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Tacrolimus vs. cyclosporine immunosuppression: results in advanced-stage disease compared with historical controls treated exclusively with cyclosporine

Mary M. Horowitz,[1] Donna Przepiorka,[2] Pamela Bartels,[3] Donald N. Buell,[3] Mei-Jie Zhang,[1] William E. Fitzsimmons,[3] Jay Erdman,[3] Chun Huang,[3] Ellen Hodosh,[3] Rochelle Maher,[3] John R. Wingard[4]

[1]International Bone Marrow Transplant Registry, Medical College of Wisconsin, Milwaukee, Wisconsin; [2]Baylor College of Medicine, Houston, Texas; [3]Fujisawa Healthcare, Deerfield, Illinois; [4]University of Florida, Gainesville, Florida

Offprint requests: William E. Fitzsimmons, PharmD, Fujisawa Healthcare, Inc., Parkway North Center, 3 Parkway North, Deerfield, IL 60015

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ABSTRACT

A phase III comparative trial of tacrolimus- vs. cyclosporine-based graft-vs.-host disease (GVHD) prophylaxis for human leukocyte antigen (HLA)-identical sibling bone marrow transplantation showed less GVHD but poorer survival in the tacrolimus arm. To test the comparability of the two treatment arms with respect to baseline survival prognosis, a matched control study using exclusively cyclosporine-treated patients from the International Bone Marrow Transplant Registry (IBMTR) database was performed. Controls were matched (2:1) based on age (within 5 years), disease, and pretransplant disease status. Two-year survival for tacrolimus-treated clinical trial patients was similar to that of their cyclosporine-treated matched controls (27 and 24%, respectively), and 2-year survival of the cyclosporine-treated clinical trial patients was similar to that of their cyclosporine-treated matched IBMTR controls (42 and 45%, respectively). Consistent with the clinical trial results, the cyclosporine-treated IBMTR controls matched to the tacrolimus group had significantly poorer 2-year survival than the cyclosporine-treated IBMTR controls matched to the cyclosporine group (24 and 45%, respectively; $p < 0.01$). No significant difference was seen in GVHD between the cyclosporine-treated clinical trial patients and their matched controls; however, the tacrolimus-treated clinical trial patients had significantly less GVHD than their cyclosporine-treated IBMTR controls ($p < 0.01$). These results support the hypothesis that the survival difference in the phase III trial resulted from an imbalance in the underlying risk factors for death in the two groups rather than from the randomized immunosuppressive regimen.

KEY WORDS:

Tacrolimus • Cyclosporine • Advanced-stage disease • Bone marrow transplantation • HLA-matched sibling donor

INTRODUCTION

A recent multicenter phase III clinical trial randomly assigned recipients of HLA-identical sibling bone marrow transplants to tacrolimus-based or cyclosporine-based immunosuppression to prevent acute GVHD. Randomization was stratified at each center based on age and donor alloimmunization status at the time of enrollment. Unexpectedly, the stratified randomization assigned more patients with advanced-stage disease to the tacrolimus group (n=68; 41%) than to the cyclosporine group (n=48; 29%, $p = 0.023$, χ^2 test) [1]. When 2-year survival rates were examined, no significant difference was seen between treatment arms among patients with nonadvanced disease (62% tacrolimus arm vs. 64% cyclosporine arm), but among patients with advanced disease, 2-year survival was 25% in the tacrolimus arm and 42% in the cyclosporine arm ($p < 0.01$, Wilcoxon test for equality of survival curves).

The difference in survival between patients with advanced-stage disease receiving cyclosporine vs. those with advanced-stage disease receiving tacrolimus was unexpected.

See page 181 for grant and support information.

Results of several previous trials demonstrated the effectiveness of tacrolimus for the prevention of GVHD without suggesting any survival disadvantage [2–7]. Given the heterogeneity of patients with advanced-stage malignancies, we hypothesized that the difference in survival was caused by an imbalance in the randomization of patients with poor prognosis. However, although multivariate analyses were performed using selected baseline/transplant factors as covariates, it was not possible to include all disease diagnosis and disease status (remission vs. relapse and number) combinations in a model. Determining the expected survival patterns of a similar population from the published literature also was not feasible because the advanced-disease population in this trial was a unique group with respect to such factors as diagnosis and stage of disease (i.e., remission or relapse status). Therefore, we performed a matched control study using exclusively cyclosporine-treated controls obtained from the International Bone Marrow Transplant Registry (IBMTR) [8].

