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# Prognostic Factors for Outcomes of Patients with Refractory or Relapsed Acute Myelogenous Leukemia or Myelodysplastic Syndromes Undergoing Allogeneic Progenitor Cell Transplantation

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## ABSTRACT

**Allogeneic progenitor cell transplantation is the only curative therapy for patients with refractory acute myelogenous leukemia or myelodysplastic syndromes. To identify prognostic factors in these patients, we performed a retrospective analysis of transplantation outcomes. Patients were selected if they had undergone an allogeneic transplantation between January 1988 and January 2002 and were not in remission or first untreated relapse at the time of transplantation. A total of 135 patients were identified. The median age was 49.5 years (range, 19-75 years). At the time of transplantation, 39.3% of patients had not responded to induction therapy, 37% had not responded to first salvage therapy, and 23.7% were beyond first salvage. Forty-one patients (30%) received unrelated donor progenitor cells. Eighty patients (59%) received either a reduced-intensity or a nonmyeloablative regimen. A total of 104 (77%) of 135 patients died, with a median survival time of 4.9 months (95% confidence interval, 3.9-6.6 months). The median progression-free survival was 2.9 months (95% confidence interval, 2.5-4.2 months). A Cox regression analysis showed that Karnofsky performance status, peripheral blood blasts, and tacrolimus exposure during the first 11 days after transplantation were predictive of survival. These data support the use of allogeneic transplantation for patients with relapsed or refractory acute myelogenous leukemia/myelodysplastic syndromes and suggest that optimal immune suppression early after transplantation is essential for long-term survival even in patients with refractory myeloid leukemias.**

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## KEY WORDS

Allogeneic progenitor cell transplantation • Refractory acute myelogenous leukemia • Myelodysplastic syndrome • Prognostic factors

## INTRODUCTION

Advances in chemotherapy have improved outcomes for patients with acute myeloid leukemia (AML) or myelodysplastic syndromes (MDS) [1,2]. Despite increases in complete remission rates, however, most patients with diploid or poor-risk cytogenetics will relapse after primary therapy [1,2]. Although response rates with salvage therapy in patients with AML/MDS after failure of primary chemotherapy have been discouraging, allogeneic transplantation has generally been associated with high complete remission rates and the potential to achieve long-term disease control [3-8]. However, relapse after transplantation remains the most important cause of treatment failure in this setting and is generally associated

with poor survival [5-11]. The incidence of disease recurrence after allogeneic transplantation has not changed with time [5,6]. Modifications of the preparative regimen by using various combinations of chemotherapy and radiotherapy have failed to reduce the risk of relapse without an increase in nonrelapse mortality [12].

The most important predictor of leukemia relapse after allogeneic transplantation is disease status at the time of transplantation. Relapse rates are 2 to 3 times higher in patients not in remission at the time of transplantation as compared with rates in those in remission [13,14]. Among patients not in remission, patients with primary induction failure tend to have better outcomes than those whose disease has relapsed and failed to respond to reinduction therapy [7,8,14-16].

Notwithstanding, long-term disease control is possible after allogeneic transplantation for refractory or relapsed AML/MDS. It is likely that the risk of relapse differs according to disease- and patient-specific characteristics. It is also possible that the degree of immune suppression, as defined by the serum levels of either cyclosporine or tacrolimus, may also affect transplantation outcomes in this patient population, because patients with lower levels may experience a more potent graft-versus-leukemia effect, and randomized trials have shown lower relapse rates in patients who receive lower doses of cyclosporine [13,17,18]. To identify prognostic factors in patients with relapsed or refractory leukemia and to define the predictive role of the levels of immune suppression as determined by tacrolimus blood levels, we performed a retrospective analysis of transplantation outcomes of patients with AML/MDS undergoing allogeneic transplantation who were not in remission at the time of transplantation and were beyond first salvage therapy. Herein are the results of this analysis.

