Published in final edited form as:

Leukemia. 2015 August ; 29(8): 1754–1762. doi:10.1038/leu.2015.75.

Primary Graft Failure after Myeloablative Allogeneic Hematopoietic Cell Transplantation for Hematologic Malignancies

Richard F. Olsson[1,2], **Brent R. Logan**[3,4], **Sonali Chaudhury**[5], **Xiaochun Zhu**[3], **Görgün Akpek**[6], **Brian J. Bolwell**[7], **Christopher N. Bredeson**[8], **Christopher C. Dvorak**[9], **Vikas Gupta**[10], **Vincent T. Ho**[11], **Hillard M. Lazarus**[12], **David I. Marks**[13], **Olle T.H. Ringdén**[1,17], **Marcelo C. Pasquini**[3], **Jeffrey R. Schriber**[14,15,*], and **Kenneth R. Cooke**[16,*]

[1]Division of Therapeutic Immunology, Department of Laboratory Medicine, Karolinska Institutet, Stockholm, Sweden

[2]Centre for Clinical Research Sörmland, Uppsala University, Uppsala, Sweden

[3]CIBMTR (Center for International Blood and Marrow Transplant Research, Department of Medicine, Medical College of Wisconsin, Milwaukee, WI

[4]Division of Biostatistics, Institute for Health and Society, Medical College of Wisconsin, Milwaukee, WI

[5]Division of Pediatric Hematology, Oncology and Stem Cell Transplant, Department of Pediatrics, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL

[6]Section of Hematology/Oncology, Banner MD Anderson Cancer Center, Gilbert, AZ

[7]Department of Hematology and Oncology, Cleveland Clinic, Cleveland, OH

[8]The Ottawa Hospital Blood and Marrow Transplant Program and the Ottawa Hospital Research Institute, Ottawa, ON, Canada

[9]Department of Pediatrics, University of California San Francisco Medical Center, San Francisco, CA

[10]Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada

[11]Center for Hematologic Oncology, Dana-Farber Cancer Institute, Boston, MA

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

[13]Pediatric Bone Marrow Transplant, University Hospitals Bristol NHS Trust, Bristol, United Kingdom

Correspondence: Richard F. Olsson, Division of Therapeutic Immunology, Department of Laboratory Medicine, Karolinska Institutet, 141 86 Stockholm, Sweden; richard.olsson@ki.se.

*Drs. Schriber and Cooke share senior author status

Conflict of Interest

The authors do not have any conflicts of interest to disclose.

Supplementary information is available on Leukemia's website.

[14]Cancer Transplant Institute, Virginia G. Piper Cancer Center, Scottsdale, AZ

[15]Arizona Oncology, Scottsdale, AZ

[16]Pediatric Blood and Marrow Transplantation Program, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD

[17]Centre for Allogeneic Stem Cell Transplantation, Stockholm, Sweden

Abstract

Clinical outcomes after primary graft failure (PGF) remain poor. Here we present a large retrospective analysis (n=23,272) which investigates means to prevent PGF and early detection of patients at high risk. In patients with hematologic malignancies, who underwent their first myeloablative allogeneic hematopoietic cell transplantation, PGF was reported in 1,278 (5.5%), and there was a marked difference in PGFs using peripheral blood stem cell compared to bone marrow grafts (2.5 vs. 7.3%; P<0.001). A 4-fold increase of PGF was observed in myeloproliferative disorders compared to acute leukemia (P<0.001). Other risk factors for PGF included recipient age below 30, HLA-mismatch, male recipients of female donor grafts, ABO-incompatibility, busulfan/cyclophosphamide conditioning, and cryopreservation. In bone marrow transplants, total nucleated cell doses ≤2.4 × 10^8/kg were associated with PGF (OR 1.39; P<0.001). The use of tacrolimus-based immunosuppression and granulocyte colony-stimulating factor were associated with decreased PGF risk. These data, allow clinicians to do more informed choices with respect to graft source, donor selection, conditioning and immunosuppressive regimens to reduce the risk of PGF. Moreover, a novel risk score determined on day 21 post-transplant may provide the rationale for an early request for additional hematopoietic stem cells.

Keywords

Allogeneic hematopoietic cell transplantation; primary graft failure; myeloablative; leukemia; myelodysplastic syndrome; myeloproliferative disorders

Introduction

Graft failure was one of the major causes of treatment failure in the early era of allogeneic hematopoietic cell transplantation (allo-HCT)[1, 2]. Today, allo-HCT is standard of care for many hematological diseases; however, graft failure remains a significant complication[3–5]. Primary graft failure (PGF) is characterized by the absence of initial donor cell engraftment; the patient never recovers from the neutropenia [absolute neutrophil count (ANC) <0.5×10^9/l] induced by the conditioning regimen. PGF is particularly devastating after myeloablative HCT because autologous hematopoietic recovery is rare, and death from infection and/or other complications of prolonged pancytopenia is likely in the absence of a second HCT. In contrast, secondary graft failure is defined as loss of donor cells after initial engraftment. The latter is more common after reduced intensity conditioning[5], and the need for a second transplant is usually less urgent since autologous hematopoietic recovery is more likely to occur. Historically, a number of factors including cell dose, cellular and humoral rejection, viral infections, and defective bone marrow stroma have been associated

with PGF[6–20]. Most previous reports on PGF have included patients with aplastic anemia, and a large analysis of risk factors for PGF in the modern era of allo-HCT for hematological malignancies has not yet been conducted. The aim of the present study was therefore to investigate risk factors for PGF after myeloablative allo-HCT in more than 20,000 patients with hematologic malignancies, and to develop a novel predictive risk score for PGF in patients that have not yet engrafted two-three weeks post-transplant to acquire more lead-time to improve the clinical outcome in patients that do not engraft.

Patients and Methods

Data Source

This retrospective study used the Center for International Blood and Marrow Transplant Research (CIBMTR) database, a voluntary research affiliation of more than 450 transplantation centers worldwide that contribute detailed data on all completed autologous- and allo-HCT to a Statistical Center at the Medical College of Wisconsin in Milwaukee. The CIBMTR maintains an extensive database including detailed transplant-related information. Participating centers are required to report all transplants consecutively; patients are followed longitudinally with yearly follow-ups and compliance is monitored by computerized checks for discrepancies, physicians' review of submitted data and on-site audits. Observational studies conducted by the CIBMTR are performed in compliance with the Privacy Rule (HIPAA) as a Public Health Authority, as well as all applicable federal regulations pertaining to the protection of human research participants.

Patient Selection

We retrieved 23,272 patients from the CIBMTR database with acute leukemia, chronic leukemia, myelodysplastic syndrome (MDS) or myeloproliferative disorder [primary myelofibrosis, polycythemia vera, essential thrombocythemia (MPD)], who were reported for their first myeloablative allo-HCT using unrelated or HLA identical sibling donors and either bone marrow (BM) or peripheral blood stem cells (PB) between 1995 and 2008. The CIBMTR working definition of regimen intensity was utilized in this study to select transplants that only included myeloablative conditioning regimens[21]. The myeloablative properties of all conditioning regimens were confirmed by reported doses of the myeloablative agents (≥5 Gy single dose or ≥8 Gy fractionated TBI, ≥9 mg/kg busulfan, or ≥150 mg/m^2 melphalan). We did not discriminate between oral and intravenous busulfan. All classification on HLA match in the present study cohort was based on Weisdorf et al[22], which classifies HLA matching in three major groups: well matched (no known disparity at HLA A,B,C,DRB1), partially matched (one locus known or likely disparity), and mismatched (≥2 locus disparity). HLA typing methodology has evolved over time, the determination of matching in the earlier years might be considered not fully matched by today's standard, but this classification enables analyses that span over a long period of time as the present study.

Study Endpoint

PGF was defined as: 1) alive on day 28 with ANC $<0.5\times10^9$/l, or 2) ANC $<0.5\times10^9$/l and donor cell infusion (donor lymphocyte infusion, boost, re-transplantation) within 28 days

post-transplant. Death (n=717) and progressive disease (n=100) within 28 days were competing risks. Chimerism data was not available for most patients in this study.