MATERIALS AND METHODS

Clinical trial

The randomized (1:1), open-label, comparative prospective study, conducted between May 1993 and December 1996, involved 329 adults (≥12 years of age) receiving allogeneic bone marrow transplants for treatment of malignancies. Eligible patients were scheduled for a primary, non–T-depleted bone marrow transplant from a genotypically HLA-identical sibling donor. Patients were required to have a serum creatinine level <3.0 mg/dL. Within each center, patients were stratified with respect to patient age (<40 years or ≥40 years) and donor/recipient sex match (alloimmunized female donor to male recipient or not). Details of the trial are published [1]. On the day before marrow transplantation, patients received either tacrolimus (Prograf, FK506; 0.03 mg/kg per 24 hours) or cyclosporine (3 mg/kg per 24 hours) as a continuous intravenous infusion. Patients in both treatment arms received a standard short-course methotrexate regimen.

A total of 116 of the 329 randomized patients had advanced-stage disease, prospectively defined to include patients whose underlying hematologic malignancy was uncontrolled (relapse or never in remission) at the time of transplantation or who had a type of malignancy that, historically, was associated with poor survival after allogeneic bone marrow transplantation (e.g., multiple myeloma, chronic lymphocytic leukemia). These 116 patients constitute the study group for this analysis.

IBMTR selection of controls

The database for advanced-stage disease patients in both arms of the phase III trial was provided to the IBMTR by the trial sponsor. An attempt was made to identify two controls for each of the 116 trial patients from among patients in the IBMTR database receiving an HLA-identical sibling donor bone marrow transplant in a North American center during a corresponding time frame (1990–1995). Because we wished to test the impact of disease status on survival without confounding by the GVHD prophylaxis regimen, all control patients received a cyclosporine-methotrexate regimen for GVHD prophylaxis. To avoid overlap, registry patients with date of birth, sex, and transplant date identical to those of any clinical trial participant were excluded. Table 1 shows the series of selection factors applied to define the database of 879 patients from which matched controls were selected. Matching criteria were diagnosis, pretransplant disease status, and age (within 5 years). If more than two controls were available for a patient, two were selected at random.

IBMTR vs. trial population comparisons

The clinical trial included a 2-year follow-up period; minimum follow-up for IBMTR control patients was 210 days. Advanced-disease patients were evaluated with respect to 2-year survival and incidence of grades II to IV acute GVHD within 100 days posttransplant. GVHD was graded according to standard criteria [9] in both the clinical trial and the IBMTR analysis. The following comparisons were made:

1) all patients (tacrolimus-treated and cyclosporine-treated) in the phase III clinical trial (clinical trial patients) vs. their cyclosporine-treated controls selected from the IBMTR database (cyclosporine-treated, matched IBMTR controls);

2) tacrolimus-treated clinical trial patients vs. their cyclosporine-treated matched IBMTR controls (cyclosporine-treated, tacrolimus-matched IBMTR controls);

3) cyclosporine-treated clinical trial patients vs. their cyclosporine-treated, matched IBMTR controls (cyclosporine-treated, cyclosporine-matched IBMTR controls); and

4) cyclosporine-treated IBMTR controls matched to patients on the tacrolimus arm of the clinical trial vs. cyclosporine-treated IBMTR controls matched to patients on the cyclosporine arm of the clinical trial.

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Table 1. *IBMTR database used to select matched controls for clinical trial participants*

Criteria	Number of patients
Same baseline diseases	15,443
Year of transplant 1990–1995	11,083
Age 15–60 years	9239
HLA-identical sibling donor	6878
Cyclosporine + methotrexate for GVHD prophylaxis	4562
North American transplant center	1448
Follow-up time ≥210 days*	1386
No overlap with the clinical trial	1381
No CML in chronic or accelerated phase	891
Pretransplant disease status known	879

**Includes all patients dying before day 210 posttransplant.*

Statistical methods

Cox proportional hazards regression analysis stratified on matched pairs [10] was used to compare the survival probability and acute GVHD rate between clinical trial patients and matched IBMTR controls, and between cyclosporine-treated, tacrolimus-matched IBMTR controls and cyclosporine-treated, cyclosporine-matched IBMTR controls. Additional variables examined include donor-patient sex match (male to male, male to female, female to male, and female to female), donor and patient cytomegalovirus (CMV) status, conditioning regimen (total-body irradiation [TBI] vs. no TBI; etoposide vs. no etoposide), Karnofsky score (≥90 vs. <90%), and time from diagnosis to transplant (≥1 vs. <1 year). A backward stepwise model building was used to identify the covariates significantly associated with the outcomes. The main effect (clinical trial patients vs. IBMTR matched controls) was in all the models. The assumption of proportional hazards over time was tested for the main effects and all explanatory covariates, using a time-dependent covariate. Nonproportional hazards were addressed by using time-dependent covariates. The relative risk (with 95% confidence interval and p value) of death was calculated based on the final Cox regression model. The Kaplan-Meier estimator was used to calculate and plot the probability of survival and acute GVHD. A stratified log-rank test was used for univariate comparisons [11].

