Published in final edited form as:
Biol Blood Marrow Transplant. 2013 November ; 19(11): . doi:10.1016/j.bbmt.2013.08.013.

PROVIDING PERSONALIZED PROGNOSTIC INFORMATION FOR ADULT LEUKEMIA SURVIVORS

Stephanie J. Lee, MD[1], **Barry Storer, PhD**[1], **Hailin Wang, MPH**[2], **Hillard M. Lazarus, MD**[3], **Edmund K. Waller, MD**[4], **Luis M. Isola, MD**[5], **Thomas R. Klumpp, MD**[6], **John Bosco C. Umejiego, MBBS**[7], **Bipin N. Savani, MD**[8], **Alison W. Loren, MD**[9], **Mitchell S. Cairo, MD**[10], **Bruce M. Camitta, MD**[11], **Corey S. Cutler, MD**[12], **Biju George, MD**[13], **H. Jean. Khoury, MD**[4], **David I. Marks, MD**[14], **David A. Rizzieri, MD**[15], **Edward A. Copelan, MD**[16], **Vikas Gupta, MD**[17], **Jane L. Liesveld, MD**[18], **Mark R. Litzow, MD**[19], **Alan M. Miller, MD**[20], **Harry C. Schouten, MD**[21], **Robert Peter Gale, MD**[22], **Jean-Yves Cahn, MD**[23], and **Daniel J. Weisdorf, MD**[24]

[1]Fred Hutchinson Cancer Research Center, Seattle, WA

[2]Center for International Blood and Marrow Transplant Research, Medical College of Wisconsin, Milwaukee, WI

[3]Seidman Cancer Center, University Hospitals Case Medical Center, Cleveland, OH

[4]Bone Marrow and Stem Cell Transplant Center, Emory University Hospital, Atlanta, GA

[5]Bone Marrow Transplant Program, Mount Sinai Medical Center, New York, NY

[6]Temple University Bone Marrow Transplant Program, Philadelphia, PA

[7]Center for International Blood and Marrow Transplant Research, Minneapolis, MN

[8]Hematology/Stem Cell Transplant, Vanderbilt University Medical Center, Nashville, TN

[9]Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

[10]Maria Fareri Children's Hospital, New York Medical College, New York, NY

[11]Midwest Center for Cancer and Blood Disorders, Medical College of Wisconsin and Children's Hospital of Wisconsin, Milwaukee, WI

[12]Dana Farber Cancer Institute, Boston, MA; Hematology

[13]Christian Medical College Hospital, Vellore, INDIA

[14]Adult BMT Unit, Bristol Children's Hospital, Bristol, UNITED KINGDOM

[15]Pediatric Blood and Marrow Transplant, Duke University Medical Center, Durham, NC

[16]Levine Cancer Institute, Carolinas Healthcare System, Charlotte, NC

[17]Princess Margaret Hospital, University of Toronto, Toronto, CANADA

CORRESPONDING AUTHOR: Stephanie J. Lee, MD, MPH; Fred Hutchinson Cancer Research Center, 1100 Fairview Ave N, D5-290,Seattle, Washington, 98109; Telephone: 206-667-5160; Fax: 206-667-1034; sjlee@fhcrc.org.

CONFLICTS OF INTEREST: None

[18]Strong Memorial Hospital, University of Rochester Medical Center, Rochester, NY

[19]Hematology and Internal Medicine, Mayo Clinic Rochester, Rochester, MN

[20]Baylor University Medical Center, Dallas, TX

[21]Interne Geneeskunde, Academische Ziekenhuis Maastricht, Maastricht, NETHERLANDS

[22]Section of Haematology, Division of Experimental Medicine, Department of Medicine, Imperial College, London, UNITED KINGDOM

[23]Department of Hematology, University Hospital, Grenoble, FRANCE

[24]Bone Marrow Transplant Program, University of Minnesota Medical Center, Minneapolis, MN

Abstract

Prediction of subsequent leukemia-free survival (LFS) and chronic graft-versus-host disease (GVHD) in adults with acute leukemia who survived at least one year after allogeneic HCT is difficult. We analyzed 3339 patients with acute myeloid leukemia (AML) and 1434 with acute lymphoblastic leukemia (ALL) who received myeloablative conditioning and related or unrelated stem cells from 1990–2005. Most clinical factors predictive of LFS in one year survivors were no longer significant after two or more years. For AML, only disease status (beyond first complete remission) remained a significant adverse risk factor for LFS two or more years after transplantation. For ALL, only extensive chronic GVHD remained a significant adverse predictor of LFS in the second and subsequent years. For patients surviving for one 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 non-cyclosporine-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.