Statistical Analysis

To summarize the characteristics of the dataset, descriptive tables of patient-, disease- and transplant-related variables were performed for all patients in the cohort as well as for patients surviving without engraftment on day 14 and day 21 following HCT. For discrete factors, the number of cases and their respective percentages were calculated. For continuous factors, the median and ranges were calculated. To determine risk factors for PGF, a forward stepwise logistic regression was used to model the odds of PGF as a function of pre-transplant prognostic factors (patient and donor age, gender match, Karnofsky/Lansky score, disease, disease status, conditioning regimen, unrelated donor age, donor pregnancies and transfusions, HLA match, ABO incompatibility, graft type, cell dose, cryopreservation, growth factor, immunosuppression, anti-thymocyte globulin (ATG), alemtuzumab, CMV match, major fungal infections pre-transplant, and year of transplant). All two-way interactions were checked, and P-values <0.05 were considered significant. After a preliminary model building stage, the model was adjusted to compensate for any center effects using generalized estimating equations with a sandwich variance estimate, and 17 cases with unknown center were excluded. Secondary objectives included evaluation and modeling of the risk of PGF in children, and in the subgroup of patients alive but without engraftment or progressive disease day 14 after HCT. Similar techniques were used for this analysis as for the analysis in the larger cohort. Patients at risk for PGF on day 21 post-transplant were randomly divided in training (2/3) and validation (1/3) datasets. By means of multivariate modelling, a risk score was created based on approximate coefficients from the logistic models built on the training dataset. A cutpoint for high vs. low risk was determined based on sensitivity and specificity in the training dataset, and the predictive capability was confirmed in the validation dataset. SAS Version 9.1 (SAS Institute, Cary, NC) were used for all analyses.

Results

PGF was reported in 1,278 out of 23,272 (5.5%) patients. In 1,253 patients the ANC was $<0.5\times10^9$/l on day 28, and 25 patients with ANC $<0.5\times10^9$/l received a second donor cell infusion before day 28 post-transplant. The main patient characteristics are described in table 1, and detailed univariate analyses are depicted in supplemental data 1. The results of the multivariate model for risk factors at transplant (table 2) are described below. Interactions were formally tested for all variables that entered the final model and none were significant besides the built-in interactions for donor/HLA and spleen status by disease.

Patient-related factors

Age ≥30 years was associated with decreased risk of PGF (OR=0.75, P<0.001), whereas female to male gender mismatch (OR=1.28, P=0.001), and Karnofsky/Lansky score <90% (OR=1.18, P=0.042) were associated with increased risk.

Disease-related factors

Compared to AML, an increased risk of PGF was observed in chronic lymphocytic leukemia (CLL) (OR=1.57, P=0.003) and chronic myelogenous leukemia (CML) (OR=1.88, P<0.001). In patients with MPD or MDS, the effect of disease was dependent on spleen status, where presence of splenomegaly was associated with even greater risk of PGF (MPD: OR=3.92, P=0.001; MDS: OR=2.34, P=0.002). After splenectomy, MPD and MDS patients had similar risk of PGF as corresponding patients with normal spleen (MPD OR=1.68, P=0.341; MDS OR=1.68, P=0.193). Due to a high percentage (≥45%) of missing data the impact of spleen status was not investigated in acute and chronic leukemia. In AML, ALL, and CML higher PGF rates were observed in advanced disease (OR=1.54, P<0.001). In MDS, disease status was not associated with PGF, and disease status was not evaluated in CLL and MPD.

Transplant-related factors

Busulfan/Cyclophosphamide (Bu/Cy) was associated with increased risk of PGF when compared to TBI/Cy (OR=1.35, P=0.002). The dose of TBI (range 5–20 Gy) or Bu (range 9–30 mg/kg) in combination with Cy did not influence PGF rates (data not shown). Donor age was not investigated in HLA identical siblings due to the close relationship to recipient age. Unrelated donor age, donor transfusions, or pregnancies did not affect PGF rates (data not shown). Well matched unrelated donors were associated with PGF when compared to HLA identical siblings (OR=1.38, P<0.001), and the highest risk of PGF was seen in mismatched donors (OR=1.79, P<0.001). Mismatched grafts had significantly higher PGF compared to both well matched (OR=1.30; P=0.019) and partially matched (OR=1.38; P=0.015) grafts, whereas partially matched grafts had similar PGF risk when compared to well matched grafts (OR=0.94; P=0.540). Minor ABO mismatch did not affect PGF, whereas in major ABO mismatch a higher risk was noted (OR=1.24, P=0.012).

The incidence of PGF was markedly lower in PB compared to BM grafts (2.5 vs. 7.3%; P<0.001). In BM, a total nucleated cell (TNC) dose ≤2.4×10^8/kg was associated with PGF (OR=1.39, P<0.001). However, low CD34 cell doses (0.1–2 × 106/kg) had no impact on PGF in 533 patients who received PB. Irrespective of graft source cryopreservation (OR=1.43, P=0.013) was associated with PGF, whereas G-CSF was observed to reduce the risk (OR=0.36, P<0.001). Compared to standard immunosuppression with cyclosporine (CSA) and methotrexate (MTX), tacrolimus and MTX (OR=0.61, P<0.001) was associated with lower PGF risk. Notably, neither ex vivo T-cell depletion (OR=1.13, P=0.383) nor in vivo T-cell depletion with ATG or alemtuzumab were associated with PGF. Pre-HCT CMV match or prior major fungal infections were not associated with PGF. Impact of viral infections was not investigated due to a high number of missing data. Transplantation after 2003 was associated with PGF (OR=1.28, P=0.011). During 1995–2002 death within 28 days post-transplant without engraftment was increased (4.17% vs. 2.13%, P<0.001), whereas disease progression within 28 days was similar (0.43% vs. 0.46%, P=0.742). Donor cell infusions within 28 days in non-engrafted subjects were more common in the early era (0.14% vs. 0.05%, P=0.028).

Children

In 5,975 children and adolescents (<21 years old) there were 406 (6.8%) PGFs. Age, disease, spleen status, HLA match, cryopreservation, and year of transplant were no longer significant when the analysis was restricted to recipients younger than 21 years (table 3). Other risk factors were similar to those reported for the whole population.

Landmark analysis on day 14 or day 21 post-transplant, and PGF risk score

Two weeks post-transplant 16,653 subjects were at risk for PGF, and the incidence of PGF was 7.7%. Most risk factors were similar to those reported at transplant (supplemental data 2). Of note, ex vivo T-cell depletion became impactful on PGF (OR=1.36, P=0.022). The incidence of PGF in patients at risk two weeks post-transplant was too low to develop a useful risk score. Three weeks post-transplant, 6,050 subjects were at risk for PGF, and the incidence of PGF was 21.0%. In the training cohort, nine variables affected the risk of PGF (table 4). In contrast to our previous analyses, PB grafts were associated with increased risk of PGF (OR=1.41, P=0.010), and ex vivo T-cell depletion remained an important risk factor (OR=2.30, P<0.001). A risk score was developed (table 5) and a cut-off at risk score 7 was noted (table 6). In the training dataset the sensitivity was 20% and the specificity 90%, whereas in the validation dataset the sensitivity was 16% and the specificity 89%. In the training and validation datasets the positive predictive values for risk score ≥7 were 36% and 28%, respectively. In both cohorts, the negative predictive values for risk score <7 were 81%.

Overall Survival and Causes of death

One-year probabilities of overall survival among patients who are alive at day 28 post transplant were 45% (95% Confidence Interval [CI],42–48 %) and 61% (95% CI, 60–62%, p<0.001) if they developed or not PGF (Figure 1). Irrespective of prior PGF, primary disease was the cause of death in approximately 30% of all deceased subjects. Infection was the second most common cause of death with similar percentages in both groups (~15%), whereas graft failure as cause of death appeared more common among patients with prior PGF (11% vs. <1%). All causes of death are depicted in supplemental data 3.