RESULTS

Matching of clinical trial patients and IBMTR controls

Two controls matched for disease, pretransplant disease status, and age were found for 100 of the 116 advanced-disease patients in the clinical trial. The demographic, disease-related, and transplant-related characteristics of the advanced-disease patients in the clinical trial and their matched IBMTR controls are summarized in Table 2.

Sixteen patients in the clinical trial (six tacrolimus, 10 cyclosporine) could not be matched with two controls (11 patients had no match, five patients had one match). Removal of the 16 unmatched patients did not alter the survival pattern differences between the two treatment arms. Survival without (vs. with) the 16 patients was 27% (vs. 25%) in the tacrolimus arm and 42% (vs. 42%) in the cyclosporine group.

Table 2. *Characteristics of advanced-disease* patients in the clinical trial and their matched IBMTR controls*

	Clinical trial	IBMTR
No. patients	100	200
No. receiving GVHD prophylaxis		
Tacrolimus and methotrexate	62	0
Cyclosporine and methotrexate	38	200
Demographic characteristics		
Median age (years)	40 (16–59)	40 (15–59)
Male	58%	61%
Cytomegalovirus-positive	61%	56%
Karnofsky score >90%	42%	48%
Type of disease		
Acute myeloid leukemia	32%	32%
Acute lymphoblastic leukemia	14%	14%
Chronic myelogenous leukemia	4%	4%
Chronic lymphocytic leukemia	2%	2%
Myelodysplastic syndrome	2%	2%
Non-Hodgkin's lymphoma	21%	21%
Hodgkin's disease	2%	2%
Multiple myeloma	23%	23%
Transplant-related variables		
Female donor	43%	42%
Donor cytomegalovirus-positive	59%	54%
Conditioning regimen		
Total-body irradiation	56%	51%
Busulfan + cyclophosphamide (cytoxan)	40%	47%
Etoposide	28%	37%

**Advanced-stage disease is defined as hematologic malignancy uncontrolled (relapse or never in remission) at the time of transplantation or a type of malignancy that, historically, has been associated with poor survival following allogeneic bone marrow transplantation (e.g., multiple myeloma, chronic lymphocytic leukemia).*

Two-year survival

Table 3 and Figs. 1–4 show Kaplan-Meier survival estimates for the four study groups. Figure 1 compares the survival curve for the 100 advanced-stage disease clinical trial patients with that of their 200 matched IBMTR controls. Two-year survival probabilities were 33% for clinical trial patients vs. 32% for their matched IBMTR controls. Survival of the 62 tacrolimus-treated clinical trial patients and their 124 matched cyclosporine-treated IBMTR controls was similar (Fig. 2), as was survival of the 38 cyclosporine-treated clinical trial patients and their 76 cyclosporine-treated matched IBMTR controls (Fig. 3). Further, cyclosporine-treated IBMTR controls matched to cyclosporine-treated clinical trial patients showed significantly higher survival than did cyclosporine-treated IBMTR controls matched to clinical trial patients receiving tacrolimus ($p < 0.01$, log-rank test) (Fig. 4).

Table 3 also shows risk ratios for 2-year mortality. Matched controls selected from the IBMTR database show a risk for death similar to that of their counterparts in the two treatment arms of the clinical trial. However, the risk of death for the IBMTR cyclosporine-treated patients matched to tacrolimus-treated patients in the clinical trial is significantly higher than that for IBMTR cyclosporine-treated

Table 3. *Probability of 2-year survival and relative risk of death for advanced-disease patients in the clinical trial vs. their matched IBMTR controls*

