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Comparison of Non-myeloablative Conditioning Regimens for Lymphoproliferative Disorders

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Abstract

Hematopoietic cell transplantation (HCT) with non-myeloablative conditioning (NMA) for lymphoproliferative diseases (LD) includes fludarabine with and without low-dose total body irradiation (TBI). Transplant outcomes were compared among patients ≥40 years with LD who received a HCT with TBI (N=382) and no-TBI (N=515) NMA from 2001 to 2011. The groups were comparable except for donor, graft, prophylaxis for graft-versus-host disease (GVHD), disease status and year of HCT. Cumulative incidences of grades II–IV GVHD at 100 days, were 29% and 20% (p=0.001), and chronic GVHD at 1 year were 54% and 44% (p=0.004) for TBI and no-TBI, respectively. Multivariate analysis of progression/relapse, treatment failure and mortality showed no outcome differences by conditioning. Full donor chimerism at day 100 was observed in 82% vs. 64% in the TBI and no-TBI groups, respectively (p=0.006). Subset of four most common conditioning/ GVHD prophylaxis combinations demonstrated higher rates of grades II–IV acute (p<0.001) and chronic GVHD (p<0.001) among recipients of TBI-mycophenolate mofetil (MMF) compared to other combinations. TBI-based NMA conditioning induces faster full donor chimerism but overall survival outcomes are comparable to no-TBI regimens. Combination of TBI and MMF are associated with higher rates of GVHD without impact on survival outcomes in patients with LD.

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Conflict of Interest:

The authors have no conflicts of interest to declare.

Keywords

Nonmyeloablative; lymphoproliferative disease; allogeneic transplant; total body irradiation; chimerism

Introduction

Nonmyeloablative (NMA) conditioning regimens for allogeneic hematopoeitic cell transplantation (HCT) are mainly immunosuppressive and less toxic to the recipients' stem cells. NMA regimens allowed options of HCTs for patients who were traditionally not eligible due to advanced age or comorbidities [1–3]. In NMA conditioning, low dose TBI (200 cGy) is utilized for immune ablation to aid achievement of donor chimerism [4]. The combinations of TBI and fludarabine (Flu) is a common NMA regimen which is most commonly combined with graft-versus-host disease (GVHD) prophylaxis using mycophenolate mofetil (MMF) and a calcineurin inhibitor (CNI) as pioneered by the Seattle group [3–4].

Transplants for lymphoproliferative diseases (LD) commonly use NMA regimens as the indolent nature of some of these diseases allow for disease control by the allograft, or graft-versus-tumor (GVT) effect. Also, NMA regimens help minimize toxicity for patients with prior autologous HCTs which are frequent in treatment of LD. Chronic lymphocytic leukemia (CLL), mantle cell lymphoma, and follicular lymphoma in particular are indications whereas NMA is the most common conditioning intensity used [5]. Since the inception of TBI-based NMA regimens, several other regimens have been used that excluded TBI and added chemotherapeutic agents commonly used to treated LD such as cyclophosphamide (Cy), rituximab, fludarabine (Flu) among others [6,7].

Nevertheless, no studies have directly addressed whether TBI-based (200 cGy) NMA conditioning regimens results in different outcomes compared to no-TBI regimens for LD [8,9]. Meta-analyses comparing different NMA regimens both with and without TBI showed conflicting results, including incidence of acute and chronic GVHD, engraftment, and survival [10–12].

The current study explored the differences in HCT outcomes using a common immune ablation method (TBI) versus disease-specific regimens (no-TBI) for LD.

Materials and Methods

Data Sources

The Center for International Blood and Marrow Transplant Research (CIBMTR) is a research working group of more than 450 transplantation centers worldwide that contribute detailed data on consecutive HCT to a Statistical Center at the Medical College of Wisconsin in Milwaukee and the National Marrow Donor Program Coordinating Center in Minneapolis [5].