Discussion

Recent data show that one year overall survival after re-transplantation due to PGF without relapse is as low as 11%[4]. Thus, the rationale for the present study was to conduct a large CIBMTR registry study to establish parameters to predict and avoid PGF in the future. Risk factors for PGF may be related to characteristics of the graft, the patient, the donor, or the transplantation procedure. In this study, graft type was the strongest risk factor in the multivariate model for PGF, with a 3 times higher risk in BM compared to PB grafts. Many factors, such as cell dose and the 10-fold higher number of CD3 cells in PB likely facilitate engraftment[23], and contribute to the lower incidence of PGF using PB. That cell dose is important for the establishment of proper graft function is also supported by previous studies showing associations between cell dose and infection, GVHD, overall treatment failure, and survival[24–29]. In the present study, BM grafts with low cell dose (TNC doses $\leq 2.4\times10^8$/kg) resulted in a 40% rise in PGF, which is similar to previously reported data[28]. Previous

studies report a weak association between CD34 cell dose of PB grafts and days to engraftment[30, 31]. However, the current analysis did not reveal any impact of PB CD34 cell dose on PGF, and even in recipients of cell doses below 2×10^6/kg we were not able to define any threshold associated with increased risk of PGF. This suggests that PB products *per se* are associated with cell doses above the threshold that would affect PGF, or other cell subtypes such as T-cells may be equally or more important for engraftment. Nevertheless, while other factors seem more important for PGF CD34 cell dose is probably important for subsequent secondary graft failure[32].

Patient-related risk factors for PGF included age below 30 years, Karnofsky/Lansky score <90%, and primary diseases such as chronic leukemia, MDS, and MPD. In reduced intensity allo-HCT, CLL has been reported to be associated with graft failure[33], and it is likely that primary disease may affect the probability of PGF indirectly due to intensity differences in pre-transplant chemotherapeutic protocols. Indeed, the disorders with the highest risk of PGF in our cohort were diseases which usually require chemotherapy of low to moderate intensity pre-transplant. Furthermore, the association between PGF and MPD has been well recognized[34, 35], and is most likely dependent on multiple factors, including the impact of a defective bone marrow stroma, splenic consumption of infused stem cells[36], and increased risk of allo-immunization following multiple transfusions[37]. Splenomegaly is a factor contributing to PGF in MPDs according to the present data. The availability of JAK2 inhibitors provides the opportunity to test whether treatment before transplantation can decrease the spleen size and offset the risk of PGF after transplantation for MPD[38]. Any further evaluations of the impact of spleen size by examination and/or imaging studies were unfortunately not possible since these data were not available in the database. The main purpose of the conditioning regimen is to suppress the recipient's hematopoietic system to prevent an immunological rejection as well as to provide space for the infused donor cells to engraft[39]. In view of this, the higher risk of PGF in patients below 30 years may reflect that children immunity rather than hematopoiesis is more resistant to conditioning. Moreover, advanced disease and Karnofsky/Lansky score <90% were associated with increased PGF risk, which may imply that the donor cells are implanted into an impaired hematopoietic microenvironment. Further studies are needed to reveal the true mechanisms behind these findings.

HLA-compatibility between donor and recipient is of major importance for predicting graft failure[40]. As expected, HLA match was associated with the risk of PGF. Well matched unrelated donors are mismatched at DPB1 in more than 80% of the cases, and DPB1 can drive T-cells and antibody responses associated with graft failure[41, 42]. Thus, the observed increased PGF risk with well matched unrelated transplants should not be surprising, since DPB1 disparity may well be responsible for the increased risk of PGF compared to HLA identical sibling grafts. Furthermore, the risk of PGF was similar in well matched and partially mismatched unrelated grafts. This was; however, rather surprising since prior studies have observed that HLA class I and HLA-C mismatches are important determinants for graft failure[43, 44]. However, the higher risk of PGF in mismatched compared to both well and partially matched unrelated grafts still suggests that immunological T cell mediated responses towards HLA contributes to PGF.

Interestingly, in the sub-analysis in children there was no HLA effect detected, whereas the increase of PGF in major ABO-incompatibility remained. In contrast to adults, almost 90% of children received BM and a slightly higher TNC dose of $\geq 3.0\times10^8$/kg was needed to reduce PGFs, which may reflect a higher median TNC dose in children due to their lower weight. Major ABO mismatch during unrelated donor allo-HCT has been associated with graft failures[8]. Our data show that this is true also for HLA identical sibling donors, and regardless of the stem cell source is BM or PB. Erythrocyte and/or plasma depletion from ABO incompatible BM or PB products may compromise stem cell and T-cell viability as well as reduce graft cell numbers. Unfortunately, the CIBMTR database did not include data on erythrocyte/plasma depletion. However, previous single center reports, where red cell depletion and plasma reduction always are performed before cell counting, have reported similar ABO-effect[8]. Major ABO-incompatibility was associated with PGF even when cell dose was adjusted for, but since hematopoietic stem cells and granulocytes do not express AB antigens the mechanism for this finding requires further investigations[45, 46]. The impact of donor gender and PGF remains unclear. However, in line with the present data male donor has previously been reported to be associated with decreased risk of PGF[47]. To date, the present study is probably the largest analysis on PGF and donor/recipient gender match. We report that female to male gender mismatch increases the risk of PGF, whereas all other gender combinations have similar risk of PGF. Thus, when considering the risk for PGF male donor is preferred to a male patient, whereas donor sex does not matter for female recipients. In association to GVHD, immunological responses against minor antigens associated with the recipients Y chromosome are well known[48, 49]; it is, however, surprising that this gender mismatch also increases PGFs. Any underlying immunological mechanism has probably no association with the Y chromosome, although the true mechanism, which may not be immunological, seems elusive. Moreover, there are previous studies that report that female recipients reject male donor grafts most likely due to an allo-immunity towards antigens associated with the Y chromosome. In general these reports refer to rejection/secondary graft failure in H-Y immunized subjects[50, 51], which may explain the discrepancy with the present analysis.

There is a well-documented association between ex vivo T-cell depletion and graft failure[52], but we did not observe such an effect in the overall population. Notably, the present study only included myeloablative conditioning regimens and increased conditioning intensity has previously been reported to decrease graft failures using T-cell depleted grafts[53–55]. Moreover, our model adjusts for cell dose suggesting that a higher graft cell dose may reduce the risk of graft failure. However, in the present analysis T-cell depleted products were still associated with PGF among patients that had not engrafted two-three weeks post-transplant. In contrast to previous reports, in vivo T-cell depletion using ATG or alemtuzumab, was not associated with graft failures[56, 57]. That T-cell depletion, in the overall population, does not increase the risk of PGF may seem counterintuitive, and we have not been able to fully explain this finding. However, since the vast majority (87%) of all T-cell depleted grafts was BM; the strong graft source effect may conceal the impact of T-cell depletion at transplant. Moreover, the association between cryopreservation of the stem cell product prior to infusion and increased PGF risk is likely attributable to T-cell impairment as well as lower cell dose after thawing[58].

With respect to factors associated with the HCT procedure, TBI/Cy conditioning and tacrolimus-based immunosuppression both were associated with decreased PGF risk. All patients receiving TBI-based myeloablative conditioning regimens received ≥5 Gy single or 8 Gy fractionated dose, and higher doses had no effect on PGF. As previously reported, G-CSF initiated within one week post-transplant diminished the PGF risk[59]. Surprisingly, in the multivariate model there was 28% higher risk of PGF in patients transplanted 2003–2008 compared to 1995–2002. This was not explained by any differences associated with the present PGF definition including deaths, progressive disease or donor cell infusions within 28 days post-transplant. Notably, the absolute number of PGFs was lower in the latter era, mainly due to increased use of PB, suggesting that even fewer PGFs should be expected in recent years. Conditioning regimens and intensity have also changed over the years, but this did not explain the increased PGF risk in the latter era. The reason for this remains to be determined.

Lastly, we developed a risk score for PGF in non-engrafted patients on day 21 post-transplant, and the predictive capability of the risk score was confirmed in a validation cohort. The time to engraftment is markedly different for BM and PB, but when we first modeled BM and PB separately we found similar results except for cell dose. We therefore chose to model them together to improve the statistical power of the analysis. The sensitivity and specificity were approximately 20% and 90%, respectively, and in the validation cohort PGF was predicted in 28% of high risk patients and no PGF was predicted in 81% of low risk patients. Since the positive predictive value of this model is low too much uncertainly exist to modify practice, besides ordering appropriate diagnostic testing, bone marrow biopsy and blood T cell chimerism, and develop contingency plans in the case of PGF.

