Biol Blood Marrow Transplant 19 (2013) 1686–1697

Providing Personalized Prognostic Information for Adult Leukemia Survivors

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Article history:
Received 28 June 2013
Accepted 25 August 2013

Key Words:
Leukemia-free survival
Chronic graft-versus-host disease
Landmark analysis
Survivorship
Prognosis

A B S T R A C T

Prediction of subsequent leukemia-free survival (LFS) and chronic graft-versus-host disease (GVHD) in adults with acute leukemia who survived at least 1 year after allogeneic hematopoietic cell transplantation is difficult. We analyzed 3339 patients with acute myeloid leukemia and 1434 patients with acute lymphoblastic leukemia who received myeloablative conditioning and related or unrelated stem cells from 1990 to 2005. Most clinical factors predictive of LFS in 1-year survivors were no longer significant after 2 or more years. For acute myeloid leukemia, only disease status (beyond first complete remission) remained a significant adverse risk factor for LFS 2 or more years after transplantation. For lymphoblastic leukemia, only extensive chronic GVHD remained a significant adverse predictor of LFS in the second and subsequent years. For patients surviving for 1 year without disease relapse or extensive chronic GVHD, the risk of developing extensive chronic GVHD in the next year was 4% if no risk factors were present and higher if noncyclosporine-based GVHD prophylaxis, an HLA-mismatched donor, or peripheral blood stem cells were used. Estimates for subsequent LFS and extensive chronic GVHD can be derived for individual patients or populations using an online calculator (http://www.cibmtr.org/LeukemiaCalculators). This prognostic information is more relevant for survivors than estimates provided before transplantation.

INTRODUCTION

Results of hematopoietic cell transplantation (HCT) are traditionally presented as overall survival, leukemia-free survival (LFS), and transplant-related mortality starting from the time of HCT. The risk of relapse and mortality is highest early after HCT and then declines with time; thus, many prognostic factors that are strongly correlated with early LFS may lose their relevance the longer a patient survives in remission.

Survivorship studies demonstrated that 2- to 5-year survivors have an estimated 80% to 95% chance of surviving 5 to 15 years,[1-5] with patients age 45 years or older and those

Financial disclosure: See Acknowledgments on page 1604.

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1083-8791/$ – see front matter © 2013 American Society for Blood and Marrow Transplantation.
http://dx.doi.org/10.1016/j.bbmt.2013.08.013

diagnosed with chronic GVHD having a lower chance of survival.[2,4,5] It is difficult, however, to use this information to counsel individual patients about future risks of relapse and treatment-related mortality, especially when patients ask, a year or more after their HCT, about their prognosis. To answer this question, one needs access to updated prognostic estimates, specific to the patient's disease, type of transplant, duration of survival since HCT, and current condition. This information is important for patients, family members, and others to have realistic expectations. A patient who is told he or she has an extremely poor prognosis before transplant but who survives at least 1 year should be given an updated prognostic estimate. Conversely, all patients should be aware of a continued risk of higher mortality than the general population, especially if this encourages compliance with medical follow-up and recommended preventive care.

METHODS

The cohort consisted of all patients aged 18 years or older who had a first myeloablative allogeneic transplant for acute myeloid leukemia (AML) or acute lymphoid leukemia (ALL) between 1990 and 2005, reported to the Center for International Blood and Marrow Transplant Research (CIBMTR), and who survived at least 1 year without relapse of their disease. Only centers with 80% completeness index at 4 years (3 years of follow-up for more than 80% of 1-year survivors) were included to minimize reporting bias. Patients with syngeneic twin, cord blood, or haploidentical donors or who received reduced-intensity/nonmyeloablative conditioning transplants were excluded. Patients receiving reduced-intensity/nonmyeloablative conditioning were excluded so we could focus on a more homogeneous patient population where we could assume a certain level of organ functioning. Comorbidity data were not collected by the CIBMTR before 2008 and would be especially important in a study of reduced-intensity/nonmyeloablative conditioning.

LFS, defined as survival without relapse, was chosen as the primary endpoint because there is only a 3% absolute survival difference between survival and LFS for patients with acute leukemia. In addition, the inclusion criteria at each landmark are based on LFS. Patients were censored at time of last follow-up. We conducted a similar analysis for extensive chronic graft-versus-host disease (GVHD), defined according to CIBMTR criteria,[6] that defines chronic GVHD as GVHD occurring after day 100 and severity as limited or extensive because the National Institutes of Health criteria are not yet used in the CIBMTR database.[7]

Potential clinical variables were current patient age, patient gender, Karnofsky performance status at transplant,[8] patient race, donor–recipient gender match,[9] donor and recipient cytomegalovirus serostatus,[10] donor type, HLA matching,[11] graft type, conditioning regimen, GVHD prophylaxis, use of antithymocyte globulin or Campath, and prior grades II to IV acute GVHD. Prior extensive chronic GVHD was evaluated as a predictor of subsequent LFS.

