Allogeneic Bone Marrow Transplantation for High-Risk Acute Lymphoblastic Leukemia During First Complete Remission


Fifty-three patients with high-risk acute lymphoblastic leukemia (ALL) under age 50 with a histocompatible sibling donor received high-dose radio-chemotherapy followed by allogeneic bone marrow transplantation (BMT). The high-risk factors used to identify the patients were: white blood cell count at initial presentation, cytogenetic abnormalities, age, extramedullary leukemic infiltration, and time from initial therapy to complete remission. Patients with one or more of the above risk factors who received BMT have a disease-free survival of 61% with a median follow-up of 66 months (range 11 months to 10.6 years), and an actuarial relapse rate of 10%. This study demonstrates that patients with high-risk ALL achieve a significant disease-free survival and cure rate with the use of allogeneic fully matched sibling BMT. However, a properly designed prospective study comparing the outcome of BMT with the best currently available chemotherapy data is required to define the ultimate role of BMT in this group of patients.

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RECENT REPORTS of chemotherapy for patients with acute lymphoblastic leukemia (ALL) describe a high complete remission (CR) rate of 75% to 90%, with approximately one third of the patients remaining in continued remission at 5 to 10 years from diagnosis. A comparison of these results from different institutions and multicenter groups is difficult due to differences in classification criteria or in identification of high-risk prognostic factors. Some of the risk factors include: Age over 30 years, a white blood cell (WBC) count at presentation in excess of 25,000/μL, extramedullary disease, the chromosomal translocation t(4;11), t(8;14) or t(9;22), null cell phenotype, and the requirement for induction chemotherapy beyond 4 weeks to achieve a CR. If a patient presents without any of these adverse factors, the probability of continued remission at 5 years (which is equivalent to cure) is 37% to 72%. However, none of the previously listed poor-prognostic variables places the patient in an unfavorable or high-risk group, with an overall probability of continued remission at 5 years of only 28%. Three other studies suggested an even lower probability of continued remission, namely 18% to 22%.

Patients who have high-risk or unfavorable ALL may benefit from high-dose radio-chemotherapy followed by allogeneic bone marrow transplantation (BMT) if they are treated early in the course of their disease. This is a report on 53 high-risk patients in whom BMT was performed while they were in first CR of ALL.

PATIENTS AND METHODS

Patients. Between May of 1979 and June of 1990, we accepted 53 patients with high-risk ALL for BMT during their first CR. Forty-four patients received transplants at the City of Hope National Medical Center (Duarte, CA) and nine patients at Stanford University Medical Center (Stanford, CA). Our criteria for high-risk patients included high WBC count at presentation (≥25,000/μL), certain cytogenetic abnormalities [t(4;11), t(8;14) and t(9;22)], age ≥30 years, extramedullary leukemia, and more than 4 weeks to achieve a remission. Patient characteristics are described in Table 1. Two patients were infants and one other child was 5 years old, whereas the other 50 patients ranged between 16 and 45 years of age (median age 24 years). Sixteen patients were age 30 or older. There were 19 females and 34 males. Immunologic phenotyping studies were performed in 45 patients with the following results: 21 patients were cALLA positive, 15 patients had T-cell ALL, 6 patients had null phenotype, and 3 patients had B-cell ALL. The WBC count at the time of presentation ranged from 1,400 to 637,000/μL and 29 patients had initial counts in excess of 25,000/μL. Twenty-six patients had cytogenetic studies performed as part of their diagnostic evaluation. Eight patients showed one of the characteristic translocations associated with ALL, namely t(4;11), t(9;22), or t(8;14), and four other patients had other clonal abnormalities such as t(7;12), t(3;12), t(2;15), or inv-1. Two patients had extramedullary disease, one with testicular and one with meningeal involvement.

Because the majority of the patients were referred to us for BMT from other hospitals, they had not been treated with a uniform remission induction regimen. However, with the exception of five patients, all had received a combination of vincristine, prednisone, daunomycin, and L-asparaginase. Eighteen patients required more than 4 weeks of therapy to enter CR.