	Probability of 2-year survival*	Comparison between designated groups		
		Relative risk of death†	95% CI	p value†
All clinical trial patients	33%	1.11	0.79–1.58	0.55
All cyclosporine-treated matched IBMTR controls	32%			
Tacrolimus-treated clinical trial patients	27%	1.16	0.74–1.81	0.51
Cyclosporine-treated, tacrolimus-matched IBMTR controls	24%			
Cyclosporine-treated clinical trial patients	42%	1.14	0.63–2.08	0.66
Cyclosporine-treated, cyclosporine-matched IBMTR controls	45%			
Cyclosporine-treated, tacrolimus-matched IBMTR controls	24%	1.70	1.17–2.46	<0.01
Cyclosporine-treated, cyclosporine-matched IBMTR controls	45%			

CI, confidence interval.
**Kaplan-Meier estimates.*
†Cox model, Wald χ^2.

patients matched to cyclosporine-treated patients in the clinical trial (risk ratio 1.70; $p < 0.01$, Wald χ^2).

Grade II–IV acute GVHD

Consistent with the results of the primary study, patients in the tacrolimus arm had a lower incidence of GVHD ($p < 0.01$, stratified log-rank test), with a relative risk of GVHD of 0.39 (Table 4). In contrast, the incidence of GVHD for cyclosporine-treated IBMTR controls matched for the tacrolimus arm was not different from that for cyclosporine-treated IBMTR controls matched for the cyclosporine arm (Table 4).

DISCUSSION

In a randomized clinical trial of GVHD prophylaxis regimens for HLA-identical marrow transplantation for hematologic malignancies [1], overall 2-year Kaplan-Meier survival estimates were 47% in the tacrolimus group and 57% in the cyclosporine group ($p < 0.02$, Wilcoxon test for the equality of survival curves). This survival difference resulted from a greater number of deaths in patients with advanced disease in the tacrolimus group (51/68, 75%) compared with the cyclosporine group (28/48, 58%), an effect not expected from results of previous trials. A lower than expected number of early deaths caused by recognized transplant regimen–related toxicity (e.g., veno-occlusive disease, pulmonary toxicity, organ failure), infection, and relapse of malignancy was observed in the advanced disease patients in the cyclosporine group (10%), suggesting that this group may have had a better prognosis at baseline than did the tacrolimus-treated group, but no conclusive evidence was provided by the clinical trial data. No single factor or interaction of any single factor with GVHD prophylaxis explained the result. The eligibility criteria of the trial

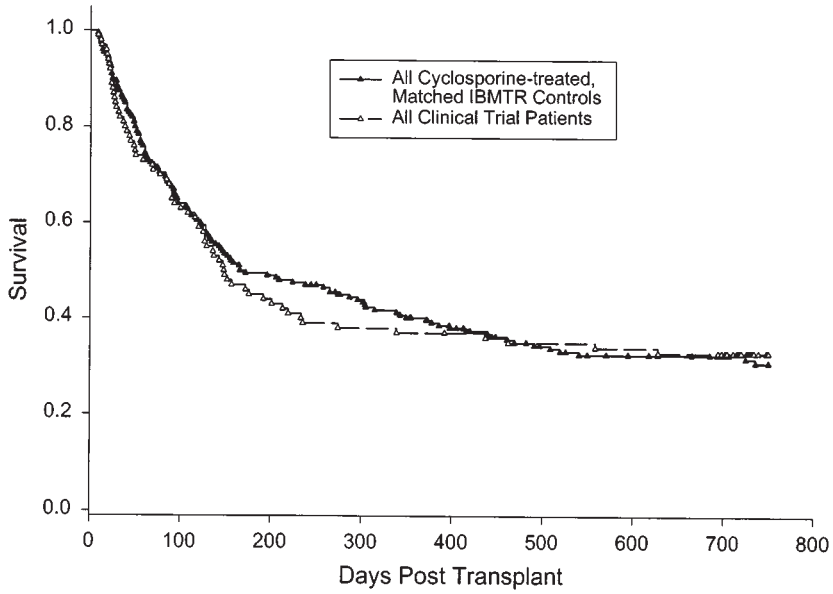

Figure 1. Two-year survival for all advanced-disease patients in the clinical trial vs. that of their matched IBMTR controls
All IBMTR patients were treated with cyclosporine. Survival patterns were comparable based on stratified log-rank test (p = *0.55).*