Disease-specific factors were disease, disease stage, extramedullary involvement at any time before transplant, cytogenetics, white blood cell count at diagnosis,[12,13] time from first complete response to transplant, and duration of remission. Cytogenetic classification was primarily based on the Southwest Oncology Group/Eastern Cooperative Oncology Group and Medical Research Council classifications, with additional classification of specific abnormalities by other schema if available.[14-19] Additional variables included secondary leukemia (AML only) and time from diagnosis to first complete remission,[18] lineage (T versus B versus other), and Philadelphia-chromosome or BCR-ABL positivity (ALL only). Because of missing data or low numbers, we could not consider percent bone marrow or peripheral blood blasts at transplant.[20] For AML, we could not consider FAB subtype[21,22] or the newer molecular markers such as NPM1, FLT3, CEBPA, and MLL[23]; pretransplant ferritin level[18]; and post-transplant minimal residual disease assessments.[24]

Statistical Considerations

Univariate screening of candidate patient and transplant variables was performed separately for ALL and AML among 1-year leukemia-free survivors, using 2-year LFS rates as the endpoint. Risk factors significant at the .05 level were then included in a multivariate analysis with stepwise backward selection at the .01 level of significance. The identified risk factors were then used at each subsequent landmark year to predict survival in the subsequent year.

Analyses were based on Poisson regression with additive risk structure. For multicategory variables, categories with similar risk contributions were pooled for simplicity. A competing risk analysis was not used because the overwhelming causes of death in the first 5 years after transplant are related to the transplant or underlying malignancy. For the chronic GVHD analysis, we excluded patients who had received T cell depletion for GVHD prophylaxis because they had an extremely low rate of chronic GVHD after 1 year that would have caused instability and boundary problems in the additive model. We also excluded patients from the chronic GVHD model if they developed extensive chronic GVHD before 1 year because we wanted our prognostic estimates to be valid for patients without prior chronic GVHD.

RESULTS

Table 1 shows the characteristics of the 3339 AML and 1434 ALL patients included in the study. Other patients (n = 4511) transplanted during the study period were not eligible for inclusion in the study because of death or relapse during the first year after HCT (n = 3828), lack of follow up (n = 301), or transplantation at centers with low completeness index (n = 382).

LFS for AML patients in this study was 90% at 2 years and 78% at 5 years. For ALL, LFS was 87% at 2 years and 71% at 5 years. Univariate analyses identified the following factors significantly associated with worse LFS. For AML, these factors were second or greater remission at transplant, relapse/refractory disease at transplant, poor-risk cytogenetics, tacrolimus-based GVHD prophylaxis, duration of remission >1 year, more recent year of transplant, donor not a matched sibling, Karnofsky performance status <90, prior extensive chronic GVHD, secondary AML, and peripheral blood stem cell graft. For ALL, these factors were second or greater remission at transplant, relapse/refractory disease at transplant, Philadelphia chromosome–positive, prior acute GVHD, prior extensive chronic GVHD, donor exposed to cytomegalovirus, female donor for male patient, Karnofsky performance status <90, and B cell lineage (Supplementary Table 1).

Table 2 summarizes the results of the multivariate analysis, considering $P < .05$ as significant. An online calculator is available at http://www.cibmtr.org/LeukemiaCalculators to allow calculation of the personalized probability of disease-free survival in the subsequent years by entering a patient's individual risk factor information. For example, a patient with AML who has intermediate-risk cytogenetics and is in second complete remission with a Karnofsky performance status of 90% to 100% at transplant and who survives for 1 year has a 12.9% chance of relapse or mortality in the next year.

Table 3 shows how risk factors are additive in calculating subsequent risk and illustrates the estimated and actual LFS and confidence intervals for patients with particular combinations of risk factors. Table 3 also shows the actual LFS of groups of patients (n > 25) with the particular combinations of risk factors transplanted in 2004 to 2005 to test the predictive ability of the model in more recently transplanted patients. Table 4 shows the results for patients transplanted for ALL. Because the formulas to calculate risks are quite complicated, use of the online calculator is recommended.

Previous CIBMTR reports have shown that 90% to 95% of chronic GVHD cases are diagnosed within the first year after HCT.[25,26] In our cohort, 89% of all cases of extensive chronic GVHD were diagnosed within the first year, and 8% of cases were diagnosed between 1 and 2 years. Only 3% of chronic GVHD developed after 2 years, so the analysis only attempted to predict onset of chronic GVHD between 1 and 2 years. We found that patients who survive to 1 year, free of their original malignancy and without any prior extensive chronic GVHD, still have a 4% chance of being diagnosed with

Table 1
Characteristics of Patients ≥18 Years Old Who Underwent Myeloablative Transplant from 1990 to 2005 for AML or ALL and Were 1-Year Survivors