## PATIENTS AND METHODS

The Department of Blood and Marrow Transplantation at M.D. Anderson Cancer Center maintains a prospective database of all patients who have undergone a progenitor cell transplantation in the institution. The database incorporates a variety of core pretransplantation and posttransplantation variables used for both prospective and retrospective analysis. Patients were selected for this analysis if they fulfilled all of the following criteria: (1) were diagnosed with AML or MDS; (2) underwent an allogeneic transplantation from a sibling-matched, a 1 antigen–related mismatched, or a matched unrelated donor at any time between January 1988 and January 2002 with 1 of the following conditioning regimens: fludarabine/melphalan, fludarabine/idarubicin/cytarabine, thiotepa/busulfan/cyclophosphamide, busulfan/cyclophosphamide, or cyclophosphamide/etoposide/total body irradiation; and (3) were not in remission or first untreated relapse at the time of transplantation. Remission was defined as morphologically normal bone marrow, without cytogenetic evidence of leukemia, and a morphologically normal peripheral blood smear with recovery of peripheral blood hematologic values, including a platelet count $>100 \times 10^9$/L and an absolute neutrophil count $>1.5 \times 10^9$/L.

All patients were treated on institutional review board–approved protocols that were active at the time. Patients and donors signed written informed consent, and unrelated donor cells were consented and procured under the auspices of the National Marrow Donor Program by following guidelines that were applicable at the time. Approval to perform this retrospective analysis was obtained from the institutional review board according to current institutional guidelines.

Tacrolimus and cyclosporine levels were monitored 2 to 3 times weekly. Trough tacrolimus levels were measured by using an immunoassay (Abbott Pharmaceutical, Irving, TX). The tacrolimus dose was adjusted to maintain trough levels between 5 and 20 ng/dL. In patients receiving cyclosporine, doses were adjusted to maintain levels of 150 to 300 ng/dL as measured by radioimmuoassay for the parent drug. Supportive care and antibacterial, antifungal, and antiviral prophylaxis followed the institutional protocols and guidelines that were active at the time.

Unadjusted survival probabilities were estimated by using the method of Kaplan and Meier [19]. Unadjusted between-group survival time comparisons were made by using the log-rank test [20]. Univariate analyses were performed for a variety of pretransplantation and transplantation variables related to overall survival, event-free survival (EFS), and nonrelapse mortality. The Cox proportional hazards (PH) regression model was used to assess the ability of patient characteristics or treatment-related variables to predict survival [21]. Regression analysis of the survival times was begun by examining a martingale residual plot for each numeric-valued candidate predictor variable, smoothed by using the lowess method of Cleveland [22], and predictive variables were transformed as suggested by these plots. Multivariate Cox models were obtained by first performing a forward selection with a $P$-value cutoff of .05. The most predictive additional variable was allowed to enter the model if its partial $P$ value was $<.05$. Association between discrete variables was assessed by the Fisher exact and generalized exact tests. All computations were performed in Splus by using standard Splus functions [23] and the Splus survival analysis package of Therneau [24].

Tacrolimus exposure during the first 100 days after transplantation was determined by plotting all tacrolimus levels against time to transplantation. The