Study Population

Eligibility for this study includes patients who were 40 years or older with LD and reported to the CIBMTR after the first allogeneic transplantation with NMA conditioning between 2001 and 2011 were included in analysis. Patients younger than 40 years were excluded as they represented less than 10% of the population. Regimens in the myeloablative or reduced intensity (RIC) range were excluded from this analysis. LD includes CLL or small-lymphocytic lymphoma (SLL), Hodgkin lymphoma (HL), and non-Hodgkin lymphoma (NHL). Recipients of cord blood grafts, ex-vivo T-cell depletion, syngeneic donors and cases with insufficient follow up (100 days, n=59) were excluded. For HCTs from unrelated donor (URD), human leukocyte antigen (HLA) matching at HLA-A, B, C, and DRB1 were included in the well matched category or 8/8 match. Recipients of at least one antigen or allele mismatched were also eligible to the study (partially matched or 7/8 match). NMA conditioning regimen was defined as TBI 200cGY [13]. Furthermore, conditioning regimens were separated in two Flu-based cohorts, with or without TBI. Overall, completeness indexes of follow-up at 3-years was 96% for TBI and 90% for no-TBI cohorts, respectively [14,15].

Diseases were grouped as low-, intermediate- grades and other diseases. Low-grade diseases included CLL, low or intermediate-grade follicular lymphoma, marginal zone lymphoma, and diffuse small cleaved cell lymphoma. Intermediate-grade diseases included high-grade follicular lymphoma, mantle cell lymphoma, diffuse large B-cell lymphoma, and T-cell lymphoma. Other diseases included HL, unknown grade follicular lymphoma, small lymphoplasmacytic lymphoma, mycosis fungoides, and other NHL.

Disease status at transplant defined groups according to disease burden, response to prior therapy and sensitivity to therapy.

Outcomes

Engraftment assessed hematopoietic recovery of neutrophils and platelets following transplant. Neutrophil engraftment was defined as neutrophil recovery 0.5×10^9/L for three consecutive laboratory values. Platelet engraftment was measured at platelet recovery 20 and 50×10^9/L without platelet transfusion for seven consecutive days on three consecutive laboratory values on different dates. The modified Glucksberg classification was used to define events of grades II–IV and III–IV acute GVHD in the first 100 days post HCT [16]. Having death without GVHD was considered a competing risk, incidences of acute and chronic GVHD were calculated. Treatment-related mortality (TRM) was defined as death without progression or relapse.

Donor chimerism analysis from peripheral blood or bone marrow source was conducted in between 21–100 days post-HCT. 90% donor chimerism was considered as full donor chimerism [17,18]. Competing risk for achieving full donor chimerism was defined as subsequent transplant, relapse or progression of primary disease, or death without achieving full donor chimerism. Conversely, loss of donor chimerism was defined as <10% donor chimerism. Donor chimerism percentages between 10% and 90% were defined as mixed chimerism. Sorted T-cell and unsorted chimerisms were analyzed separately. For the

analysis of temporal achievement of full chimerism, the first day of achieving full donor chimerism was measured.

Statistical Analysis

The main comparison for this study was between TBI and no-TBI regimen. Univariate analysis of neutrophil and platelet recovery, TRM, GVHD and relapse or progression was conducted. Covariates for Cox hazard regression multivariate analysis for overall mortality, TRM, acute and chronic GVHD, disease progression and treatment failure were age, disease grouped by grade and histology, sensitivity to therapy prior to HCT, transplant year, history of prior autologous HCTs, Karnofsky Performance Score (KPS) at time of preparative regimen, use of anti-thymocyte globulin (ATG) and/or campath, use of rituximab before or after HCTs, graft source use, and donor type by HLA match status. Interaction test between the main effect and all covariates was performed and none was identified.

Donor chimerism between days 21–100 post HCT was analyzed in years 2008 and 2011, due to the completeness of the data. Median of days to achieve complete donor chimerism was assessed for groups with and without TBI. Then, proportions of patients achieving full donor chimerism were assessed for three time periods: days 21–45, 46–75, and 76–100. Median donor cell percentage for each time period was also assessed for both sorted T-lymphocyte (lymphoid lineage) and unsorted cell chimerism. If there was no chimerism tested for the time period then the available value from the previous time period were presumed for cumulative donor chimerism achievement. There were no chimerism discrepancies that could modify the chimerism status, i.e. from mixed to full donor chimerism, or from mixed chimerism to loss of chimerism among cases with multiple assessments in a single period.

Practices of NMA regimen often include the same GVHD prophylaxis as a treatment package, making it difficult to test a single component separately. To address this, the most common NMA regimen/GVHD prophylaxis combinations used for CLL, follicular lymphoma, and mantle cell lymphoma were identified and compared in a subset analysis. The method of analysis was the same as for the main comparison.