Characteristics	AML	ALL
	n (%)	n (%)
Number of patients	3339	1434
Number of centers	244	228
Age at transplantation, yr, median (range)	37 (18-69)	29 (18-64)
Recipient age in decades, yr		
18-29	977 (29)	746 (52)
30-39	937 (28)	370 (26)
40-49	958 (29)	236 (16)
50+	467 (14)	82 (6)
Sex		
Male	1752 (52)	883 (62)
Female	1587 (48)	551 (38)
Donor–recipient sex match		
Male donor–male recipient	1021 (31)	560 (39)
Male donor–female recipient	832 (25)	303 (21)
Female donor–male recipient	721 (22)	314 (22)
Female donor–female recipient	745 (22)	247 (17)
Missing	20 (1)	10 (1)
Donor–recipient CMV match		
Negative donor–negative recipient	904 (27)	462 (32)
Negative donor–positive recipient	768 (23)	305 (21)
Positive donor–positive recipient	1130 (34)	420 (29)
Positive donor–negative recipient	395 (12)	180 (13)
Missing	142 (4)	67 (5)
Karnofsky score at transplant		
<90 Karnofsky	754 (23)	317 (22)
≥90 Karnofsky	2474 (74)	1076 (75)
Missing	111 (3)	41 (3)
Race/ethnicity of recipient		
White	2816 (84)	1191 (83)
African American	70 (2)	31 (2)
Asian	287 (9)	125 (9)
Hispanic	89 (3)	59 (4)
Other	59 (2)	20 (1)
Missing	18 (1)	8 (1)
Disease status at transplant		
CR1	1981 (59)	830 (58)
CR2	648 (19)	351 (24)
>CR2	41 (1)	58 (4)
Relapse	383 (11)	118 (8)
Primary induction failure	251 (8)	50 (3)
Missing	35 (1)	27 (2)
Cytogeneticgroups		
Good	384 (12)	56 (4)
Intermediate/normal	1832 (55)	596 (42)
Poor risk	334 (10)	353 (25)
Missing	789 (24)	429 (30)
Ph+/BCR-ABL+		
No		722 (50)
Yes		283 (20)
Missing		429 (30)
T lineage vs. B lineage		
B lineage		933 (65)
T lineage		241 (17)
Other		148 (10)
Missing		112 (8)
Type of AML		
Denovo	2832 (85)	
Secondary	415 (12)	
Missing	92 (3)	
HLA match		
HLA-identical sibling	2221 (67)	835 (58)
Other related donor	58 (2)	26 (2)
Well-matched URD	479 (14)	250 (17)
Partially matched URD	328 (10)	190 (13)
Mismatched URD	166 (5)	83 (6)
Missing	87 (3)	50 (3)
Source of stem cell		
Bone marrow	2269 (68)	1039 (72)
Peripheral blood	1070 (32)	395 (28)
Conditioning regimen based on distribution		
Bu+Cy±other	1410 (42)	184 (13)
TBI+Cy±Bu±other	1897 (57)	1243 (87)
Bu+Fludara±other (no TBI)	32 (1)	7 (<1)
GVHD prophylaxis		
Ex vivo T cell depletion	322 (10)	148 (10)
CsA±other	2428 (73)	1018 (71)
Tacrolimus±other	519 (16)	244 (17)
Other	70 (2)	24 (2)
Chronic GVHD		
No chronic GVHD	1560 (47)	648 (45)
Limited GVHD	652 (20)	295 (21)
Extensive GVHD	1105 (33)	487 (34)
Missing	22 (1)	4 (<1)
Acute GVHD grades II-IV		
No	2355 (71)	934 (65)
Yes	955 (29)	496 (35)
Missing	29 (1)	4 (<1)
Year of transplant		
1990-1993	876 (26)	352 (24)
1994-1997	924 (28)	368 (26)
1998-2001	679 (20)	298 (21)
2002-2005	860 (26)	416 (29)
Median follow-up of survivors, mo (range)	96 (12-249)	87 (12-240)

CMV indicates cytomegalovirus; CR, complete remission; URD, unrelated donor; Bu, busulfan; MTX, methotrexate; CsA, cyclosporine; CY, cyclophosphamide; TBI, total body irradiation.

extensive chronic GVHD within the subsequent year. This estimate ranges from 2% to 18% based on risk factors and was higher if a patient received noncyclosporine-based GVHD prophylaxis without antithymocyte globulin or Campath, received peripheral blood, or had a donor other than an HLA-identical sibling (Table 5).

DISCUSSION

Our results allow updated prognostic estimates to be calculated for individual patients based on their clinical characteristics, using a formula derived from an analysis of thousands of patients. We conclude that most factors predictive of LFS at the time of and after HCT lose their impact once patients survive without relapse for 2 or more years. People with a history of extensive chronic GVHD have a lower LFS compared with those without chronic GVHD up to 6 years post-HCT for ALL but not for AML. AML that is in relapse or refractory at the time of transplant also remains an adverse prognostic factor even for 5-year disease-free survivors, but this is not operative in ALL. Conversely, it is notable that factors such as age and donor type were not significantly predictive of outcome for patients after they had survived the first year.