**Table 1.** *Patient and Treatment Characteristics (N = 135)*

| Variable | n (%) | Median (Range) |
|---|---|---|
| **Sex** | | |
| Female | 58 (43.0) | |
| Male | 77 (57.0) | |
| **Age at BMT (y)** | | 49.5 (19-75) |
| **Diagnosis** | | |
| AML | 93 (68.9) | |
| MDS | 24 (17.8) | |
| MDS/AML | 18 (13.3) | |
| **No. prior therapies** | | 2 (0-9) |
| **Disease status before SCT** | | |
| Primary induction failure | 53 (39.3) | |
| First relapse refractory | 50 (37.0) | |
| >First relapse refractory | 32 (23.7) | |
| **Cytogenetics** | | |
| Good | 4 (3.0) | |
| Intermediate | 63 (46.7) | |
| Bad | 62 (45.9) | |
| Missing | 6 (4.4) | |
| **Zubrod performance status before transplantation** | | |
| 0 | 22 (16.3) | |
| 1 | 98 (72.6) | |
| 2 | 13 (9.6) | |
| Missing | 2 (1.5) | |
| **Stem cell type** | | |
| BM | 69 (51.1) | |
| PBPC | 66 (48.9) | |
| **Donor type** | | |
| Related | 94 (69.6) | |
| Matched unrelated | 41 (30.4) | |
| **Donor sex** | | |
| Female | 64 (47.4) | |
| Male | 71 (52.6) | |
| **Conditioning regimen** | | |
| Fludarabine/melphalan | 43 (31.9) | |
| Fludarabine/idarubicin/cytarabine | 16 (11.9) | |
| Fludarabine/busulfan | 21 (15.6) | |
| Cyclophosphamide/TBI ± others | 7 (5.2) | |
| Busulfan/cyclophosphamide ± others | 48 (35.6) | |
| **Nonablative or reduced-intensity conditioning** | | |
| Yes | 80 (59) | |
| No | 55 (41) | |
| **GVHD prophylaxis** | | |
| Tacrolimus based | 107 (79.3) | |
| Cyclosporine based | 28 (20.7) | |
| **% BM blasts before SCT** | | 23 (0-100) |
| **% PB blasts before SCT** | | 6 (0-99) |
| **Absolute PB blast count before SCT** | | 114 (0-60 670) |
| **Albumin before SCT, g/dL** | | 3.4 (2.3-4.7) |

SCT indicates stem cell transplantation; AML, acute myelogenous leukemia; MDS, myelodysplastic syndrome; TBI, total body irradiation; GVHD, graft-versus-host disease; BM, bone marrow; PB, peripheral blood; BMT, bone marrow transplantation; PBPC, peripheral blood progenitor cells.

area under the curve (AUC) of tacrolimus levels over time was derived by using standard methods. For each of several initial time periods, varying from 1 to 50 days, the AUC formed by tacrolimus levels over a specific time period was used as a surrogate for tacrolimus exposure, and this value was then analyzed as a potential predictor of transplantation outcomes. For the analyses summarized here, a quadratic function of $Z = log(AUC\ of\ tacrolimus\ levels\ for\ the\ first\ 11\ days\ after\ transplantation)$ was used—specifically, $b_1Z + b_2Z^2$, because this provided the best prediction of survival time among all values considered.

## RESULTS

### Patient and Treatment Characteristics

A total of 135 patients were identified who fulfilled our eligibility criteria. Patient and treatment characteristics are summarized in Table 1. In brief, the median age of the patients at the time of transplantation was 49.5 years (range, 19-75 years), the median time to transplantation was 12 months (range, 0.9-54 months), and the median number of prior therapies before transplantation for refractory disease was 2 (range, 0-9). At the time of transplantation, 39.3% of patients had not responded to induction therapy, 37% had not responded to first salvage therapy, and 23.7% were beyond first salvage. Forty-six percent of patients had poor-risk cytogenetic abnormalities, as defined by partial or complete deletion of chromosomes 5 or 7, trisomy 8, abnormalities of chromosome 11, presence of t(9,22), or complex (>3) cytogenetic abnormalities.

Forty-one patients (30%) received unrelated donor progenitor cells. Eighty patients (59%) received either a reduced-intensity or a nonmyeloablative regimen, whereas the remaining 55 patients (41%) received a myeloablative regimen that included either busulfan/cyclophosphamide combinations or total body irradiation. The nonmyeloablative or reduced-intensity conditioning regimens were fludarabine/melphalan, fludarabine/idarubicin/cytarabine, or fludarabine/busulfan combinations. Graft-versus-host disease (GVHD) prophylaxis consisted primarily of tacrolimus/methotrexate (79.3% of patients) and cyclosporine combinations (in the remaining 20.7%).

