy to understand is the marked decrease in skin toxicity, which was one of the serious problems with our prior regimen. Previously, 20% of patients had severe skin toxicity lasting longer than 14 days, whereas no patient in the current study experienced this level of toxicity. In terms of resource utilization, the use (median during both treatment steps) of 7 units of RBCs and 9 platelet transfusions is less than the 11 units of blood and 23 platelet transfusions required during ABMT supported by 4HC-purged bone marrow. The total number of days of hospitalization was similar, 48 days (2-step stem cell) versus 49 days (purged-bone marrow).

Improved treatments are needed for patients with AML. HDAC has been demonstrated to be superior to standard-dose ara-C, but for most patients with intermediate-risk disease, DFS is only 30% [5-7]. No additional agents are currently available, and there are no modifications of HDAC regimens that appear to produce superior results. On the other hand, ablative therapy with allogeneic BMT has been clearly demonstrated to reduce relapse rates in patients with first-remission AML [8]. Some of the effectiveness of allogeneic BMT is related to the graft-versus-leukemia effect, but the preparative regimen also appears to have a role. More intensive preparative regimens have been shown to significantly reduce the relapse rate, suggesting that the regimen is important [9]. T-cell depletion does not markedly increase the relapse rate in AML patients (in contrast to that in CML patients), and, recently, excellent results have been obtained with T-cell-depleted allogeneic BMT. This finding suggests that the ablative regimen is the critical factor in reducing relapse [10].

Autologous transplantation has been pursued as a postremission therapy for AML based on the hope that the ablative regimen would reduce relapse and lead to improved outcomes. However, the role of ABMT in the management of first-remission AML remains undefined at this time. Two large phase III studies have been reported with somewhat conflicting results [5,11]. A large European study [11] demonstrated an improvement in DFS from ABMT, whereas an American study [5] did not. However, both studies were plagued by the fact that a low percentage of patients received the intended therapy. In the European study, only 68% of remission patients reached the point of randomization/allocation, and, of patients randomized to receive ABMT, only 74% did so. In the American study, a similar pattern was observed, with only 67% of remission patients reaching randomization/allocation and with only 54% of patients randomized to ABMT receiving the transplant.

It is difficult to know all the factors that led to such a high dropout rate in the ABMT arm, but lack of physician

enthusiasm was a possible contributing factor. The influence on ultimate outcome of the intensity of chemotherapy given before ABMT is unknown, but the absence of any intermediate- or high-dose ara-C in the American study may have contributed to the suboptimal result in the autograft arm.

It is not the purpose of the current study to compare outcomes to other forms of therapy, but several observations can be made. For first-remission patients with favorable cytogenetic subtypes of AML, several treatment options can result in >50% likelihood of prolonged DFS. Patients with FAB M3 and WBC counts <10,000/μL have 4-year DFS >70%, whereas those with higher WBC counts do more poorly (DFS <40%) [12-14]. Patients with t(8,21) have prolonged DFS of 50% to 70% [7,15-17], and those with inv16q have DFS of 40% to 60% [7,15-17]. Although ABMT may not be necessary as a first treatment option in this favorable group of patients, the outcome appears to be at least as good, with no significant increase in treatment mortality. It should be noted that most of the FAB M3 patients in this trial never received ATRA and that favorable outcomes were not limited to those with low WBC count. Further understanding of prognostic factors in patients with promyelocytic leukemia may help us to better select those patients who will fare best with ablative therapy as the initial approach. Our patients with FAB M4Eo fared very well, with no relapses in 8 patients, suggesting that initial ABMT may be a valid approach.

Patients with poor-risk cytogenetics have fared poorly with most forms of therapy. Allogeneic transplantation appears to be the treatment of choice for those younger patients with a matched sibling donor, but even with these the cure rate is only 25% [18-21]. None of the 7 patients with –7/–5 in this trial remained in remission, and improved approaches are needed.

For the large group of patients with intermediate-risk AML, the projected DFS of 51% compares favorably with the 30% DFS reported after HDAC postremission therapy. Neither WBC count ≥100,000/μL nor age ≥40 years was detrimental to this outcome.

Autologous stem cell transplantation remains a promising therapy in the management of AML [22-27]. The 2-step approach outlined here allows a high percentage of patients to remain in remission, yield adequate doses of stem cells that can engraft rapidly, and proceed to transplantation. In the setting of rapid engraftment, patients can tolerate very intensive preparative regimens with little mortality and very acceptable morbidity. This reduction in toxicity has allowed us to safely extend age eligibility into the seventh decade. Recent data suggest that posttransplantation immunotherapy may be able to further reduce relapse rates and that additional studies are warranted [28].

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