Overall, the likelihood of subsequent survival is high but varies depending on certain clinical variables. Many reports suggest that extensive chronic GVHD is associated with higher transplant-related mortality and lower survival. Severity of chronic GVHD according to National Institutes of Health criteria and continued need for immunosuppression are also associated with these outcomes, but the CIBMTR database lacked adequate data to test these hypotheses.[27] Using available data, chronic GVHD was an adverse prognostic factor for ALL but not AML. This could be because the

Table 2
Additive Effects on Subsequent 1-Year Event Rates Among AML/ALL Disease-Free Survivors at Various Landmark Times Post-HCT: (a) AML and (b) ALL

(a) AML

	1 Year		2 Years		3 Years		4 Years		5 Years
No. at risk	3315		2824		2535		2277		1967
No. of events	434		193		123		61		50
Patient years of follow-up during interval	3012		2677		2403		2133		1776
Background rate for general population*	.0027		.0028		.0029		.0031		.0033
	N		N		N		N		N	
Baseline rate for transplanted patients if no risk factors present†		.089		.049		.033		.021		.019
+ Poor risk cytogenetics	334	**.087**‡	267	.033§	238	.020	206	.022	167	−.015
+ Second or greater remission at HCT	689	**.049**‡	586	**.060**‖	507	.024§	451	.002	387	.018§
+ Relapse/refractory at HCT	626	**.162**‡	475	**.039**‖	418	**.035**‖	370	**.028**‖	318	**.029**‖
+ Karnofsky performance status <90 at HCT	746	**.050**‡	597	.008	527	.024§	468	−.001	412	.010

(b) ALL

	1 Year		2 Years		3 Years		4 Years		5 Years
No. at risk	1426		1113		977		867		
No. of events	280		92		39		45		
Patient years of follow-up during interval	1240		1042		921		1450		
Background rate for general population*	.0018		.0020		.0020		.0021		
	N		N		N		N		
Baseline rate for transplanted patients if no risk factors present†		.098		.065		.022		.012	
+ Philadelphia/BCR-ABL+	280	.124‡	199	.031§	165	.029§	145	.014	
+ Second or greater remission at HCT	407	.126‡	308	.006	271	.031§	237	.016§	
+ Relapse/refractory at HCT	167	.316‡	106	−.004	93	−.001	85	.017	
+ Extensive chronic GVHD, past or current	451	.085‡	375	.047‖	332	.023§	299	.034‡	

The formula to convert the event rate per person-year (x) into the probability of an event over the year (p) for a single person is $p = 1 - \text{exponent}(-x)$, with x being the sum of the baseline rate and any additional risk factors. If the event rate is <.2, then the probability of an event is approximately equal to the event rate, but at greater values of the event rate, the event rate is greater than the probability of an event expressed as a percentage. Values are in bold if $p < .05$.

* Death rate expected in a general population cohort with similar sex and age distribution, for comparison with the transplanted population.

† Event rate per person-year at risk (= approximate probability of death/relapse) in a population of patients transplanted for AML or ALL if no risk factors are present.

‡ $P < .01$.

§ $P < .2$.

‖ $P < .05$.

graft-versus-leukemia effect was less potent for ALL so the increased transplant-related mortality was consequently more influential on overall survival than in AML.

This analysis has a number of limitations. We used CIBMTR data, which includes hundreds of centers, so our results are generalizable but may not reflect the practices and success rates of any particular center. We lacked some clinical details such as molecular markers, evidence of minimal residual disease, and chronic GVHD incidence and severity according to the National Institutes of Health consensus conference that might have contributed to refinement of the prognostic estimates. The study population includes only myeloablative recipients who survived at least 1 year without recurrent disease, and our results are only applicable to similar patients. The median patient age is likely lower than in current practice, although age was not a significant prognostic factor in the multivariate analysis. Similar analyses could be performed for the reduced-intensity and nonmyeloablative approaches once sufficient numbers of survivors with enough follow-up and comorbidity data are available. The low number of relapses and deaths in survivors during the 1-year time periods of analysis may have also limited the power to identify significant prognostic factors. Transplantation practices are constantly evolving, and some innovations such as use of tyrosine kinase inhibitors in BCR-ABL–positive ALL may overcome the currently identified negative prognostic factors.[28] However, many more patients will need to be accrued to confirm this hypothesis and provide an estimate of any beneficial effect. Studies such as ours that require large number of patients to personalize prognostic estimates will always necessarily lag behind the newest innovations. The fact that patients

Table 3
Examples of 2-Year Estimated and Actual LFS, 95% Confidence Intervals (CIs) for 1-Year AML Survivors, and Observed LFS from the 2 Most Recent Years