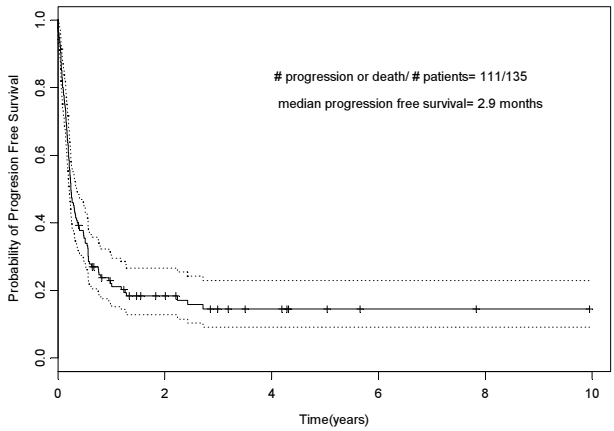


**Figure 1.** Kaplan-Meier curve for survival.

**Table 2.** *Univariate Analysis of Transplantation Outcomes*

| Variable | NRM (% at 180/360 d) | Survival (% at 1/2 y) | Event-Free Survival (% at 1/2 y) |
|---|---|---|---|
| **Age at BMT (y)** | | | |
| <50 | 59/52 | 32/25 | 22/16 |
| ≥50 | 54/54 | 26/22 | 23/21 |
| **Diagnosis** | | | |
| AML | 60/57 | 28/24 | 22/18 |
| MDS | 46/46 | 29/21 | 17/17 |
| MDS/AML | 63/50 | 32/26 | 32/27 |
| **No. prior therapies** | | $P = .03$ | $P = .02$ |
| <2 | 55/55 | 40/34 | 30/30 |
| ≥2 | 60/53 | 24/19 | 19/14 |
| **Disease status before SCT** | | | $P = .05$ |
| Primary induction failure | 62/62 | 36/29 | 26/26 |
| First relapse refractory | 55/45 | 26/19 | 22/17 |
| >First relapse refractory | 53/53 | 20/20 | 16/8 |
| **Cytogenetics** | | $P = .10$ | |
| Good | 38/NA | 25/NA | 25/NA |
| Intermediate | 66/62 | 32/30 | 25/23 |
| Bad | 49/49 | 25/18 | 18/15 |
| **Zubrod performance status before SCT** | $P = .001$ | $P = .0002$ | $P = .001$ |
| 0–1 | 60/56 | 32/26 | 25/21 |
| 2 | NA/NA | 0/NA | NA/NA |
| **Stem cell type** | | | |
| BM | 59/55 | 31/26 | 25/21 |
| PBPC | 56/51 | 26/20 | 19/15 |
| **Donor type** | | | |
| Related | 65/62 | 31/25 | 23/20 |
| Matched unrelated | 43/38 | 28/24 | 24/19 |
| Mismatched related | 63/NA | 17/NA | 8/NA |
| **Nonablative or reduced-intensity conditioning** | | | |
| Yes | 53/49 | 27/22 | 24/20 |
| No | 63/59 | 31/25 | 20/16 |
| **% BM blasts before SCT** | | | $P = .02$ |
| <10% (n = 58) | 60/54 | 37/29 | 30/28 |
| ≥10% (n = 60) | 56/52 | 25/21 | 18/14 |
| **Absolute PB blast count before SCT** | | $P = .01$ | $P = .001$ |
| <100/μL (n = 73) | 58/55 | 36/32 | 30/28 |
| ≥100/μL | 56/51 | 22/15 | 15/10 |
| **PB platelets before SCT** | $P = 10$ | $P = .01$ | |
| <30 (n = 65) | 50/45 | 22/16 | 16/14 |
| ≥30 (n = 70) | 63/59 | 35/30 | 27/22 |
| **Albumin before SCT, g/dL** | $P = .001$ | $P = .0003$ | $P = .001$ |
| <3.4 (n = 60) | 43/39 | 18/15 | 15/11 |
| ≥3.4 (n = 75) | 68/65 | 37/30 | 28/25 |
| **AUC tacrolimus day 11** | | | |
| >94.8 | 62/62 | 34/27 | 23/19 |
| ≤94.8 | 51/46 | 27/23 | 23/21 |

NRM indicates nonrelapse mortality; BMT, bone marrow transplantation; AML, acute myelogenous leukemia; MDS, myelodysplastic syndrome; SCT, stem cell transplantation; NA, not applicable; BM, bone marrow; PBPC, peripheral blood progenitor cells; PB, peripheral blood; AUC, area under the curve.