SQL developer (Oracle, Redwood City, CA) and SAS 9.2 (SAS Institute, Cary, NC) were used for the analyses.

Results

Study Population

As in Table 1, both cohorts were well balanced for age (median age 57 for TBI vs. 56 for no-TBI cohorts, p=0.13), sex (male 74 vs. 67%, p=0.05), donor sex (61 vs. 66%, p=0.16), time from diagnosis to transplant (median 51 vs. 47 months, p=0.31). Recipients of TBI based regimens were more frequently with performance score (KPS) lower than 90% compared to no-TBI (32% vs. 22%, p=0.003). 48 patients (16%) in TBI cohort and 38 patients (9%) in no-TBI cohort received autologous transplant(s) prior to the first allogeneic HCTs (p=0.005).

TBI was performed less frequently later in the period (years 2009–2011 9% vs. 11%, p<0.001), included more recipients of URD (62% vs. 47%, p<0.001), PBSC (94% vs. 85%, p<0.001), less frequently used rituximab in the conditioning (7% vs. 40%, p<0.001) and used more frequently CNI and MMF based combination of GVHD prophylaxis (87% vs. 15%, p<0.001). Furthermore, TBI cohort had more CMV mismatches (44% vs. 38%, p=0.003) and had less cases with sensitivity to prior therapy (48% vs. 60%, p<0.001) as well as less cases with complete remission at the time or preparative regimen (33% vs. 25%, p<0.001).

Hematologic Recovery

In the TBI cohort, 40% and 60% never dropped neutrophil and platelet counts below the level of engraftment compared to 24% and 43% in the no-TBI group, respectively. Neutrophil recovery by day 28 post HCT was >95% for both groups (p=0.12). Platelet recovery 20×10^9/L by day 100 were 84% (95% Confidence Interval [CI], 77–85%) and 92% (95% CI, 88–94%, p=0.03) for TBI and no-TBI cohorts respectively. Corresponding incidences of platelet recover 50×10^9/L by day 100 were 79% (95% CI, 70–85%) and 92% (95% CI, 88–95%, p<0.001).

Acute and Chronic GVHD

Incidences for grades II–IV acute GVHD at 100 days were 29% (95% CI, 25–34%) and 20% (95% CI, 16–23%, p=0.001) for TBI and no-TBI groups, respectively (Fig 1a). Corresponding incidences of grade III–IV acute GVHD were 13% (95% CI, 10–17%) and 7% (95% CI, 5–9% p=0.002). Multivariate analysis of grade II–IV acute GVHD confirmed a higher incidence with TBI (HR 1.51, 95% CI 1.19–2.00, p=0.001, Table 2). Other covariates associated with this outcome included no prior history of autologous transplant (HR 12.11, 95% CI 4.95–29.63, p<0.001) and resistance to (HR 2.01, 95% CI, 1.35–2.99, p<0.001) or no known prior treatment (HR 1.933, 95% CI 1.47–2.55, p<0.001, Table 2).

Incidences of chronic GVHD at 1-year were 54% and 44% for TBI (95% CI 48–59%) and no-TBI groups (95% CI 39–48%), respectively (p=0.004, Figure 1b). Multivariate analysis showed higher rates of chronic GVHD with TBI (HR 1.32, 95% CI 1.10–1.59, p=0.003, Table 2) compared to no-TBI. Other covariates associated with this outcomes were partially matched URD graft source (HR 1.50, 95% CI, 1.08–2.08, p=0.015) and ATG or campath use (HR 0.60, 95% CI, 0.47–0.75, p<0.001, Table 2).

Transplant Related Mortality and Disease Progression

Cumulative incidence of TRM at 1 year were 18% (95% CI, 14–22%) and 16% (95% CI, 13–19%, p=0.36) for TBI and no-TBI, respectively. Multivariate analysis of TRM showed no difference between TBI and no-TBI cohorts (p=0.48, Table 2). Other covariates associated with TRM were: increasing patient age (age 60, HR 1.58 95% CI, 1.12–2.24, p=0.009) and partially matched URD source graft (HR 2.63, 95% CI, 1.79–3.87, p<0.001, Table A).