All retrospective registry studies are dependent on the quality of data input. Indeed the CIBMTR routinely monitor data reported from participating centers to ensure data quality. There are; however, limitations associated with the retrospective nature of this study, but it is likely the only feasible strategy to study a rare event such as PGF. The power of the present risk score to predict PGF is limited, but due to the high specificity we believe that it contributes to the future management of patients who have not yet engrafted on day 21 post-transplant. In high risk patients, we suggest that G-CSF treatment is started, although the present analysis only show that pre-planned G-CSF starting within one week post-transplant decrease the risk of PGF, and the transplant physician may initiate early planning for a rescue transplant, whereas in low risk patients there is no reason for an early planning since a significant number of these patients will engraft.

In conclusion, PGF remains an important clinical problem in myeloablative allo-HCT. In this largest PGF analysis ever undertaken, we have identified many important risk factors, which should prove helpful in assessing the risk of PGF pre-transplant, and allow clinicians to make more informed choices for their patients with respect to BM versus PB, donor selection, immunosuppressive regimens, and when to plan for a rescue transplantation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

The first author (R.F.O.) thanks the Swedish Society for Medical Research (SSMF), the Swedish Medical Society, the Centre for Clinical Research Sörmland, Uppsala University, the David and Astrid Hagelén's Foundation and Karolinska Institutet for their financial support.

The CIBMTR is supported by Public Health Service Grant/Cooperative Agreement U24-CA076518 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 5U10HL069294 from NHLBI and NCI; a contract HHSH250201200016C with Health Resources and Services Administration (HRSA/DHHS); two Grants N00014-12-1-0142 and N00014-13-1-0039 from the Office of Naval Research; and grants from *Actinium Pharmaceuticals; Allos Therapeutics, Inc.; *Amgen, Inc.; Anonymous donation to the Medical College of Wisconsin; Ariad; Be the Match Foundation; *Blue Cross and Blue Shield Association; *Celgene Corporation; Chimerix, Inc.; Fred Hutchinson Cancer Research Center; Fresenius-Biotech North America, Inc.; *Gamida Cell Teva Joint Venture Ltd.; Genentech, Inc.;*Gentium SpA; Genzyme Corporation; GlaxoSmithKline; Health Research, Inc. Roswell Park Cancer Institute; HistoGenetics, Inc.; Incyte Corporation; Jeff Gordon Children's Foundation; Kiadis Pharma; The Leukemia & Lymphoma Society; Medac GmbH; The Medical College of Wisconsin; Merck & Co, Inc.; Millennium: The Takeda Oncology Co.; *Milliman USA, Inc.; *Miltenyi Biotec, Inc.; National Marrow Donor Program; Onyx Pharmaceuticals; Optum Healthcare Solutions, Inc.; Osiris Therapeutics, Inc.; Otsuka America Pharmaceutical, Inc.; Perkin Elmer, Inc.; *Remedy Informatics; *Sanofi US; Seattle Genetics; Sigma-Tau Pharmaceuticals; Soligenix, Inc.; St. Baldrick's Foundation; StemCyte, A Global Cord Blood Therapeutics Co.; Stemsoft Software, Inc.; Swedish Orphan Biovitrum; *Tarix Pharmaceuticals; *TerumoBCT; *Teva Neuroscience, Inc.; *THERAKOS, Inc.; University of Minnesota; University of Utah; 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, Health Resources and Services Administration (HRSA) or any other agency of the U.S. Government.

References

1. Jonson FL, Hartmann JR, Thomas ED, Chard RL, Hersman JA, Buckner CD, et al. Marrow transplantation in treatment of children with aplastic anaemia or acute leukaemia. Arch Dis Child. 1976; 51:403–410. [PubMed: 8016]
2. Storb R, Thomas ED, Weiden PL, Buckner CD, Clift RA, Fefer A, et al. Aplastic anemia treated by allogeneic bone marrow transplantation: a report on 49 new cases from Seattle. Blood. 1976; 48:817–841. [PubMed: 11859]
3. Remberger M, Mattsson J, Olsson R, Ringden O. Second allogeneic hematopoietic stem cell transplantation: a treatment for graft failure. Clin Transplant. 2011; 25:E68–E76. [PubMed: 20946467]
4. Schriber J, Agovi MA, Ho V, Ballen KK, Bacigalupo A, Lazarus HM, et al. Second unrelated donor hematopoietic cell transplantation for primary graft failure. Biol Blood Marrow Transplant. 2010; 16:1099–1106. [PubMed: 20172038]
5. Olsson R, Remberger M, Schaffer M, Berggren DM, Svahn BM, Mattsson J, et al. Graft failure in the modern era of allogeneic hematopoietic SCT. Bone marrow transplantation. 2013; 48:537–543. [PubMed: 23222384]
6. Mattsson J, Ringden O, Storb R. Graft Failure after Allogeneic Hematopoietic Cell Transplantation. Biol Blood Marrow Transplant. 2008; 14:165–170.
7. Crocchiolo R, Ciceri F, Fleischhauer K, Oneto R, Bruno B, Pollichieni S, et al. HLA matching affects clinical outcome of adult patients undergoing haematopoietic SCT from unrelated donors: a study from the Gruppo Italiano Trapianto di Midollo Osseo and Italian Bone Marrow Donor Registry. Bone marrow transplantation. 2009; 44:571–577. [PubMed: 19363528]
8. Remberger M, Watz E, Ringden O, Mattsson J, Shanwell A, Wikman A. Major ABO blood group mismatch increases the risk for graft failure after unrelated donor hematopoietic stem cell transplantation. Biol Blood Marrow Transplant. 2007; 13:675–682. [PubMed: 17531777]
9. Cudkowicz G, Bennett M. Peculiar immunobiology of bone marrow allografts. I. Graft rejection by irradiated responder mice. J Exp Med. 1971; 134:83–102. [PubMed: 4397663]
10. Kiessling R, Hochman PS, Haller O, Shearer GM, Wigzell H, Cudkowicz G. Evidence for a similar or common mechanism for natural killer cell activity and resistance to hemopoietic grafts. Eur J Immunol. 1977; 7:655–663. [PubMed: 336380]