### Survival

A total of 104 (77%) of 135 patients died, with median survival time of 4.9 months (95% confidence interval, 3.9-6.6 months; Figure 1). Univariate survival analyses within patient subgroups are summarized in Table 2. The most important individual predictors of a short survival were ≥2 prior therapies, Zubrod performance status of 2, high peripheral blood blast count, low peripheral blood platelets, and low albumin.

### Disease-Free Survival

A total of 111 (82%) patients either died or had disease progression. The median progression-free survival was 2.9 months (95% confidence interval, 2.5-4.2 months; Figure 2). On univariate analysis (Table 2), the most important predictors for a short progression-free survival were ≥2 prior therapies, disease status beyond refractory first relapse, Karnofsky performance status >1, ≥10% bone marrow blasts, high peripheral blood blast count, and low albumin.

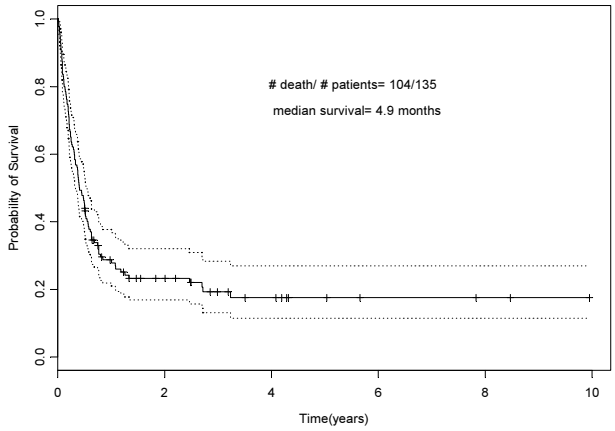


**Figure 2.** Kaplan-Meier curve for event-free survival.

### Nonrelapse Mortality

Nonrelapse mortality for all patients was 30% at 6 months and 43% at 12 months (Figure 3). On univariate analysis, a low albumin level before transplantation and a Karnofsky performance status of >1 predicted higher nonrelapse mortality.

### Effect of Immune-Suppressive Levels after Transplantation

The median AUC of tacrolimus levels during the first 11 days after transplantation was 94.8 (range, 36.9-210.2). On univariate analysis, tacrolimus levels above or below the median were associated with a 38% versus 54% 1-year nonrelapse mortality rate, a 34% versus 27% 1-year survival rate, and a 23% versus 23% EFS rate, respectively.

### Multivariate Analysis

Fitted multivariate Cox PH models for overall survival and EFS are summarized in Tables 3 and 4, respectively. The Cox PH regression analysis showed that performance status, peripheral blood blasts, and tacrolimus exposure as defined by the AUC of tacrolimus levels during the first 11 days were predictive of survival. As noted previously, tacrolimus exposure over the first 11 days (AUC) had a log quadratic relationship with the log hazard of death; the death rate initially decreased with AUC but then increased at higher levels. It is important to note that the predicted survival probabilities with any cutoff time in the range of 11 to 15 days were very near the corresponding predicted probabilities for the optimal 11-day cutoff. Thus, in terms of the ability to predict survival time, the total amount of tacrolimus over any initial time period in this range should predict outcome equally well. A similar pattern was seen with EFS in which, in addition to 11-day tacrolimus exposure, a Karnofsky performance status of >1, disease status beyond first relapse, and peripheral blood blasts were also predictive. These statistical results should not, however, be construed to imply that GVHD prophylaxis may be discontinued after 15 days, because that was not done with these patients, but rather that optimal immune suppression during the first 15 days after transplantation favorably affects transplantation outcomes. Our data would suggest that to maintain the optimal tacrolimus exposure during the first 15 days after transplantation, the optimal target range of serum tacrolimus levels during these days should be between 7 and 9 ng/dL.