Forty-seven patients (89%) were within the first 120 days after entering remission when preparation for BMT was started, and five patients (9%) were between 5 and 7 months after entering remission. The average time from diagnosis to BMT was 5.5 months. One patient was transplanted 19 months after first CR. This patient had been sent for consultation as a patient in early relapse. Review of the bone marrow showed continued remission; however, because of the presence of various high-risk factors at the time of initial disease presentation, we offered to proceed with BMT.

Preparative regimen and supportive care. Three successive preparatory regimens were used. The first 17 patients received cytosine-arabinoside (5 mg/kg) on day −8 and day −3, cyclophosphamide (100 mg/kg) on day −5, and single-dose (1,000 cGy) total dose of irradiation (10 Gy). The next 24 patients received cyclophosphamide (50 mg/kg) on day −6 and day −3, daunomycin (50 mg/m²) on day −4 and −3, and L-asparaginase (500 units/kg) on day −4 to −3. The last 8 patients received total body irradiation (10 Gy) and cyclophosphamide (50 mg/m²) on day −4, daunomycin (50 mg/m²) on day −3, and L-asparaginase (500 units/kg) on day −2. Fifty-three of 54 patients (98%) achieved CR after preparative chemotherapy. One patient receiving cyclophosphamide, daunomycin, and L-asparaginase died from sepsis and multiorgan failure.

Support. Seventy patients received autologous bone marrow transplantation. Twenty-nine patients received allogeneic bone marrow transplantation. Of the latter group, 10 patients received fully matched sibling BMT and 19 patients received mismatched BMT.

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body irradiation (TBI) on day −1, followed by marrow grafting on day 0.8 The next 17 patients were prepared with 1,320 cGy of fractionated TBI including partial lung shielding9 delivered between day −7 through day −4 and cyclophosphamide (100 mg/kg) on day −3. The subsequent 19 patients received the same TBI regimen followed by VP-16 (60 mg/kg) on day −3.10 The marrow inoculum for all patients was obtained from histocompatible sibling donors. Supportive care measures administered after BMT were identical to those reported previously.2

Graft-versus-host disease (GVHD) prophylaxis. A combination of methotrexate and prednisone was used to prevent GVHD for the first group of patients.2 The next cohort participated in a prospective randomized trial and received either methotrexate/prednisone or cyclosporine/prednisone.11 The subsequent group participated in a study randomizing between cyclosporine/prednisone versus cyclosporine/prednisone/methotrexate (trial still ongoing).

Informed consent. All clinical protocols were reviewed and approved by the Institutional Review Board of City of Hope National Medical Center and the Administrative Panel on Human Subjects in Medical Research at Stanford University Medical Center. The risks and benefits for each patient were explained in detail in at least two outpatient visits and again on the date of admission. Written consent was then obtained from the patient and, in the case of minors, from the parents or guardian. Risks and benefits were also discussed with the potential donors before initiation of therapy.

Statistical analysis. Statistical analysis to test for predictors of prolonged survival was performed using the Cox proportional hazard regression model.14 The method of Kaplan and Meier was used to calculate disease-free survival and the actuarial relapse.15

**RESULTS**

Survival. At the date of evaluation (May 15, 1991), 34 patients were alive and in continued CR (Fig 1). The actuarial disease-free survival was 61%. Follow-up of the surviving patients ranged from 11 months to over 10.6 years, with a median observation time of 5.5 years. Seven patients had a follow-up period of less than 2 years after BMT. The estimated 3-year survival rate is 67% (confidence interval [c.i.] 54% to 80%). The 5-year survival rate is estimated to be 61% (c.i. 47% to 75%). One patient (unique patient number 216) who had relapsed 530 days after BMT was reintroduced into another CR and received a second BMT after marrow ablation with a combination of high-dose busulfan (16 mg/kg) and high-dose VP-16 (60 mg/kg, infused on day −3). However, this patient died of another recurrence of his disease, 449 days after his second marrow transplant (979 days after the initial transplant procedure).