11. Murphy WJ, Kumar V, Bennett M. Acute rejection of murine bone marrow allografts by natural killer cells and T cells. Differences in kinetics and target antigens recognized. J Exp Med. 1987; 166:1499–1509. [PubMed: 3316472]
12. Raff RF, Deeg HJ, Loughran TP Jr, Graham TC, Aprile JA, Sale GE, et al. Characterization of host cells involved in resistance to marrow grafts in dogs transplanted from unrelated DLA-nonidentical donors. Blood. 1986; 68:861–868. [PubMed: 3530349]
13. Raff RF, Sandmaier BM, Graham T, Loughran TP Jr, Pettinger M, Storb R. 'Resistance' to unrelated, DLA-nonidentical canine marrow grafts is unrestricted by the major histocompatibility complex. Experimental hematology. 1994; 22:893–897. [PubMed: 8062888]
14. Barge AJ, Johnson G, Witherspoon R, Torok-Storb B. Antibody-mediated marrow failure after allogeneic bone marrow transplantation. Blood. 1989; 74:1477–1480. [PubMed: 2790180]
15. Moeller E. Contact-Induced Cytotoxicity by Lymphoid Cells Containing Foreign Isoantigens. Science. 1965; 147:873–879. [PubMed: 14245768]
16. Storb R, Floersheim GL, Weiden PL, Graham TC, Kolb HJ, Lerner KG, et al. Effect of prior blood transfusions on marrow grafts: abrogation of sensitization by procarbazine and antithymocyte serum. J Immunol. 1974; 112:1508–1516. [PubMed: 4592604]
17. Taylor PA, Ehrhardt MJ, Roforth MM, Swedin JM, Panoskaltsis-Mortari A, Serody JS, et al. Preformed antibody, not primed T cells, is the initial and major barrier to bone marrow engraftment in allosensitized recipients. Blood. 2007; 109:1307–1315. [PubMed: 17018854]
18. Warren RP, Storb R, Weiden PL, Su PJ, Thomas ED. Lymphocyte-mediated cytotoxicity and antibody-dependent cell-mediated cytotoxicity in patients with aplastic anemia: distinguishing transfusion-induced sensitization from possible immune-mediated aplastic anemia. Transplant Proc. 1981; 13:245–247. [PubMed: 7022832]
19. Nordlander A, Mattsson J, Sundberg B, Sumitran-Holgersson S. Novel antibodies to the donor stem cell population CD34+/VEGFR-2+ are associated with rejection after hematopoietic stem cell transplantation. Transplantation. 2008; 86:686–696. [PubMed: 18791450]
20. Cutler C, Kim HT, Sun L, Sese D, Glotzbecker B, Armand P, et al. Donor-specific anti-HLA antibodies predict outcome in double umbilical cord blood transplantation. Blood. 2011; 118:6691–6697. [PubMed: 21940825]
21. Bacigalupo A, Ballen K, Rizzo D, Giralt S, Lazarus H, Ho V, et al. Defining the intensity of conditioning regimens: working definitions. Biol Blood Marrow Transplant. 2009; 15:1628–1633. [PubMed: 19896087]
22. Weisdorf D, Spellman S, Haagenson M, Horowitz M, Lee S, Anasetti C, 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. [PubMed: 18541193]
23. Korbling M, Anderlini P. Peripheral blood stem cell versus bone marrow allotransplantation: does the source of hematopoietic stem cells matter? Blood. 2001; 98:2900–2908. [PubMed: 11698269]
24. Bortin MM, Gale RP, Kay HE, Rimm AA. Bone marrow transplantation for acute myelogenous leukemia. Factors associated with early mortality. Jama. 1983; 249:1166–1175. [PubMed: 6337286]
25. Ringden O, Barrett AJ, Zhang MJ, Loberiza FR, Bolwell BJ, Cairo MS, et al. Decreased treatment failure in recipients of HLA-identical bone marrow or peripheral blood stem cell transplants with high CD34 cell doses. Br J Haematol. 2003; 121:874–885. [PubMed: 12786798]
26. Ringden O, Nilsson B. Death by graft-versus-host disease associated with HLA mismatch, high recipient age, low marrow cell dose, and splenectomy. Transplantation. 1985; 40:39–44. [PubMed: 3892795]
27. Sierra J, Storer B, Hansen JA, Bjerke JW, Martin PJ, Petersdorf EW, et al. Transplantation of marrow cells from unrelated donors for treatment of high-risk acute leukemia: the effect of leukemic burden, donor HLA-matching, and marrow cell dose. Blood. 1997; 89:4226–4235. [PubMed: 9166868]
28. Storb R, Prentice RL, Thomas ED. Marrow transplantation for treatment of aplastic anemia. An analysis of factors associated with graft rejection. The New England journal of medicine. 1977; 296:61–66. [PubMed: 136605]

29. Tollemar J, Ringden O, Bostrom L, Nilsson B, Sundberg B. Variables predicting deep fungal infections in bone marrow transplant recipients. Bone marrow transplantation. 1989; 4:635–641. [PubMed: 2555004]
30. Zaucha JM, Gooley T, Bensinger WI, Heimfeld S, Chauncey TR, Zaucha R, et al. CD34 cell dose in granulocyte colony-stimulating factor-mobilized peripheral blood mononuclear cell grafts affects engraftment kinetics and development of extensive chronic graft-versus-host disease after human leukocyte antigen-identical sibling transplantation. Blood. 2001; 98:3221–3227. [PubMed: 11719357]
31. Nakamura R, Auayporn N, Smith DD, Palmer J, Sun JY, Schriber J, et al. Impact of graft cell dose on transplant outcomes following unrelated donor allogeneic peripheral blood stem cell transplantation: higher CD34+ cell doses are associated with decreased relapse rates. Biol Blood Marrow Transplant. 2008; 14:449–457. [PubMed: 18342788]
32. Nakamae H, Storer B, Sandmaier BM, Maloney DG, Davis C, Corey L, et al. Cytopenias after day 28 in allogeneic hematopoietic cell transplantation: impact of recipient/donor factors, transplant conditions and myelotoxic drugs. Haematologica. 2011; 96:1838–1845. [PubMed: 21880629]
33. Delgado J, Thomson K, Russell N, Ewing J, Stewart W, Cook G, et al. Results of alemtuzumab-based reduced-intensity allogeneic transplantation for chronic lymphocytic leukemia: a British Society of Blood and Marrow Transplantation Study. Blood. 2006; 107:1724–1730. [PubMed: 16239425]
34. Abelsson J, Merup M, Birgegard G, WeisBjerrum O, Brinch L, Brune M, et al. The outcome of allo-HSCT for 92 patients with myelofibrosis in the Nordic countries. Bone marrow transplantation. 2012; 47:380–386. [PubMed: 21552298]
35. Ballen KK, Woolfrey AE, Zhu X, Ahn KW, Wirk B, Arora M, et al. Allogeneic hematopoietic cell transplantation for advanced polycythemia vera and essential thrombocythemia. Biol Blood Marrow Transplant. 2012; 18:1446–1454. [PubMed: 22449610]
36. Akpek G, Pasquini MC, Logan B, Agovi MA, Lazarus HM, Marks DI, et al. Effects of spleen status on early outcomes after hematopoietic cell transplantation. Bone marrow transplantation. 2013; 48:825–831. [PubMed: 23222382]
37. Champlin RE, Horowitz MM, van Bekkum DW, Camitta BM, Elfenbein GE, Gale RP, et al. Graft failure following bone marrow transplantation for severe aplastic anemia: risk factors and treatment results. Blood. 1989; 73:606–613. [PubMed: 2644980]
38. Gupta V, Hari P, Hoffman R. Allogeneic hematopoietic cell transplantation for myelofibrosis in the era of JAK inhibitors. Blood. 2012; 120:1367–1379. [PubMed: 22700718]
39. Kang HJ, Shin HY, Park JE, Chung NG, Cho B, Kim HK, et al. Successful engraftment with fludarabine, cyclophosphamide, and thymoglobulin conditioning regimen in unrelated transplantation for severe aplastic anemia: A phase II prospective multicenter study. Biol Blood Marrow Transplant. 2010; 16:1582–1588. [PubMed: 20685256]
40. Petersdorf EW, Gooley TA, Anasetti C, Martin PJ, Smith AG, Mickelson EM, et al. Optimizing outcome after unrelated marrow transplantation by comprehensive matching of HLA class I and II alleles in the donor and recipient. Blood. 1998; 92:3515–3520. [PubMed: 9808542]
41. Fleischhauer K, Locatelli F, Zecca M, Orofino MG, Giardini C, De Stefano P, et al. Graft rejection after unrelated donor hematopoietic stem cell transplantation for thalassemia is associated with nonpermissive HLA-DPB1 disparity in host-versus-graft direction. Blood. 2006; 107:2984–2992. [PubMed: 16317094]
42. Spellman S, Bray R, Rosen-Bronson S, Haagenson M, Klein J, Flesch S, et al. The detection of donor-directed, HLA-specific alloantibodies in recipients of unrelated hematopoietic cell transplantation is predictive of graft failure. Blood. 2010; 115:2704–2708. [PubMed: 20089963]
43. Morishima Y, Sasazuki T, Inoko H, Juji T, Akaza T, Yamamoto K, et al. The clinical significance of human leukocyte antigen (HLA) allele compatibility in patients receiving a marrow transplant from serologically HLA-A, HLA-B, and HLA-DR matched unrelated donors. Blood. 2002; 99:4200–4206. [PubMed: 12010826]
44. Petersdorf EW, Hansen JA, Martin PJ, Woolfrey A, Malkki M, Gooley T, et al. Major-histocompatibility-complex class I alleles and antigens in hematopoietic-cell transplantation. The New England journal of medicine. 2001; 345:1794–1800. [PubMed: 11752355]