Figure 4 illustrates the manner in which the predicted EFS probability under the fitted Cox PH model summarized in Table 4 varies with tacrolimus exposure and peripheral blood blasts. Within each row, the plots correspond to the 10th, 50th, and 90th percentile of the tacrolimus exposure. These plots show that tacrolimus exposures that are either too low or too

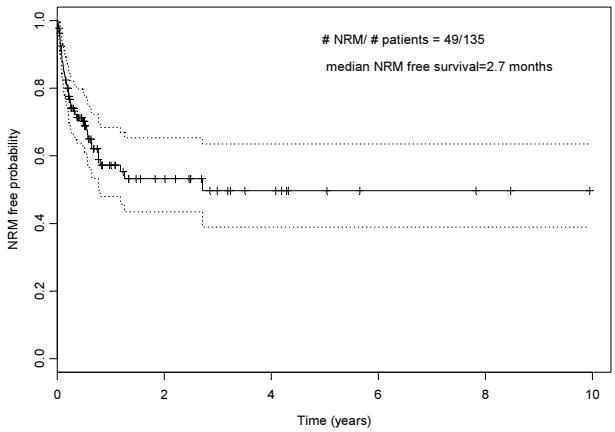


**Figure 3.** Kaplan-Meier curve for nonrelapse mortality–free survival.

**Table 3.** *Cox Proportional Hazards Model for Overall Survival (N = 135; 104 Deaths)*

| Variable | Coefficient | SE | *P* Value |
|---|---|---|---|
| PS = 2 | 1.13 | 0.35 | .001 |
| log (PB blasts) | 0.15 | 0.06 | .02 |
| log (AUC up to day 11) | −0.27 | 0.36 | .002 |
| log (AUC up to day 11)^2 | 3.10 | 0.79 | |

PS indicates performance status; PB, peripheral blood; AUC, area under the curve.

**Table 4.** *Cox Proportional Hazards Model for Event-Free Survival (N = 135; 111 Events)*

| Variable | Coefficient | SE | *P* Value |
|---|---|---|---|
| PS = 2 | 1.22 | 0.35 | .0004 |
| First relapse refractory | 0.67 | 0.26 | .01 |
| log (PB blasts) | 0.18 | 0.06 | .005 |
| log (AUC up to day 11) | −0.14 | 0.35 | .001 |
| log (AUC up to day 11)^2 | 2.65 | 0.78 | |

PS indicates performance status; PB, peripheral blood; AUC, area under the curve.

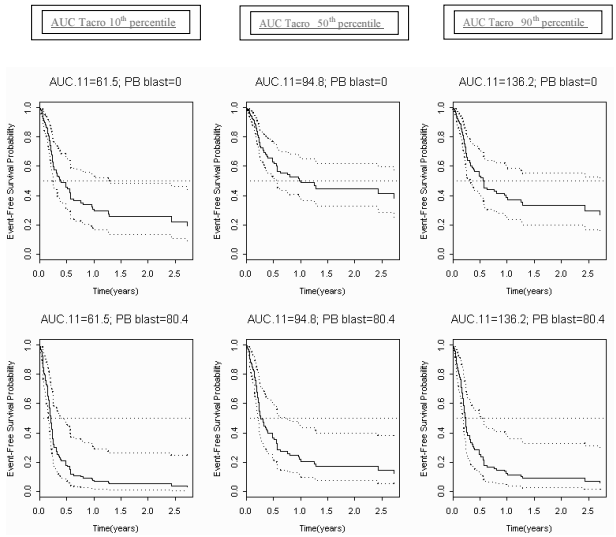


**Figure 4.** Effect of tacrolimus AUC on event-free survival. Row 1 includes patients with a peripheral blood blast count of 0 and is modeled with a tacrolimus AUC at the 10th, 50th, and 90th percentiles. Row 2 depicts outcomes for patients with an absolute peripheral blood blast count of 80/dL.

high may adversely affect transplantation outcomes regardless of tumor burden, as defined by peripheral blood blasts, although the magnitude of the effect may be more important for patients with a low tumor burden. Our data suggest that the optimal range of serum tacrolimus levels during the first 15 days would be between 7 and 9 ng/dL, regardless of other prognostic factors, in patients with refractory or relapsed myeloid leukemias.