Keywords

leukemia-free survival; chronic graft-versus-host disease; landmark analysis; survivorship; prognosis

INTRODUCTION

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

Survivorship studies demonstrated that two to five year survivors have an estimated 80–95% chance of surviving five to fifteen years,[1–5] with patients age 45 years or older and those diagnosed with chronic GVHD having a lower chance of survival.[2, 4, 5] It is difficult, however, to utilize this information to counsel individual patients about future risks of relapse and treatment-related mortality, especially when a patient asks, “Now that I’m one [or three or four etc.] years after my HCT, what is my prognosis now?” In order 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 they have an extremely poor prognosis prior to transplant but who survives at least one 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.

PATIENTS AND METHODS

The cohort consisted of all patients aged 18 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 one year without relapse of their disease. Only centers with 80% completeness index at four years (three years of follow up for more than 80% of one year survivors) were included to minimize reporting bias. Patients with syngeneic twin, cord blood, or haploidentical donors or who received reduced intensity/nonmyeloablative conditioning (RIC/NMA) transplants were excluded. Patients receiving RIC/NMA conditioning were excluded so we could focus on a more homogeneous patient population where we could assume a certain level of organ functioning. Co-morbidity data were not collected by CIBMTR before 2008, and would be especially important in a study of RIC/NMA.

Leukemia free survival (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] which defines chronic GVHD as GVHD occurring after day 100, and severity as limited or extensive because the NIH criteria are not yet used in the CIBMTR database.[7]

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

Disease-specific factors included disease, disease stage, extramedullary involvement at any time before transplant, cytogenetics, white blood 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 (CR),[18] lineage (T vs. B vs. other) and Philadelphia-chromosome or BCR-ABL positivity (ALL only). Due to 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] pre-transplant 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 one-year leukemia-free survivors, using two-year LFS as the endpoint. Risk factors significant at the 0.05 level were then included in a multivariate analysis with stepwise backwards selection at the 0.01 level of significance. The risk factors that were identified 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 multi-category 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 five 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 one year which 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 prior to one year since 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).

Leukemia-free survival for AML patients in this study was 90% at two years and 78% at five years. For ALL, LFS was 87% at two years and 71% at five years. Univariate analyses identified the following factors significantly associated with worse LFS: AML: 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 less than 90, prior extensive chronic GVHD, secondary AML, and peripheral blood stem cell graft. ALL: 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 less than 90, and B cell lineage. (Supplementary Table 1)

Table 2 summarizes the results of the multivariate analysis, considering $p<0.05$ 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 90–100% at transplant, and who survives for one 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 2004–2005, 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 90–95% 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 one-two years. Only 3% of chronic GVHD developed after two years, so the analysis only attempted to predict onset of chronic GVHD between one and two years. We found that patients who survive to one year, free of their original malignancy and without any prior extensive chronic GVHD, still have a 4% chance of being diagnosed with 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 non-cyclosporine-based GVHD prophylaxis without ATG or Campath, 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 following HCT lose their impact once patients survive without relapse for two or more years. People with a history of extensive chronic GVHD have a lower LFS compared to those without chronic GVHD up to six years post HCT for ALL but not for AML. Acute myeloid leukemia that is in relapse or refractory at the time of transplant also remains an adverse prognostic factor even for five 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 NIH 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 the data that are available, chronic GVHD was an adverse prognostic factor for ALL but not AML. This could be because the 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 NIH consensus conference that might have contributed to refinement of the prognostic estimates. The study population includes only myeloablative recipients who survived at least one 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 non-myeloablative approaches once sufficient numbers of survivors with enough follow-up and co-morbidity data are available. The low number of relapses and deaths in survivors during the one 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 transplanted in the last two years of the study (2004–2005) had remarkably similar survival to the entire cohort suggests that therapeutic advances may be more impactful within the first year after transplantation than in later post-transplant years. Since our study started with one-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 two or more years after HCT. The public availability of the online calculators allows patient 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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 (NIAID); a Grant/Cooperative Agreement 5U01HL069294 from NHLBI and NCI; a contract HHSH234200637015C with Health Resources and Services Administration (HRSA/DHHS); two 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 Institute of Health, the Department of the Navy, the Department of Defense, or any other agency of the U.S. 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(2):295–302. [PubMed: 19597425]
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(10):3784–3792. [PubMed: 17671231]
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(6):1011–1016. [PubMed: 20065176]
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(1):14–21. [PubMed: 10387937]