Causes for failure. Nineteen patients died during the observation period (Table 2). The most common cause of death was relapse.15 Other causes included death from infection (7 patients), intercurrent disease (3 patients), and GVHD (1 patient). Nine patients died before their CR could be confirmed clinically. Eight patients were relapse-free without BMT (6 patients) or died of sepsis related to BMT (2 patients). Two patients died of GVHD-related complications.

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**Table 1. Patient Characteristics**

<table>
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<tr>
<th>Risk factors</th>
<th>Alive and Free of Disease</th>
<th>P Value*</th>
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**Abbreviations:** CR, complete remission; Ara C, cytosine arabinoside; Cy, cyclophosphamide; TBI, total body irradiation; FTBI, fractionated TBI; Mtx, methotrexate; Pred, prednisone; Csa, cyclosporine.

*Cox multivariate stepwise proportional hazard analysis: age and time from initial therapy to CR are continuous variables.

†Eight weeks to achieve CR.

‡t(1;11), t(9;22), or t(8;14).

§t(7;12), t(3;12), t(2;15), or inv-1.

[]Four patients crossed over to Csa/Pred for GVHD therapy after failing Mtx/Pred prophylaxis.

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**Fig 1. Actuarial disease-free survival and relapse for 53 patients with high-risk ALL in first CR for whom BMT was used.**
death was interstitial pneumonia, in six patients. Four patients relapsed between day +87 and +530 and the actuarial relapse rate is 10% (c.i. 1% to 19%), as illustrated in Fig 1. Six patients developed grade II through IV GVHD, which was the cause of death in two. Two patients died of complications related to chronic GVHD. Other causes for failure included sepsis, fungal disease, hepatic failure, and encephalopathy.

Prognostic factors. A multivariate stepwise Cox proportional hazard analysis of patient characteristics was performed to determine indicators of prolonged disease-free survival. Continuous independent variables in the model were age and time from initial CR. Categorical variables in the model were sex, immunophenotype, WBC count, cytogenetics, and number of risk factors (Table 1). Factors associated with prolonged disease-free survival were male sex ($P = .016$), younger age ($P = .003$), and shorter time to CR ($P = .014$).

**DISCUSSION**

This study focuses on the results obtained in 53 patients with high-risk ALL who have been treated with bone marrow ablation followed by allogeneic BMT during first CR. Our selection criteria for BMT, namely high WBC count ($\geq 25,000/\mu$L), certain cytogenetic abnormalities, age ($\geq 30$), extramedullary leukemia, and time to achieve a CR ($> 4$ weeks) have remained unchanged throughout the study. Eighty-nine percent of the patients were transplanted within the first 4 months after achieving a CR. This treatment modality leads to substantially prolonged disease-free survival and cure. Only seven patients in this series have not yet been observed longer than 2 years.

During this trial period we also accepted nine adult patients with ALL in first CR who did not fulfill any of the defined high-risk criteria. At the time of this evaluation, seven of them are alive and in continued CR for 11 months to over 10 years. One patient died of interstitial pneumonia and one of recurrent ALL. These nine patients are not included in the analysis reported here.

Nineteen patients died during the course of this study. Fifteen patients died of BMT-related complications, most frequently due to supervening interstitial pneumonia (6 of 15). Four patients have relapsed, for an actuarial relapse rate of 10%. Three of these four patients had a WBC count exceeding 100,000/$\mu$L at initial presentation.

Three successive myeloablative immunosuppressive combinations have been used in this study. The latest regimen consists of fractionated TBI and high-dose VP-16. The rationale to proceed with this new regimen was based primarily on data in patients with advanced leukemias for whom the relapse rate was found to be 32%. This actuarial relapse rate can be considered to be relatively low in comparison with other preparatory regimens, and has been subsequently confirmed by a separate study. Because the preparatory regimens used in the trial reported here have been used in a sequential fashion, it is difficult to compare their relative efficacy and merits. There were only four cases (11%) of fatal interstitial pneumonitis with the more recent use of fractionated TBI with cyclophosphamide or VP-16 ($n = 36$) compared with 4 (23%) of 17 patients who had been treated earlier with single-dose TBI ($P \neq$ not significant). Both cases of fatal sepsis and the single case of fatal leukoencephalopathy were encountered in the group of 17 patients who received cytosine-arabinoside, cyclophosphamide, and single-fraction TBI. Conversely, only a single patient relapsed who received cytosine-arabinoside, cyclophosphamide, and single-fraction TBI compared with three patients who received fractionated TBI/cyclophosphamide. No relapses have been observed in patients receiving the FTBI/VP-16 regimen, although the follow-up is relatively short for this last group of patients (median 21 months).