## DISCUSSION

Allogeneic transplantation is the only curative option for patients with refractory AML/MDS. Notwithstanding, long-term disease control is achieved in only a small fraction of patients with refractory leukemia who undergo this procedure [7,8,15,16]. This retrospective analysis confirms results published in other single-institution studies and registry analyses. Particularly, patients with primary induction failure tend to have better outcomes than patients with refractory relapsed disease.

This analysis is the first to include a large proportion of patients with refractory AML/MDS who received allografts after a reduced-intensity or nonablative regimen. These data suggest that for patients with refractory AML/MDS, the use of a reduced-intensity regimen is associated with outcomes similar to those of patients receiving a more intense ablative regimen. However, because this was a retrospective analysis, the results should be viewed with caution and should stimulate the development and implementation of further prospective trials.

The primary cause of treatment failure after allogeneic transplantation for patients with refractory AML/MDS is recurrent disease. Our data, as well as experiences from other centers, demonstrate that >50% of relapses occur within the first 3 months after stem cell transplantation. Thus, strategies that are aimed at improving transplantation outcomes in this patient population must be implemented very early after transplantation and must target disease recurrence. Our analyses indicate that a strategy of reducing immune suppression to enhance a graft-versus-leukemia effect early after transplantation, unfortunately, will be associated with inferior treatment outcomes and that, at least during the first 10 to 15 days, tacrolimus levels should be maintained within therapeutic ranges to reduce early nonrelapse mortality. Whether rapid immune suppression withdrawal after that time could improve outcomes was not addressed in this study and requires further exploration.

Immune manipulation through dose reduction of immunosuppression has been studied previously. Sullivan et al. [25,26] reported on 16 patients with refractory or relapsed leukemia who underwent an allograft without any posttransplantation GVHD prophylaxis. The incidence of acute GVHD was 100%, and the survival rate was 37% at 18 months. Our results concerning the importance of immune suppressive levels during the first 10 days after transplantation confirm those reported by Bacigalupo et al. [27], who performed a randomized trial of high-dose versus low-dose cyclosporine in patients with myeloid leukemias who were undergoing allografting. The EFS rate was superior in patients randomized to receive the lower cyclosporine dose of 1 mg/kg (49% versus 27%), because of a lower relapse rate in the low-dose arm. It is interesting to note that in that study, there were no significant differences in cyclosporine serum levels after the first month after transplantation.

We hypothesized that the leukemic burden, as measured by the peripheral blood blast count, and bone marrow leukemia infiltrate would be important prognostic factors for outcome. Univariate analysis suggested that these factors could play a role in overall survival and EFS, but only peripheral blood blast count was predictive on multivariate analysis. This suggests that leukemic burden may contribute to transplantation outcomes and that developing strategies that could safely achieve leukemia burden reduction, without undue delay of the initiation of the preparative regimen, may be worthwhile to explore. At M.D. Anderson Cancer Center, we are exploring gemtuzumab administration 12 days before initiation of a reduced-intensity regimen of fludarabine/melphalan to further pursue this hypothesis.

In summary, these data support the use of allogeneic transplantation for patients with relapsed or refractory AML/MDS; however, patients with a very

poor performance status should be encouraged to seek nontransplantation therapies or palliative care because the likelihood of benefiting from allografting is small. All patients should be treated under the umbrella of a clinical trial aimed at exploring or defining the role of new therapeutic strategies.

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