45. Daniel-Johnson J, Schwartz J. How do I approach ABO-incompatible hematopoietic progenitor cell transplantation? Transfusion. 2011; 51:1143–1149. [PubMed: 21382041]
46. Kelton JG, Bebenek G. Granulocytes do not have surface ABO antigens. Transfusion. 1985; 25:567–569. [PubMed: 4071602]
47. Davies SM, Kollman C, Anasetti C, Antin JH, Gajewski J, Casper JT, et al. Engraftment and survival after unrelated-donor bone marrow transplantation: a report from the national marrow donor program. Blood. 2000; 96:4096–4102. [PubMed: 11110679]
48. Nash RA, Pepe MS, Storb R, Longton G, Pettinger M, Anasetti C, et al. Acute graft-versus-host disease: analysis of risk factors after allogeneic marrow transplantation and prophylaxis with cyclosporine and methotrexate. Blood. 1992; 80:1838–1845. [PubMed: 1391947]
49. Saliba RM, de Lima M, Giralt S, Andersson B, Khouri IF, Hosing C, et al. Hyperacute GVHD: risk factors, outcomes, and clinical implications. Blood. 2007; 109:2751–2758. [PubMed: 17138825]
50. Rufer N, Starobinski M, Chapuis B, Gratwohl A, Jeannet M, Helg C, et al. Clinical consequences of sensitisation to minor histocompatibility antigens before allogeneic bone marrow transplantation. Bone marrow transplantation. 1998; 22:895–898. [PubMed: 9827818]
51. Stern M, Passweg JR, Locasciulli A, Socie G, Schrezenmeier H, Bekassy AN, et al. Influence of donor/recipient sex matching on outcome of allogeneic hematopoietic stem cell transplantation for aplastic anemia. Transplantation. 2006; 82:218–226. [PubMed: 16858285]
52. Marmont AM, Horowitz MM, Gale RP, Sobocinski K, Ash RC, van Bekkum DW, et al. T-cell depletion of HLA-identical transplants in leukemia. Blood. 1991; 78:2120–2130. [PubMed: 1912589]
53. Soderling CC, Song CW, Blazar BR, Vallera DA. A correlation between conditioning and engraftment in recipients of MHC-mismatched T cell-depleted murine bone marrow transplants. J Immunol. 1985; 135:941–946. [PubMed: 3891856]
54. Seidel MG, Fritsch G, Matthes-Martin S, Lawitschka A, Lion T, Potschger U, et al. In vitro and in vivo T-cell depletion with myeloablative or reduced-intensity conditioning in pediatric hematopoietic stem cell transplantation. Haematologica. 2005; 90:1405–1414. [PubMed: 16219578]
55. Devine SM, Carter S, Soiffer RJ, Pasquini MC, Hari PN, Stein A, et al. Low risk of chronic graft-versus-host disease and relapse associated with T cell-depleted peripheral blood stem cell transplantation for acute myelogenous leukemia in first remission: results of the blood and marrow transplant clinical trials network protocol 0303. Biol Blood Marrow Transplant. 2011; 17:1343–1351. [PubMed: 21320619]
56. Small TN, Avigan D, Dupont B, Smith K, Black P, Heller G, et al. Immune reconstitution following T-cell depleted bone marrow transplantation: effect of age and posttransplant graft rejection prophylaxis. Biol Blood Marrow Transplant. 1997; 3:65–75. [PubMed: 9267666]
57. Meijer E, Cornelissen JJ, Lowenberg B, Verdonck LF. Antithymocyteglobulin as prophylaxis of graft failure and graft-versus-host disease in recipients of partially T-cell-depleted grafts from matched unrelated donors: a dose-finding study. Experimental hematology. 2003; 31:1026–1030. [PubMed: 14585365]
58. Fernyhough LJ, Buchan VA, McArthur LT, Hock BD. Relative recovery of haematopoietic stem cell products after cryogenic storage of up to 19 years. Bone marrow transplantation. 2013; 48:32–35. [PubMed: 22659683]
59. Khoury HJ, Loberiza FR Jr, Ringden O, Barrett AJ, Bolwell BJ, Cahn JY, et al. Impact of posttransplantation G-CSF on outcomes of allogeneic hematopoietic stem cell transplantation. Blood. 2006; 107:1712–1716. [PubMed: 16239431]

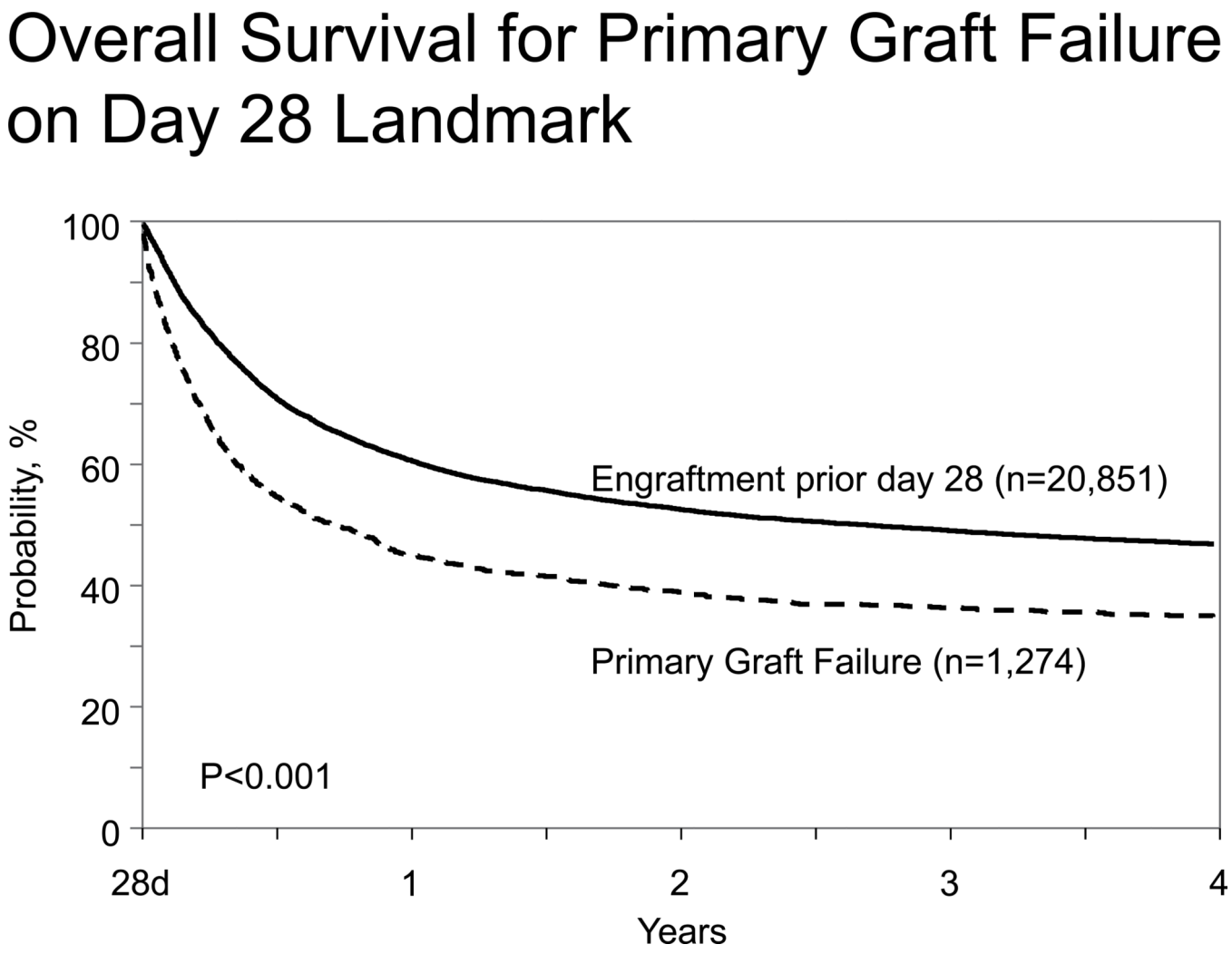

Figure 1.
Landmark analysis for overall survival on day 28 post-transplant in subjects who have engrafted successfully versus those with PGF.

Table 1

Characteristics of patients at risk for PGF after first myeloablative allo-HCT.