Incidences of disease progression or relapse at 5 years were 36% (95% CI, 31–41%) and 38% (95% CI, 33–42% p=0.16) for TBI and no-TBI cohorts, respectively. Multivariate

analysis of progression/relapse showed no difference between two cohorts (p=0.68, Table A). Other covariates with significant association were KPS <90% (HR 1.42, 95% CI, 1.10–1.983, p=0.007) and use of ATG or campath (HR 1.55, 95% CI, 1.22–1.97, p<0.001, Table A).

Survival

Figure 1c and 1d illustrated the adjusted PFS and adjusted OS, respectively. Multivariate analysis for treatment failure preventing PFS were similar for both cohorts (HR 0.97, 95% CI, 0.81–1.51, p=0.70, Table 2). Associated covariates for treatment failure were KPS <90% (HR 1.34, 95% CI, 1.10–1.62, p=0.041) and partially matched URD source graft (HR 1.79, 95% CI 1.36–2.34, p<0.001, Table A).

Multivariate analysis for overall mortality were similar for both cohorts (HR 1.09, 95% CI, 0.91–1.32, p=0.35, Table A). Additional covariates that were associated with overall mortality in main analysis were: patient age ≥60 at transplant (HR 1.66, 95% CI, 1.28–2.15, p<0.001), KPS <90 (HR 1.49, 95% CI, 1.21–1.83, p<0.001), and partially matched URD graft source use (HR 1.94, 95% CI, 1.46–2.59, p<0.001, Table A).

Causes of Death

Primary disease was the most common cause of death in both cohorts. TBI group had more deaths due primarily to GVHD (17% vs. 8%) and organ failure (15% vs. 12%) and no-TBI group had more deaths from infection (18 vs. 11%) compared to TBI (p<0.001). Reviewing contributing causes of death, the similar trend was found. TBI cohort had 16% and no-TBI cohort had 9% deaths contributed by GVHD (p=0.007). However, deaths related to infection were similar between two cohorts (16% in TBI and 15% in no-TBI cohorts, p=0.92).

Chimerism Analysis

Chimerism analysis with unsorted specimen was available in 62 and 88 patients; and T-cell chimerism was available in 34 and 70 patients in the TBI and no-TBI groups, respectively. Among unsorted chimerism, achievement of full donor chimerism by day 100 was observed in 82% and 64% in the TBI and no-TBI cohorts, respectively (p=0.006). Loss of donor chimerism after initially achieving full donor chimerism was not observed in any cohort. 10% vs. 31% of TBI and no-TBI cohorts achieved only mixed chimerism. Median donor chimerism by day 100 was 100% vs. 95% for TBI and no-TBI groups, respectively (Figure 2a). The median donor chimerism among patients with mixed unsorted chimerism from both treatment groups at the last period analyzed (day 76–100) was 79% (N= 26, range 32–89%) for all patients. Among patients with lymphocyte chimerism, achievement of full donor chimerism by day 100 was observed in 53% and 59% in the TBI and no-TBI groups respectively (p=0.027). Loss of T-cell donor chimerism was not found in any cohort. 26% vs. 37% of TBI and no-TBI maintained mixed T-cell chimerism during the period. Median donor T-cell chimerism by day 100 was 94.5% and 95% for TBI and no-TBI groups (p=0.84) (Figure 2b). The median donor chimerism among patients with mixed T-cell chimerism from both treatment groups at the last period analyzed (day 76–100) was 70% (N= 37, range 19–89%) for all patients.

Subset Analysis

Five groups were analyzed: flu/ TBI-CNI-MMF (TBI-MMF cohort, n=230), flu/cy/ rituximab-CNI- methotrexate (MTX) (FCR cohort, n=97), FCR-CNI-MTX-in vivo T-cell depletion including campath and rabbit or horse ATG (FCR-in vivo TCD cohort, n=59), flu/cy-CNI-MTX (FC cohort, n=82), and others (n=231).

When comparing the above groups, FCR contained more cases of follicular lymphoma (61% vs. 21–31%, p=0.031) in relapsed status (37% vs. 25–29%, p<0.001). TBI-MMF and FCR-in vivo TCD groups include more URD recipients (67% and 98% respectively, vs. 25–28%, p<0.001). TBI-MMF and FC groups included less number of patients with KPS 90% (31% and 26% respectively, vs. 7–11%, p<0.001).