While no doubt exists as to the contribution of these risk factors to poor prognosis of ALL, their individual potency as high-risk predictors remains uncertain. As shown in Table 1, approximately two thirds of the patients had at least one risk factor and the remaining patients had two or more high-risk features at presentation. Of this group, there were seven adults whose only risk factor was age $\geq 30$ years. Abnormal cytogenetics were included as high risk only if they were previously associated with a poor outcome. Eighteen patients achieved a CR after 4 weeks. Although the time to achieve a CR may be related to intensity of the induction therapy (and therefore more applicable to current intensive induction therapies), all but five patients received anthracyclines as part of the induction therapy.

The analysis of risk factors as described in Table 1 shows three patient characteristics that were associated with a higher mortality: female sex, older age, and a longer time period to achieve CR. These characteristics reflect the natural history of the underlying disease when treated with conventional chemotherapy, where older age and a prolonged period to achieve a remission is associated with decreased disease-free survival. It is unclear why female patients did not fare as well as male patients.

The optimum timing of marrow transplantation for patients with ALL remains an important question. For patients in second remission, prospective studies have shown that marrow transplantation during second CR results in 27% to 63%, with the more favorable results reported for children. Results of marrow transplantation for adults with ALL in first CR have also been encouraging. This study, which expands on our previous experience, and a recent review of the results from several transplant centers, suggests that the European Bone Marrow Transplant Group, and the International Bone Marrow Transplant Registry, suggest a 40% to 71% disease-free survival from 2 to 10 years.
years for patients transplanted in first CR. The vast majority of these patients are likely to be cured of their disease. An even more impressive result for BMT was reported for a group of 32 children with poor-prognosis ALL. The actuarial disease-free survival with a median follow-up of 30 months was 84% at 5 years with an actuarial relapse rate of 3.5%. 30

Our study suggests that marrow transplantation should be considered during first CR for the majority of adult patients under the age of 50 years with high-risk ALL who have a histocompatible sibling donor. These high-risk patients can expect to enjoy an actuarial disease-free survival rate of 61% with a relatively low actuarial relapse rate of 10%. Patients presenting with characteristics as shown in Table 1 have a poor outcome when treated with intensive modern-day chemotherapy, with disease-free survival of only 18% to 28%.34 For them, BMT offers a higher chance of disease-free survival and cure. Moreover, the results with marrow transplantation are likely to improve further as some of the causes for transplant-related morbidity and mortality (ie, GVHD and cytomegalovirus-associated interstitial pneumonia) are now more effectively prevented or treated.

Ideally, BMT may be reserved for patients with high-risk ALL after recurrence of their disease and attainment of a second remission. However, patients would need to be reinduced into a complete second remission, retain or regain a good performance status, and then require having immediate acceptance at a BMT center. Unfortunately, many patients who relapse will die of their illness or from chemotherapy-associated complications. Such complications from reinduction chemotherapy are likely to affect biologic reserves and can impact unfavorably on the final outcome. Because of serious side effects encountered during reinduction chemotherapy, a sizable fraction of these patients will never be transplanted, and those who do are likely to start off at a disadvantage.

The data presented here compare favorably with the results of chemotherapy studies in patients with high-risk ALL. The ultimate role of BMT as a treatment modality in first CR of ALL remains to be determined. This determination will require a prospective trial in which the outcome of BMT in first CR is compared with that of the "best" chemotherapy and BMT during second remission, with all patients registered at the time of initial presentation.

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