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(16):2230–2239. [PubMed: 21464398]
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(2):204–217. [PubMed: 6996481]
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(12):945–956. [PubMed: 16338616]
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(3): 183–191. [PubMed: 15937497]
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(8):1596–1599. [PubMed: 12886248]
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(36):5695–5702. [PubMed: 17116940]
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(7):748–758. [PubMed: 18541193]
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(3):903–909. [PubMed: 18519812]
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(2):426–434. [PubMed: 18398065]
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(13):4075–4083. [PubMed: 11110676]
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(7):2322–2333. [PubMed: 9746770]
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(12):766–771. [PubMed: 14677116]
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(8):3189–3197. [PubMed: 17170120]
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(1):28–35. [PubMed: 18158958]
19. Pullarkat V, Slovak ML, Kopecky KJ, Forman SJ, Appelbaum FR. Impact of cytogenetics on the outcome of adult acute lymphoblastic leukemia: results of Southwest Oncology Group 9400 study. Blood. 2008; 111(5):2563–2572. [PubMed: 18156492]
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(2):108–114. [PubMed: 15682071]

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(7):1007–1016. [PubMed: 16019551]
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(30):7676–7684. [PubMed: 16186596]
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(18):1909–1918. [PubMed: 18450602]
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(3):206–212. [PubMed: 12652472]
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(24):6714–6720. [PubMed: 21493797]
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(2):406–414. [PubMed: 12091329]
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(15):4242–4249. [PubMed: 21791424]
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. Biology of blood and marrow transplantation: journal of the American Society for Blood and Marrow Transplantation. 2012; 18(1):16–17. [PubMed: 21963620]

Table 1

Characteristics of patients ≥18 years of age who underwent a myeloablative transplant 1990–2005 for acute myelogenous leukemia or acute lymphoblastic leukemia, and were one year survivors.

Characteristics	AML N (%)	ALL N (%)
Number of Patients	3339	1434
Number of Centers	244	228
Age at transplantation, median (range)	37 (18–69)	29 (18–64)
Recipient age in decades		
18–29yrs	977 (29)	746 (52)
30–39yrs	937 (28)	370 (26)
40–49yrs	958 (29)	236 (16)
50+yrs	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		
Caucasian	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)

Characteristics	AML N (%)	ALL N (%)
Relapse	383 (11)	118 (8)
Primary Induction Failure	251 (8)	50 (3)
Missing	35 (1)	27 (2)
Cytogenetic groups		
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		

Characteristics	AML N (%)	ALL N (%)
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 grade 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, months	96 (12 – 249)	87 (12 – 240)

Abbreviations: AML = Acute myelogenous leukemia, ALL = Acute lymphoblastic leukemia, GVHD = graft versus host disease, CMV = cytomegalovirus, CR = Complete remission, URD=unrelated donor, Bu = Busulfan, MTX = Methotrexate, CsA = Cyclosporine, CY = Cyclophosphamide, TBI = Total body irradiation,

Table 2

Additive effects on subsequent one year event rates among AML/ALL disease-free survivors at various landmark times post-HCT. (a) Acute myeloid leukemia (b) Acute lymphoblastic leukemia. 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 – exponent (−x), with x being the sum of the baseline rate and any additional risk factors. If the event-rate is less than 0.2 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.