Variable	N	PGF (%)	P-value[a]
Number of patients	23272	1278 (5)	
Number of centers	372	249	
Year of transplant			<0.001
1995–1996	4449	333 (7)	
1997–1998	3933	227 (6)	
1999–2000	3336	200 (6)	
2001–2002	2887	135 (5)	
2003–2004	3151	152 (5)	
2005–2006	3374	144 (4)	
2007–2008	2142	87 (4)	
Recipient age (years), median (range)	35 (<1–75)	31 (<1 – 66)	<0.001
0–10	2558	172 (7)	
11–20	3417	234 (7)	
21–30	3876	233 (6)	
31–40	4758	253 (5)	
41–50	5146	249 (5)	
51–60	3084	122 (4)	
>60	433	15 (3)	
Donor/recipient gender match			<0.001
Male/Male	8347	447 (5)	
Female/Male	4979	338 (7)	
Male/Female	5375	254 (5)	
Female/Female	4458	231 (5)	
Unknown	113	8 (7)	
Karnofsky/Lansky score (%)			<0.001
≥90	16439	892 (5)	
<90	5643	343 (6)	
Unknown	1190	43 (4)	
Disease			<0.001
AML	8300	337 (4)	
ALL	5762	280 (5)	
CLL	844	44 (5)	
CML	5776	440 (8)	
MDS	2128	127 (6)	
MPD[b]	462	50 (11)	
Conditioning regimen			<0.001

Variable	N	PGF (%)	P-value[a]
TBI Cy and other	11921	636 (5)	
Bu Cy and other	7779	473 (6)	
TBI and other	1418	79 (6)	
Bu and other	1400	48 (3)	
Melphalan and other	166	6 (4)	
Unknown dosage[c]	588	36 (6)	
HLA match status[d]			<0.001
Related			
- HLA identical sibling	10059	477 (5)	
Unrelated			
- Well matched	7445	421 (6)	
- Partially matched	3695	203 (5)	
- Mismatched	1831	159 (9)	
- Unknown	242	18 (7)	
Graft type			<0.001
BM	14272	1051 (7)	
PB	8906	219 (2)	
BM+PB	94	8 (9)	
GVHD prophylaxis			<0.001
CSA + MTX +/− other	13349	837 (6)	
CSA + MMF +/− other	256	8 (3)	
CSA +/− other	1764	83 (5)	
Tacrolimus + MTX +/− other	4336	140 (3)	
Tacrolimus + MMF +/− other	539	13 (2)	
Tacrolimus +/− other	601	12 (2)	
Ex vivo T-cell depletion	1817	128 (7)	
MTX +/− other	171	17 (10)	
Other or none	439	45 (10)	
Median follow-up of survivors Range (months)	62 (<1–179)	70 (1 – 171)	

[a] Chi-Square.

[b] Myeloproliferative disorder (MPD) including primary myelofibrosis, polycythemia vera, and essential thrombocythemia.

[c] Reported as myeloablative, but unknown dose of the myeloablative agent (TBI, busulfan, or melphalan).

[d] HLA match status: Well matched was defined as no known disparity at HLA A,B,C,DRB1, partially matched as one locus known or likely disparity with their donors and mismatched as ≥2 locus disparity.

Table 2

Multivariate risk model for PGF in all patients at risk at transplant.

Variable		N	OR	Lower	Upper	P-value
Recipient age (years)						<0.001
	<30 years	9440	1.00			
	≥30 years	13815	0.75	0.65	0.86	<0.001
Donor/recipient gender match						<0.001
	Other	18166	1.00			
	Female/Male	4976	1.28	1.10	1.49	0.001
	Unknown	113	1.39	0.64	2.99	0.406
Karnofsky/Lansky score (%)						0.005
	≥90	16431	1.00			
	<90	5634	1.18	1.01	1.38	0.042
	Unknown	1190	0.69	0.49	0.96	0.030
Disease						<0.001
	AML[a]	8296	1.00			
	ALL[a]	5758	1.12	0.90	1.39	0.299
	CLL	843	1.57	1.17	2.10	0.003
	CML[a]	5771	1.88	1.57	2.25	<0.001
	MDS[b]	2126	1.38	1.07	1.79	0.013
	MPD[b,c]	461	1.81	0.97	3.39	0.062
Disease status - AML/ALL/CML[d]						<0.001
	Early	10203	1.00			
	Intermediate	5534	0.98	0.84	1.15	0.816
	Advanced	3746	1.54	1.25	1.89	<0.001
	Unknown	342	0.85	0.52	1.40	0.533
Spleen status - MPD						<0.001
	Normal	181	1.00			
	Splenectomy	91	1.68	0.58	4.87	0.341

Variable		N	OR	Lower	Upper	P-value
	Splenomegaly[e]	161	3.92	1.79	8.55	0.001
	Unknown	28	0.82	0.10	6.76	0.854
Spleen status - MDS						0.007
	Normal	1671	1.00			
	Splenectomy	89	1.68	0.77	3.65	0.193
	Splenomegaly[e]	174	2.34	1.36	4.03	0.002
	Unknown	192	1.50	0.84	2.66	0.167
Conditioning regimen						0.018
	TBI Cy and other	11905	1.00			
	Bu Cy and other	7778	1.35	1.11	1.65	0.002
	Bu and other	1400	1.19	0.87	1.62	0.285
	Melphalan and other	166	1.27	0.60	2.66	0.533
	TBI and other	1418	1.30	0.98	1.73	0.069
	Unknown dosage[f]	588	1.60	0.98	2.61	0.060
HLA match status[g]						<0.001
	Related					
	- HLA identical sibling	10059	1.00			
	Unrelated					
	- Well matched	7439	1.38	1.15	1.64	<0.001
	- Partially matched	3686	1.29	1.05	1.60	0.018
	- Mismatched	1829	1.79	1.41	2.27	<0.001
	- Unknown	242	1.79	1.09	2.94	0.021
ABO incompatibilities						0.010
	Matched	10821	1.00			
	Major	5584	1.24	1.05	1.46	0.012
	Minor	4327	1.04	0.85	1.27	0.693
	Unknown	2523	1.35	1.07	1.71	0.013
Graft type						<0.001

Variable		N	OR	Lower	Upper	P-value
	BM[h]	14255	1.00			
	PB	8906	0.29	0.23	0.37	<0.001
	BM+PB	94	0.97	0.49	1.91	0.921
BM-total nucleated cell dose (10^8/kg)						<0.001
	≤2.4	5773	1.00			
	>2.4	7369	0.72	0.61	0.84	<0.001
	Unknown	1113	1.00	0.76	1.30	0.980
Cryopreservation						0.026
	No	13299	1.00			
	Yes	2112	1.43	1.08	1.89	0.013
	Unknown	7844	0.94	0.78	1.14	0.530
Growth factor[i]						<0.001
	No	14390	1.00			
	G-CSF	7213	0.36	0.30	0.44	<0.001
	GM-CSF	505	0.70	0.43	1.15	0.155
	Both G-CSF and GM-CSF	69	0.57	0.16	2.02	0.381
	Unknown	1078	0.63	0.45	0.87	0.005
GVHD prophylaxis						<0.001
	CSA+MTX+/− other	13348	1.00			
	CSA +− other	2020	0.73	0.58	0.92	0.007
	Tacrolimus + MTX +/− other	4336	0.61	0.48	0.78	<0.001
	Tacrolimus +/− other	1140	0.50	0.30	0.82	0.007
	Ex vivo T-cell depletion	1817	1.13	0.86	1.49	0.383
	Other or unknown	594	1.87	1.20	2.93	0.006
Year of Transplant						0.011
	1995–2002	14588	1.00			
	2002–2008	8667	1.28	1.06	1.56	0.011

[a] Early disease status.

[b] Normal spleen.

[c] Myeloproliferative disorder (MPD) including primary myelofibrosis, polycythemia vera, and essential thrombocythemia.

[d] Disease status pre-transplant defined as: Early=AML or ALL in first CR; CML in first chronic phase. Intermediate=AML or ALL in second CR, third CR or fourth CR; CML in accelerated phase or greater than or equal to second chronic phase. Advanced=primary induction failure and relapse for AML and ALL; CML in blastic phase.

[e] Splenomegaly data on size of the spleen by examination and/or imaging studies were not available in the database.

[f] Reported as myeloablative, but unknown dose of the myeloablative agent (TBI, busulfan, or melphalan).

[g] HLA match status: Well matched was defined as no known disparity at HLA A,B,C,DRB1, partially matched as one locus known or likely disparity with their donors and mismatched as ≥2 locus disparity.

[h] BM TNC $\leq 2.4 \times 10^8$/kg.

[i] Growth factor, G-CSF, GM-CSF or both were delivered to promote engraftment. This was pre-planned and initiated between day -1 and day 7.

Table 3

Multivariate risk model for PGF in children (<21 years old) at risk at transplant.