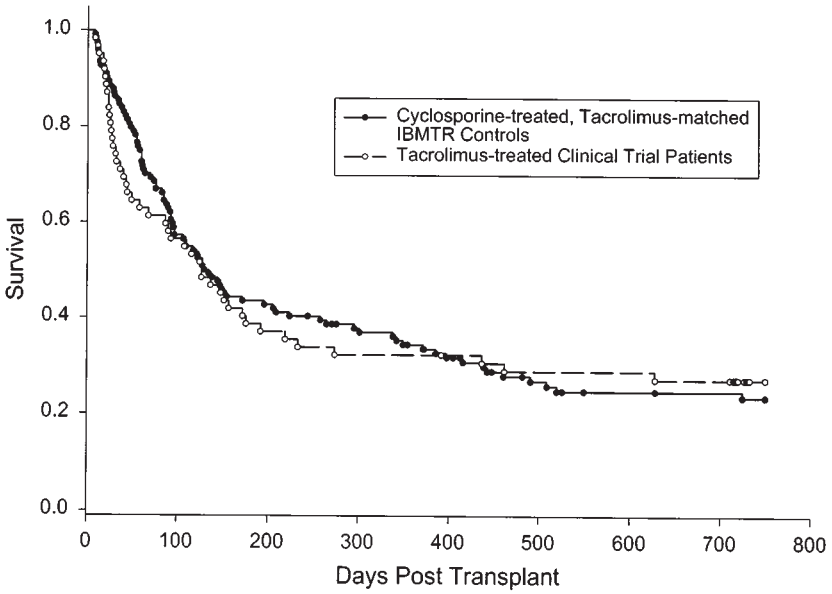

Figure 2. Two-year survival for tacrolimus-treated, advanced-disease patients in the clinical trial vs. that of their matched IBMTR controls
All IBMTR patients were treated with cyclosporine. Survival patterns were comparable based on stratified log-rank test (p = *0.51).*

permitted a heterogeneous patient population and some diseases that are not common indications for allogeneic transplantation. Finding comparable groups in the published literature was not possible.

In the present study, the large clinical database maintained by the IBMTR was used to compare the survival of patients in the clinical trial with that of matched controls, all of whom received cyclosporine and methotrexate for GVHD prophylaxis, to assess the prognosis of the two clinical trial groups. The hypothesis was that if patients in the two arms of the trial had inherently different prognoses regardless of GVHD prophylaxis, then groups formed by similarly treated matched controls for each arm would also have different survival despite receiving the same GVHD prophylaxis. This was confirmed in both Kaplan-Meier and Cox regression analyses (Table 3), in which patients matched to those in the tacrolimus arm of the clinical trial had lower survival than did patients matched to the cyclo-

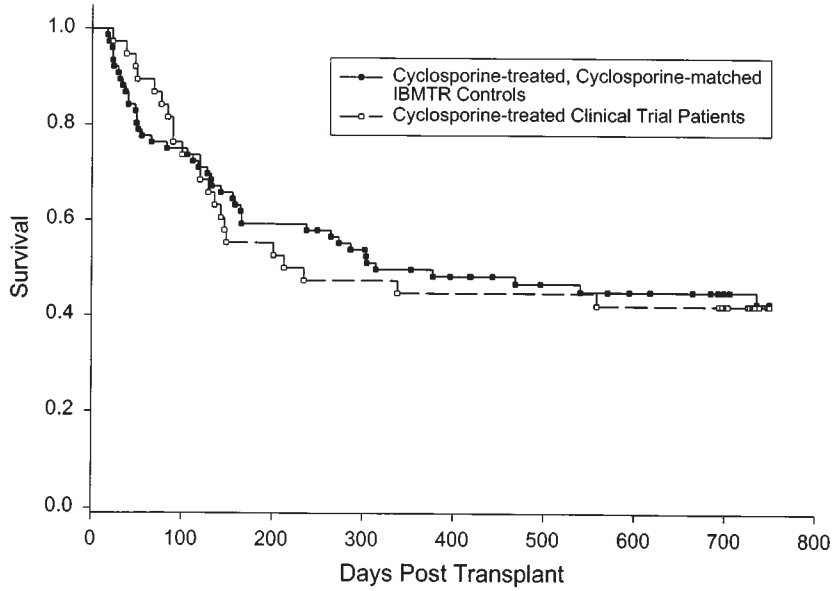

Figure 3. Two-year survival for cyclosporine-treated, advanced-disease patients in the clinical trial vs. that of their matched IBMTR controls
All IBMTR patients were treated with cyclosporine. Survival patterns were comparable based on stratified log-rank test (p = *0.88).*