Risk Factors	N	Estimated LFS	95% CI	Observed LFS (1990-2005)	95% CI	N Recent 2 Years (2004-2005)	Observed LFS	95% CI
No risk factors	1408	91.5%	90.1-93.0	91.4%	89.9-92.9	170	91.8%	87.5-96.1
Poor-risk cytogenetics	173	83.9%	79.4-88.6	83.6%	78.1-89.1	47	84.4%	73.8-95.0
Second or later complete remission	488	87.1%	84.4-89.9	87.2%	84.2-90.2	88	87.4%	80.4-94.4
Relapse/refractory at transplant	329	77.9%	74.2-81.7	79.9%	75.5-84.3	40	82.5%	70.7-94.3
Karnofsky performance status <90 at transplant	310	87.1%	83.9-90.3	89.0%	85.5-92.5	33	87.9%	76.8-99.0
Poor risk cytogenetics + relapse/refractory	39	71.4%	66.5-76.6	79.1%	66.2-92.0	7	—	—
Karnofsky performance status <90 at transplant + relapse/refractory	205	74.1%	70.3-78.0	72.1%	65.8-78.4	27	56.6%	36.4-76.8
Karnofsky performance status <90 at transplant + relapse/refractory + poor risk cytogenetics	25	67.9%	63.2-73.0	56.0%	36.5-75.5	3	—	—

Table 4
Examples of 2-Year Estimated and Actual LFS, 95% Confidence Intervals (CIs) for 1-Year ALL Survivors, and Observed LFS from the 2 Most Recent Years

Risk Factors	N	Estimated LFS	95% CI	Observed LFS (1990-2005)	95% CI	N Recent 2 Years (2004-2005)	Observed LFS	95% CI
No risk factors	441	90.6%	88.1-93.3	90.5%	87.7-93.3	42	84.6%	73.3-95.9
Philadelphia/BCR-ABL+	138	80.1%	74.5-86.1	82.9%	76.5-89.3	35	78.7%	64.7-92.7
Second or later complete remission	250	79.9%	75.6-84.5	80.5%	75.5-85.5	37	80.2%	67.0-93.4
Relapse/refractory at transplant	89	66.1%	58.7-74.4	64.4%	54.3-74.5	6	—	—
Extensive chronic GVHD, past or current	158	83.2%	78.7-88.1	83.5%	77.7-89.3	34	82.4%	69.6-95.2
Philadelphia/BCR-ABL+ and relapse/refractory at transplant	22	58.4%	51.1-66.8	54.5%	33.7-75.3	2	—	—
Extensive chronic GVHD, past or present and relapse/refractory at transplant	48	60.7%	53.5-68.9	72.7%	60.0-85.4	9	—	—
Extensive chronic GVHD, past or present and relapse/refractory at transplant and Philadelphia/BCR-ABL+	9	53.6%	46.8-61.5	—	—	0	—	—

transplanted in the last 2 years of the study (2004 to 2005) had remarkably similar survival rates to the entire cohort suggests that therapeutic advances may have more of an impact within the first year after transplantation than in later post-transplant years. Because our study started with 1-year survivors, our results may not be as susceptible to being outdated as quickly as other studies that focus on the early post-transplant period.

Nevertheless, patients and their physicians, as well as people designing clinical research studies involving the survivor population, may benefit from results that update LFS based on the most current patient characteristics, including the fact that patients have already survived for some period of time. Patients who enter HCT with multiple adverse disease factors may benefit from knowing that most of these poor risk factors lose their potency once a patient survives 2 or more years after HCT. The public availability of the online calculators allows patients and physicians to calculate individualized and current prognostic estimates, based on the best available data derived from thousands of patients. They may then apply their own "sensitivity" analyses to incorporate new information, and the calculators can be formally updated regularly based on more recent cohorts to reflect evolving medical practice.

Table 5
Additive Effects on Subsequent 1-Year Probability of Developing Chronic GVHD Among AML/ALL Disease-Free Survivors at 1 Year

Chronic GVHD*		1 Year
No. at risk		2836
No. of events		127
Patient years of follow-up		2481
	N	
Baseline rate for transplanted patients if no risk factors present†		.019
+ Noncyclosporine-based GVHD prophylaxis without antithymocyte globulin or Campath	356	**.087**‡
+ Peripheral blood stem cell graft	755	**.048**‡
+ Donor other than HLA-identical sibling	734	**.044**‡

The formula to convert the event rate per person-year (x) into the probability of an event over the year (p) for a single person is $p = 1 - \text{exponent}(-x)$, with x being the sum of the baseline rate and any additional risk factors. If the event rate is <.2, then the probability of an event is approximately equal to the event rate, but at greater values of the event rate, the event rate is greater than the probability of an event expressed as a percentage.

* Excluding 384 patients receiving T cell–depleted grafts, who experienced 3 events in 347 person years, or .009 events per person year at risk.

† Event rate per person-year at risk (= approximate probability of chronic GVHD) in a population of patients transplanted for acute leukemia if no risk factors are present.

‡ $P < .01$ (values are in bold if $P < .05$).