The cumulative incidences of acute GVHD, grades II to IV at 100 days were 35% of TBI-MMF (95% CI 29–42%), 20% of FCR (95% CI 12–28% for both), 12% of FC (95% CI 5–22%), 11% of FCR-in vivo TCD (95% CI 5–19%), and 29% of others (95% CI 23–35, p<0.001, Figure 3a). Chronic GVHD at 1 year in TBI-MMF cohort was 55% and in other cohorts was 41–48% (p=0.11, Figure 3b,4a). Multivariate analysis demonstrated that TBI-MMF was associated with higher incidence of chronic GVHD (Figure 4b).

TRM (p=0.053), progression/relapse (p=0.58), PFS (p=0.11), and OS (p=0.06) showed no statistical difference from multivariate analyses among five groups (Figures 3c, 3d).

Discussion

NMA HCTs with or without TBI have been used to treat patients with LD. This study demonstrated that use of a general immunoablative regimen with TBI results in no major differences in post-HCT outcomes compared to disease specific regimens using chemotherapy. Additionally, TBI appears to cause less ablation of hematopoiesis as a greater proportion of patients do not become neutropenic compared to chemotherapy only regimens. This translated in faster time to full donor chimerism, but no difference in proportion of donor chimerism by day 100. One important difference in outcomes noted in this study was a higher rate of GVHD with TBI regimens, which maintained after adjusting to differences in the donor type and graft source between the two cohorts. Subset analysis suggests that the choice of GVHD prophylaxis can modulate this complication post HCT as MMF based regimens associated with higher GVHD rates compared to other combinations.

Other single center experiences with NMA regimens in specific LD showed that OS and PFS for CLL (2-year OS 60% and DFS 52%) and follicular lymphoma (2-year DFS of 64% in high grade and 83% in low grade) were comparable with this study [8,10,19]. Also, median survival for patients with advanced CLL or follicular lymphoma utilizing low dose TBI (OS 64–86% at 4 years) from previous studies were comparable, when contrasted to other conditioning regimens without TBI (OS 46–84% at 4–5 years) [8,10]. Three-year rates of relapse were comparable with other reported studies for follicular lymphomas of 20–45% on average, although some studies had relapse rates 10% at 2–3 years [9,11,20].

In this study, increased acute GVHD incidence in TBI group could also be the effect of donor chimerism, suggested by a faster achievement of full donor chimerism [7,20,21]. Despite similar T-cell donor chimerism and day 100 donor chimerism between the groups, makes this argument less plausible. Alternatively, the cohorts differed in GVHD prophylaxis regimens, which could be responsible for the difference of acute GVHD incidence. For chronic GVHD, both use of ATG or campath and HLA-matching were associated with lower rates of chronic GVHD as previously observed [23]. Furthermore, the use of rituximab was more common in the no-TBI cohort which could mitigate the incidence of GVHD. Exposure to rituximab was tested in the statistical models and it was not significantly associated with any of the outcomes tested.

Moreover, a systematic review of 11 studies showed increased incidence of grades III–IV acute GVHD for patients received MMF when compared to those received MTX for GVHD prophylaxis (RR 1.61, 95% CI 1.18–2.30) [23]. Chen G et al. reported that tacrolimus (TAC)/MMF resulted in higher grades III–IV acute GVHD (49%) when compared with TAC/MTX (19%), TAC/micro-MTX/MMF (23%) following myeloablative conditioning ($p<0.015$) [25–26]. Also, this is comparable with other single-center NMA and MA studies which revealed that MMF-based GVHD prophylaxis increased incidences of acute GVHD (11.6–54.5%) when compared with other regimen [25–27].

In studying TBI-based NMA conditioning regimen, Kornbilt et al explained that addition of Flu-TBI (2 Gy) reduced graft rejection by hastening donor chimerism [28]. Although both groups with and without fludarabine demonstrated near-complete donor granulocyte chimerism, median number of days of absolute granulocyte counts 500 cells/L was higher in Flu/TBI.