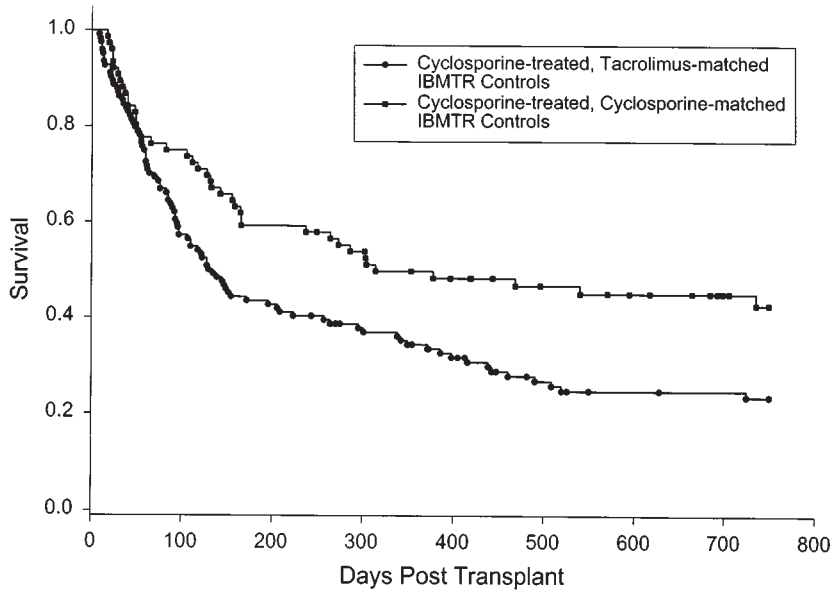

Figure 4. Two-year survival for IBMTR patients treated with cyclosporine and matched to advanced-disease patients in the clinical trial treated with tacrolimus or cyclosporine

Cyclosporine-treated IBMTR patients matched to tacrolimus-treated clinical trial patients had a lower survival than did those matched to cyclosporine-treated clinical trial patients based on log-rank test ($p < 0.01$).

sporine arm, even though all of the matched controls received cyclosporine-based GVHD prophylaxis.

The primary clinical trial comparing tacrolimus with cyclosporine showed a lower incidence of grade II–IV acute GVHD for tacrolimus-treated patients compared with cyclosporine-treated patients. This was true for all patients (32 vs. 44%) and for advanced disease patients (31 vs. 54%). Interestingly, comparison of the two cyclosporine-treated matched control groups showed no difference in the incidence of GVHD. Thus, diagnosis and disease stage had an impact on survival but not on the risk of GVHD.

The randomized clinical trial is a powerful tool for making unbiased assessments of treatment effects. Its use is based on the assumption that randomization is the method most likely to produce groups that are similar in their measurable and unmeasurable baseline characteristics. Stratification helps to ensure such comparability for characteristics known to be important for prognosis. Occasionally, however, despite random assignment and stratification, treatment groups are disparate for one or more factors that may confound an outcome of interest or produce an outcome unexpected from prior studies. This may occur when factors that

Table 4.

Grades II to IV acute GVHD within 100 days posttransplant

		Comparison between designated groups		
	Grade II–IV acute GVHD*	Relative risk†	95% CI	p value†
All clinical trial patients	42%	0.73	0.46–1.18	0.20
All cyclosporine-treated matched IBMTR controls	48%			
Tacrolimus-treated clinical trial patients	28%	0.39	0.19–0.81	0.01
Cyclosporine-treated, tacrolimus-matched IBMTR controls	50%			
Cyclosporine-treated clinical trial patients	58%	1.59	0.79–3.21	0.19
Cyclosporine-treated, cyclosporine-matched IBMTR controls	45%			
Cyclosporine-treated, tacrolimus-matched IBMTR controls	50%	1.10	0.71–1.71	0.67
Cyclosporine-treated, cyclosporine-matched IBMTR controls	45%			

The same standard GVHD grading system was used for all groups.

**Kaplan-Meier estimates.*

†Cox model, Wald χ^2.

CI, confidence interval.

affect the primary efficacy endpoint differ from those affecting an important safety endpoint.

Herein, we have found that differences in the combination of diagnosis, pretransplant disease status, and age between the two treatment arms within the advanced disease group of patients confounded the analysis of survival. It is not yet clear which specific combination of these factors resulted in the imbalance in the mortality risk between the two treatment arms. The results of the clinical trial and this matched control study underscore the importance of incorporating stratification for potential risk factors affecting survival (e.g., disease diagnosis and disease status) into the design of studies evaluating agents for the prophylaxis of GVHD.

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