ACKNOWLEDGMENTS

Financial Disclosure: The CIBMTR is supported by Public Health Service Grant/Cooperative Agreement U24-CA76518 from the National Cancer Institute (NCI), the National Heart, Lung and Blood Institute (NHLBI), and the National Institute of Allergy and Infectious Diseases; a Grant/Cooperative Agreement 5U01HL069294 from NHLBI and NCI; a contract HHSH234200637015C with Health Resources and Services Administration; 2 grants (N00014-06-1-0704 and N00014-08-1-0058) from the Office of Naval Research; and grants from Allos, Inc.; Amgen, Inc.; Angioblast; anonymous donation to the Medical College of Wisconsin; Ariad; Be the Match Foundation; Blue Cross and Blue Shield Association; Buchanan Family Foundation; CaridianBCT; Celgene Corporation; CellGenix, GmbH; Children's Leukemia Research Association; Fresenius-Biotech North America, Inc.; Gamida Cell Teva Joint Venture Ltd.; Genentech, Inc.; Genzyme Corporation; GlaxoSmithKline; HistoGenetics, Inc.; Kiadis Pharma; The Leukemia & Lymphoma Society; The Medical College of Wisconsin; Merck & Co, Inc.; Millennium: The Takeda Oncology Co.; Milliman USA, Inc.; Miltenyi Biotec, Inc.; National Marrow Donor Program; Optum Healthcare Solutions, Inc.; Osiris Therapeutics, Inc.; Otsuka America Pharmaceutical, Inc.; RemedyMD; Sanofi; Seattle Genetics; Sigma-Tau Pharmaceuticals; Soligenix, Inc.; StemCyte, A Global Cord Blood Therapeutics Co.; Stemsoft Software, Inc.; Swedish Orphan Biovitrum; Tarix Pharmaceuticals; Teva Neuroscience, Inc.; THERAKOS, Inc.; and Wellpoint, Inc. The views expressed in this article do not reflect the official policy or position of the National Institutes of Health, the Department of the Navy, the Department of Defense, or any other agency of the US Government.

REFERENCES

1. Abou-Mourad YR, Lau BC, Barnett MJ, et al. Long-term outcome after allo-SCT: close follow-up on a large cohort treated with myeloablative regimens. *Bone Marrow Transplant*. 2010;45:295-302.
2. Bhatia S, Francisco L, Carter A, et al. Late mortality after allogeneic hematopoietic cell transplantation and functional status of long-term survivors: report from the Bone Marrow Transplant Survivor Study. *Blood*. 2007;110:3784-3792.
3. Martin PJ, Counts GW Jr, Appelbaum FR, et al. Life expectancy in patients surviving more than 5 years after hematopoietic cell transplantation. *J Clin Oncol*. 2010;28:1011-1016.
4. Socie G, Stone JV, Wingard JR, et al. Long-term survival and late deaths after allogeneic bone marrow transplantation. Late Effects Working Committee of the International Bone Marrow Transplant Registry. *N Engl J Med*. 1999;341:14-21.
5. Wingard JR, Majhail NS, Brazauskas R, et al. Long-term survival and late deaths after allogeneic hematopoietic cell transplantation. *J Clin Oncol*. 2011;29:2230-2239.
6. Shulman HM, Sullivan KM, Weiden PL, et al. Chronic graft-versus-host syndrome in man. A long-term clinicopathologic study of 20 Seattle patients. *Am J Med*. 1980;69:204-217.