a) Acute Myeloid Leukemia		**1 year**		**2 years**		**3 years**		**4 years**		**5 years**
N at risk		3315		2824		2535		2277		1967
N of events		434		193		123		61		50
Patient years of follow-up during interval		3012		2677		2403		2133		1776
Background rate for general population[1]		0.0027		0.0028		0.0029		0.0031		0.0033
	N		N		N		N		N	
Baseline rate for transplanted patients if no risk factors present[2]		0.089		0.049		0.033		0.021		0.019
+ Poor risk cytogenetics	334	**0.087** ***	267	0.033 *	238	0.020	206	0.022	167	−0.015
+ Second or greater remission at HCT	689	**0.049** ***	586	**0.060** **	507	0.024 *	451	0.002	387	0.018 *
+ Relapse/refractory at HCT	626	**0.162** ***	475	**0.039** **	418	**0.035** **	370	**0.028** **	318	**0.029** **
+ Karnofsky performance status < 90 at HCT	746	**0.050** ***	597	0.008	527	0.024 *	468	−0.001	412	0.010

b) Acute Lymphoblastic Leukemia		**1 year**		**2 years**		**3 years**		**4 years**	**5 years**
N at risk		1426		1113		977		867	
N of events		280		92		39		45	
Patient years of follow-up during interval		1240		1042		921		1450	
Background rate for general population[1]		0.0018		0.0020		0.0020		0.0021	
	N		N		N		N		
Baseline rate for transplanted patients if no risk factors present[2]		0.098		0.065		0.022		0.012	
+ Philadelphia/BCR-ABL+	280	**0.124** ***	199 *	0.031	165	0.029 *	145	0.014	
+ Second or greater remission at HCT	407	**0.126** ***	308	0.006	271	0.031 *	237	0.016 *	
+ Relapse/refractory at HCT	167	**0.316** ***	106	−0.004	93	−0.001	85	0.017	

b) Acute Lymphoblastic Leukemia		**1 year**		**2 years**		**3 years**		**4 years**	**5 years**
+ Extensive chronic GVHD, past or current	451	**0.085** ***	375	**0.047** **	332	0.023 *	299	**0.034** ***	

1 death rate expected in a general population cohort with similar sex and age distribution, for comparison with the transplanted population

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

*** p<0.2;

**** p<0.05;

***** p<0.01.

Values are in bold if p<0.05

1 death rate expected in a general population cohort with similar sex and age distribution, for comparison with the transplanted population

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

*** p<0.2;

**** p<0.05;

***** p<0.01.

Values are in bold if p<0.05

Table 3

Examples of 2 year estimated and actual leukemia free survival (LFS) and 95% confidence intervals for 1 year acute myeloid leukemia survivors. Observed LFS from the two most recent years is also shown

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	-	-

Biol Blood Marrow Transplant. Author manuscript; available in PMC 2014 November 01.

Table 4

Examples of 2 year estimated and actual leukemia free survival (LFS) and 95% confidence intervals for 1 year acute myeloid leukemia survivors. Observed LFS from the two most recent years is also shown

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	-	-

Table 5

Additive effects on subsequent one year probability of developing chronic graft-versus-host disease among AML/ALL disease-free survivors at one year. 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 – exponent (−x), with x being the sum of the baseline rate and any additional risk factors. If the event-rate is less than 0.2 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.

Chronic Graft-versus-host disease[1]		**1 year**
N at risk		2836
N of events		127
Patient years of follow-up		2481
	N	
Baseline rate for transplanted patients if no risk factors present [2]		0.019
+ non cyclosporine-based graft-versus-host disease prophylaxis without ATG or Campath	356	**0.087** ***
+ peripheral blood stem cell graft	755	**0.048** ***
+ donor other than HLA-identical sibling	734	**0.044** ***

[1] excluding 384 patients receiving T-cell depleted grafts, who experienced 3 events in 347 person years, or 0.009 events per person year at risk.

[2] 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<0.01.

Values are in bold if p<0.05