Variable		N	OR	Lower	Upper	P-value
Donor/recipient gender match						<0.001
	Other	4517	1.00			
	Female/Male	1432	1.54	1.20	1.96	<0.001
	Unknown	26	2.92	1.00	8.56	0.050
Karnofsky/Lansky score (%)						<0.001
	≥90%	4725	1.00			
	<90%	994	1.57	1.22	2.03	<0.001
	Unknown	256	0.68	0.34	1.39	0.291
Disease						<0.001
	AML	1806	1.00			
	ALL	2796	1.16	0.86	1.55	0.329
	CLL	155	1.80	1.03	3.13	0.039
	CML	764	1.97	1.36	2.85	<0.001
	MDS	402	1.10	0.65	1.85	0.734
	MPD[a]	52	0.93	0.28	3.02	0.898
Conditioning regimen						0.034
	TBI Cy and other	3597	1.00			
	Bu Cy and other	1646	1.46	1.10	1.93	0.008
	Bu and other	164	1.08	0.43	2.71	0.868
	Melphalan and other	10	3.67	0.60	22.31	0.158
	TBI and other	465	1.49	1.01	2.20	0.046
	Unknown dosage[b]	93	2.22	1.12	4.40	0.022
ABO incompatibilities						0.018
	Matched	2772	1.00			
	Major	1489	1.50	1.14	1.97	0.004
	Minor	1112	1.48	1.07	2.06	0.019

Variable		N	OR	Lower	Upper	P-value
	Unknown	602	1.58	1.06	2.35	0.024
Graft type						0.001
	BM[c]	4792	1.00			
	PB	1171	0.61	0.40	0.92	0.018
	BM+PB	12	3.00	1.02	8.82	0.046
BM-total nucleated cell dose (10^8/kg)						0.050
	≥3.0	2182	1.00			
	<3.0	2174	1.37	1.06	1.77	0.015
	Unknown	436	1.15	0.76	1.75	0.503
Growth factor[d]						<0.001
	No	3830	1.00			
	G-CSF	1753	0.37	0.27	0.50	<0.001
	GM-CSF	110	1.05	0.48	2.32	0.897
	Unknown	282	0.80	0.47	1.36	0.409
GVHD prophylaxis						0.014
	CSA+MTX+/− other	3702	1.00			
	CSA +− other	759	0.71	0.51	1.00	0.047
	Tacrolimus + MTX +/− other	573	0.66	0.38	1.14	0.139
	Tacrolimus +/− other	131	0.25	0.06	0.97	0.045
	Ex vivo T-cell depletion	602	1.30	0.87	1.95	0.196
	Other or unknown	208	1.31	0.87	1.99	0.195

[a] Myeloproliferative disorder (MPD) including primary myelofibrosis, polycythemia vera, and essential thrombocythemia.

[b] Reported as myeloablative, but unknown dose of the myeloablative agent (TBI, busulfan, or melphalan).

[c] BM TNC ≥3.0×10^8/kg.

[d] Growth factor, G-CSF, GM-CSF or both were delivered to promote engraftment. This was pre-planned and initiated between day -1 and day 7.

Leukemia. Author manuscript; available in PMC 2016 January 31.

Table 4

Multivariate risk model for PGF in patients at risk on day 21 post-transplant (training dataset).

Variable	N	OR	Lower	Upper	P-value
Recipient age (years)					0.010
<30	1915	1.00			
≥30	2144	0.79	0.66	0.94	0.010
Karnofsky/Lansky score (%)					0.027
≥90%	2876	1.00			
<90%	1016	1.23	1.01	1.51	0.043
Unknown	167	0.75	0.51	1.10	0.142
Disease					<0.001
AML[a]	1186	1.00			
ALL[a]	972	1.04	0.79	1.36	0.779
CLL	125	1.54	1.00	2.39	0.051
CML[a]	1296	1.58	1.27	1.98	<0.001
MDS	369	1.27	0.96	1.68	0.096
MPD[b]	111	1.79	1.04	3.07	0.034
Disease status - AML/ALL/CML[c]					0.020
Early	1773	1.00			
Intermediate	1011	0.89	0.71	1.11	0.304
Advanced	599	1.30	0.97	1.73	0.075
Unknown	71	0.84	0.45	1.58	0.596
HLA match status[d]					0.018
Related					
- HLA identical sibling	1522	1.00			
Unrelated					
- Well matched	1390	1.15	0.90	1.45	0.263
- Partially matched	712	1.06	0.81	1.39	0.661
- Mismatched	406	1.56	1.18	2.07	0.002

Variable	N	OR	Lower	Upper	P-value
- Unknown	29	0.76	0.29	2.01	0.581
Graft type/total nucleated cell dose (10^8/kg)					0.010
BM >2.4	1440	1.00			
BM ≤2.4	1702	1.32	1.09	1.60	0.005
PB	659	1.41	1.09	1.83	0.010
BM unknown total nucleated cell dose	258	1.22	0.88	1.71	0.238
Conditioning regimen					<0.001
TBI+/− other	2518	1.00			
Other	1541	1.53	1.24	1.89	<0.001
GVHD prophylaxis					<0.001
Calcineurin inhibitor[d] + MTX+/− other	3410	1.00			
Ex vivo T-cell depletion	255	2.30	1.75	3.03	<0.001
Other GVHD prophylaxis	394	1.72	1.33	2.22	<0.001

[a] Early disease status.

[b] Myeloproliferative disorder (MPD) including primary myelofibrosis, polycythemia vera, and essential thrombocythemia.

[c] Disease status pre-transplant defined as: Early=AML or ALL in first CR; CML in first chronic phase. Intermediate=AML or ALL in second CR, third CR or fourth CR; CML in accelerated phase or greater than or equal to second chronic phase. Advanced=primary induction failure and relapse for AML and ALL; CML in blastic phase.

[d] HLA match status: Well matched was defined as no known disparity at HLA A,B,C,DRB1, partially matched as one locus known or likely disparity with their donors and mismatched as ≥2 locus disparity.

Table 5

Weighted risk scores for PGF in all patients who are at risk for graft failure on day 21 post-transplant

Day 21 weighted PGF risk scores	Score
Recipient age	
≥30 years	0
<30 years	1
Karnofsky/Lansky score	
≥90%	0
<90%	1
Disease	
AML	0
ALL	0
MDS	1
CLL	2
CML	2
MPD[a]	3
Disease status[b]	
Other	0
Advanced AML/ALL/CML	1
HLA match status[c]	
HLA identical sibling	0
Well matched unrelated	0
Partially matched unrelated	0
Mismatched unrelated	2
Graft type/total nucleated cell dose (TNC)	
BM TNC >2.4 × 10^8/kg	0
BM TNC ≤2.4 × 10^8/kg	1
Peripheral blood	2
Conditioning regimen	
TBI+/− other	0
Other	2
GVHD prophylaxis	
Calcineurin inhibitor[d] + MTX +- other	0
Other GVHD prophylaxis	3
T-cell depletion	4

[a] Myeloproliferative disorder (MPD) including primary myelofibrosis, polycythemia vera, and essential thrombocythemia.

[b] Disease status pre-transplant defined as: Other= AML, ALL, and CML early/intermediate; CLL, MDS, and MPD irrespective of disease status. Advanced=primary induction failure and relapse for AML and ALL; CML in blastic phase.

[c] HLA match status: Well matched was defined as no known disparity at HLA A,B,C,DRB1, partially matched as one locus known or likely disparity with their donors and mismatched as ≥2 locus disparity.

[d] Cyclosporine or tacrolimus.

Table 6

Validation of the PGF prediction score determined on day 21 post-transplant

A. Day 21 PGF Prediction Score								
	Training dataset				Validation dataset			
Score	**N**	**No PGF**	**PGF**	**P-value**	**N**	**No PGF**	**PGF**	**P-value**
<7	3192	2590 (81%)	602 (19%)	<0.001	1548	1248 (91%)	300 (19%)	0.003
≥7	437	278 (64%)	159 (36%)		205	147 (72%)	58 (28%)	
Unknown	432	352 (81%)	80 (19%)		259	190 (73%)	69 (27%)	
Total	4061	3220 (79%)	841 (21%)		2012	1585 (79%)	427 (21%)	