7. Filipovich AH, Weisdorf D, Pavletic S, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease. I. Diagnosis and staging working group report. *Biol Blood Marrow Transplant*. 2005;11:945-956.
8. Song KW, Lipton J. Is it appropriate to offer allogeneic hematopoietic stem cell transplantation to patients with primary refractory acute myeloid leukemia? *Bone Marrow Transplant*. 2005;36:183-191.
9. Gorin NC, Labopin M, Polge E, et al. Risk assessment in adult acute lymphoblastic leukaemia before early haemopoietic stem cell transplantation with a geno-identical donor: an easy clinical prognostic score to identify patients who benefit most from allogeneic haemopoietic stem cell transplantation. *Leukemia*. 2003;17:1596-1599.
10. Yakoub-Agha I, Mesnil F, Kuentz M, et al. Allogeneic marrow stem-cell transplantation from human leukocyte antigen-identical siblings versus human leukocyte antigen-allelic-matched unrelated donors (10/10) in patients with standard-risk hematologic malignancy: a prospective study from the French Society of Bone Marrow Transplantation and Cell Therapy. *J Clin Oncol*. 2006;24:5695-5702.
11. Weisdorf D, Spellman S, Haagenson M, et al. Classification of HLA-matching for retrospective analysis of unrelated donor transplantation: revised definitions to predict survival. *Biol Blood Marrow Transplant*. 2008;14:748-758.
12. Laport GG, Alvarnas JC, Palmer JM, et al. Long-term remission of Philadelphia chromosome-positive acute lymphoblastic leukemia after allogeneic hematopoietic cell transplantation from matched sibling donors: a 20-year experience with the fractionated total body irradiation-etoposide regimen. *Blood*. 2008;112:903-909.
13. Marks DI, Perez WS, He W, et al. Unrelated donor transplants in adults with Philadelphia-negative acute lymphoblastic leukemia in first complete remission. *Blood*. 2008;112:426-434.
14. Slovak ML, Kopecky KJ, Cassileth PA, et al. Karyotypic analysis predicts outcome of preremission and postremission therapy in adult acute myeloid leukemia: a Southwest Oncology Group/Eastern Cooperative Oncology Group Study. *Blood*. 2000;96:4075-4083.
15. Grimwade D, Walker H, Oliver F, et al. The importance of diagnostic cytogenetics on outcome in AML: analysis of 1,612 patients entered into the MRC AML 10 trial. The Medical Research Council Adult and Children's Leukaemia Working Parties. *Blood*. 1998;92:2322-2333.
16. Fung HC, Stein A, Slovak M, et al. A long-term follow-up report on allogeneic stem cell transplantation for patients with primary refractory acute myelogenous leukemia: impact of cytogenetic characteristics on transplantation outcome. *Biol Blood Marrow Transplant*. 2003;9:766-771.
17. Moorman AV, Harrison CJ, Buck GA, et al. Karyotype is an independent prognostic factor in adult acute lymphoblastic leukemia (ALL): analysis of cytogenetic data from patients treated on the Medical Research Council (MRC) UKALLXII/Eastern Cooperative Oncology Group (ECOG) 2993 trial. *Blood*. 2007;109:3189-3197.
18. Armand P, Kim HT, Cutler CS, et al. A prognostic score for patients with acute leukemia or myelodysplastic syndromes undergoing allogeneic stem cell transplantation. *Biol Blood Marrow Transplant*. 2008;14:28-35.
19. Pullarkat V, Slovak ML, Kopecky KJ, et al. Impact of cytogenetics on the outcome of adult acute lymphoblastic leukemia: results of Southwest Oncology Group 9400 study. *Blood*. 2008;111:2563-2572.
20. Wong R, Shahjahan M, Wang X, et al. Prognostic factors for outcomes of patients with refractory or relapsed acute myelogenous leukemia or myelodysplastic syndromes undergoing allogeneic progenitor cell transplantation. *Biol Blood Marrow Transplant*. 2005;11:108-114.
21. Thomas X, Le Q, Botton S, et al. Autologous or allogeneic stem cell transplantation as post-remission therapy in refractory or relapsed acute myeloid leukemia after highly intensive chemotherapy. *Leuk Lymphoma*. 2005;46:1007-1016.
22. Jourdan E, Boiron JM, Dastugue N, et al. Early allogeneic stem-cell transplantation for young adults with acute myeloblastic leukemia in first complete remission: an intent-to-treat long-term analysis of the BGMT experience. *J Clin Oncol*. 2005;23:7676-7684.
23. Schlenk RF, Dohner K, Krauter J, et al. Mutations and treatment outcome in cytogenetically normal acute myeloid leukemia. *N Engl J Med*. 2008;358:1909-1918.
24. Stirewalt DL, Guthrie KA, Beppu L, et al. Predictors of relapse and overall survival in Philadelphia chromosome-positive acute lymphoblastic leukemia after transplantation. *Biol Blood Marrow Transplant*. 2003;9:206-212.
25. Arora M, Klein JP, Weisdorf DJ, et al. Chronic GVHD risk score: a Center for International Blood and Marrow Transplant Research analysis. *Blood*. 2011;117:6714-6720.
26. Lee SJ, Klein JP, Barrett AJ, et al. Severity of chronic graft-versus-host disease: association with treatment-related mortality and relapse. *Blood*. 2002;100:406-414.
27. Arai S, Jagasia M, Storer B, et al. Global and organ-specific chronic graft-versus-host disease severity according to the 2005 NIH Consensus Criteria. *Blood*. 2011;118:4242-4249.
28. Oliansky DM, Larson RA, Weisdorf D, et al. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the treatment of adult acute lymphoblastic leukemia: update of the 2006 evidence-based review. *Biol Blood Marrow Transplant*. 2012;18:16-17.

APPENDIX

Supplementary Table 1
Univariate Analyses of Risk Factors for Rate of Mortality + Relapse During Second-Year Post- HCT

	AML			ALL		
	N	Rate Difference (95% CI)	*P*	N	Rate Difference (95% CI)	*P*
ANC engraftment						
<16 days	1439	Ref		573	Ref	
≥16 days	1844	−.024 (−.052-.003)	.09	837	.024 (−.029-.078)	.37
Platelet engraftment						
<23 days	1215	Ref		469	Ref	
≥23 days	1109	−.009 (−.043-.025)	.60	547	.046 (−.019-.110)	.17
Gender						
Male	1740	Ref		878	Ref	
Female	1575	−.008 (−.035 - .019)	.56	548	−016 (−070-.038)	.56
Donor−recipient gender						
Other	2585	Ref		1105	Ref	
Female/male	716	.009 (−.025-.043)	.61	313	.135 (.059-.211)	.0005
KPS at HCT						
90-100	2465	Ref		1071	Ref	
<90	746	.086 (.048-.125)	<.0001	315	.086 (.014-.157)	.02
Duration of remission						
<1 year	382	Ref		277	Ref	
≥1 year	558	.108 (.050-.166)	.0003	171	.087 (−.036-.209)	.16
Extramedullary disease						
Absent	2918	Ref		1085	Ref	
Present	369	.042 (−.006-.090)	.09	325	−.006 (−.068-.057)	.86
Stem cell source						
Marrow	2252	Ref		1033	Ref	
PBSC	1063	.034 (.003-.064)	.03	393	.046 (−.017-.108)	.15
Acute GVHD						
Grades 0-I	2347	Ref		928	Ref	
Grades II-IV	945	.013 (−.018-.043)	.41	495	.074 (.016-.133)	.01
Race						
White	2797	Ref		1184	Ref	
Other	501	−.012 (−.049-.024)	.51	234	.034 (−.042-.110)	.38
Recipient CMV serostatus						
Negative	1292	Ref		638	Ref	
Positive	1888	.012 (−.016-.040)	.41	722	.036 (−.019-.090)	.20
Donor CMV serostatus						
Negative	1663	Ref		761	Ref	
Positive	1517	−.000 (−.028-.027)	.98	599	.094 (.037-.151)	.001
TBI in conditioning						
No	1435	Ref		190	Ref	
Yes	1880	−.000 (−.027-.027)	.99	1236	−.073 (−.161-.015)	.11
WBC count at diagnosis						
<30	2035	Ref	.90*	803	Ref	.97*
30-100	585	−.013 (−.048-.022)	.48	247	−.035 (−.102-.031)	.30
>100	267	.017 (−.037-.071)	.54	162	.038 (−.054-.129)	.42
Time from first CR to HCT						
<6 mo	1557	Ref	.08*	624	Ref	.92*
6-12 mo	286	−.029 (−.067-.009)	.13	152	−.000 (−.074-.075)	.99
>12 mo	44	−.063 (−.130-.004)	.07	23	−.010 (−.176 - .156)	.91
Age at transplant						
18-29	972	Ref	.50*	740	Ref	.15*
30-44	1441	−.015 (−.046-.017)	.36	521	.043 (−.015-.101)	.14
45-69	902	.035 (−.003-.074)	.07	165	.041 (−.048-.130)	.36
Donor HLA match						
HLA-identical sibling	2200	Ref	.001*	827	Ref	.88*
Well matched	478	.043 (.000-.085)	.05	250	.013 (−.061-.087)	.73
Other matching	550	.060 (.018-.101)	.005	299	−.022 (−.086-.043)	.52
Cytogenetic risk						
Good	383	Ref	.32*	55	Ref	.76*
Intermediate/normal	1824	−.003 (−.046-.040)	.89	595	−.035 (−.183-.112)	.64
Poor	334	.072 (.006-.138)	.03	352	.018 (−.136-.172)	.82
Unknown	774	.000 (−.047-.048)	.99	424	−.048 (−.197-.101)	.53
GVHD prophylaxis						
Cyclosporin-based	2192	Ref	.05*	897	Ref	.71*
Tacrolimus-based	411	.063 (.015-.112)	.01	217	.029 (−.050-.107)	.47
T cell depletion	322	.010 (−.036-.057)	.66	148	−.005 (−.092-.081)	.91
Antithymocyte globulin/Campath	338	.024 (−.023-.071)	.32	140	.034 (−.063-.132)	.49
Other	46	.051 (−.085-.188)	.46	22	−.005 (−.217-.206)	.96
Disease status at HCT						
First remission	1971	Ref	<.0001*	827	Ref	<.0001*
Second remission	648	.048 (.012-.083)	.008	349	.105 (.040-.169)	.001

(*Continued*)

Supplementary Table 1
(*continued*)

	AML			ALL		
	N	Rate Difference (95% CI)	*P*	N	Rate Difference (95% CI)	*P*
Remission > second	41	−.030 (−.117-.058)	.50	58	.129 (−.023-.281)	.10
Relapse/refractory	626	.165 (.119-.212)	<.0001	167	.308 (.186-.429)	<.0001
AML origin						
De novo	2822	Ref			Not applicable	
Secondary	412	.045 (−.000-.091)	.05			
Chronic extensive GHVD						
None	2256	Ref		962	Ref	
Prior or current	1026	.051 (.020-.083)	.002	451	.099 (.037-.161)	.002
Year of transplant						
Continuous, per year	3315	.003 (.000-.006)	.03	1426	.004 (−.002-.010)	.17
Philadelphia-BCR/ABL						
Negative		Not applicable		722	Ref	.08*
Positive				280	.102 (.022-.182)	.01
Unknown				424	−.005 (−.063-.053)	.86
Time from diagnosis to first CR						
0-8 wk		Not applicable		880	Ref	
>8 wk				372	.044 (−.018-.106)	.16
Type of ALL						
T cell		Not applicable		240	Ref	.003*
B cell				929	.104 (.041-.166)	.001
Other				147	.124 (.018-.229)	.02

ANC indicates absolute neutrophil count; KPS, Karnofsky performance status; PBPC, peripheral blood progenitor cells; CMV, cytomegalovirus; TBI, total body irradiation; WBC, white blood cell; CR, complete remission; BCR-ABL, breakpoint cluster region-Abelson gene rearrangement.

* Overall *P* value.