The current study is a retrospective analysis from a large number of transplant centers. The major pitfall is based on the decision to select a particular regimen, which was based on clinical evaluation by the treating physician. The selection of the study population separated by conditioning regimens demonstrated differences between groups. Several approaches were taken to minimize the heterogeneity of the population, including restricting the age to patients older than 40, selection of common indications and excluding practices that are not commonly performed, such as T-cell depletion, cord blood and use of mismatched URD. Furthermore, the regression analysis was able to adjust for the remainder differences between the cohorts.

Nevertheless, this study was a large comparison of NMA regimens among HCT recipients with LD. This study demonstrated that TBI based and non-TBI based NMA regimens with fludarabine achieved similar disease control and survival outcomes. TBI regimens lead to faster full donor chimerism. Lastly the results of this study raises the hypotheses that differences on GVHD rates observed were possibly related to the specific GVHD prophylaxis most commonly used with TBI NMA regimens.

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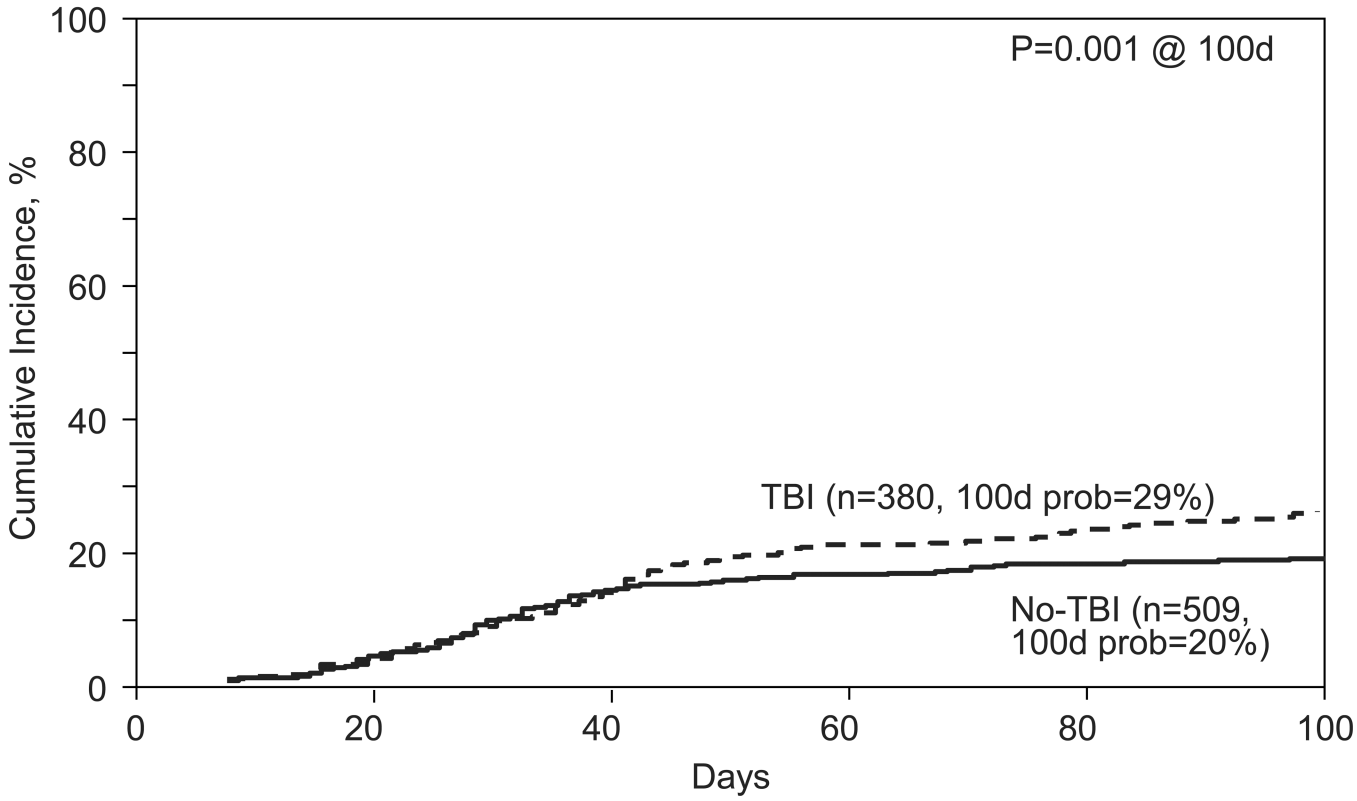
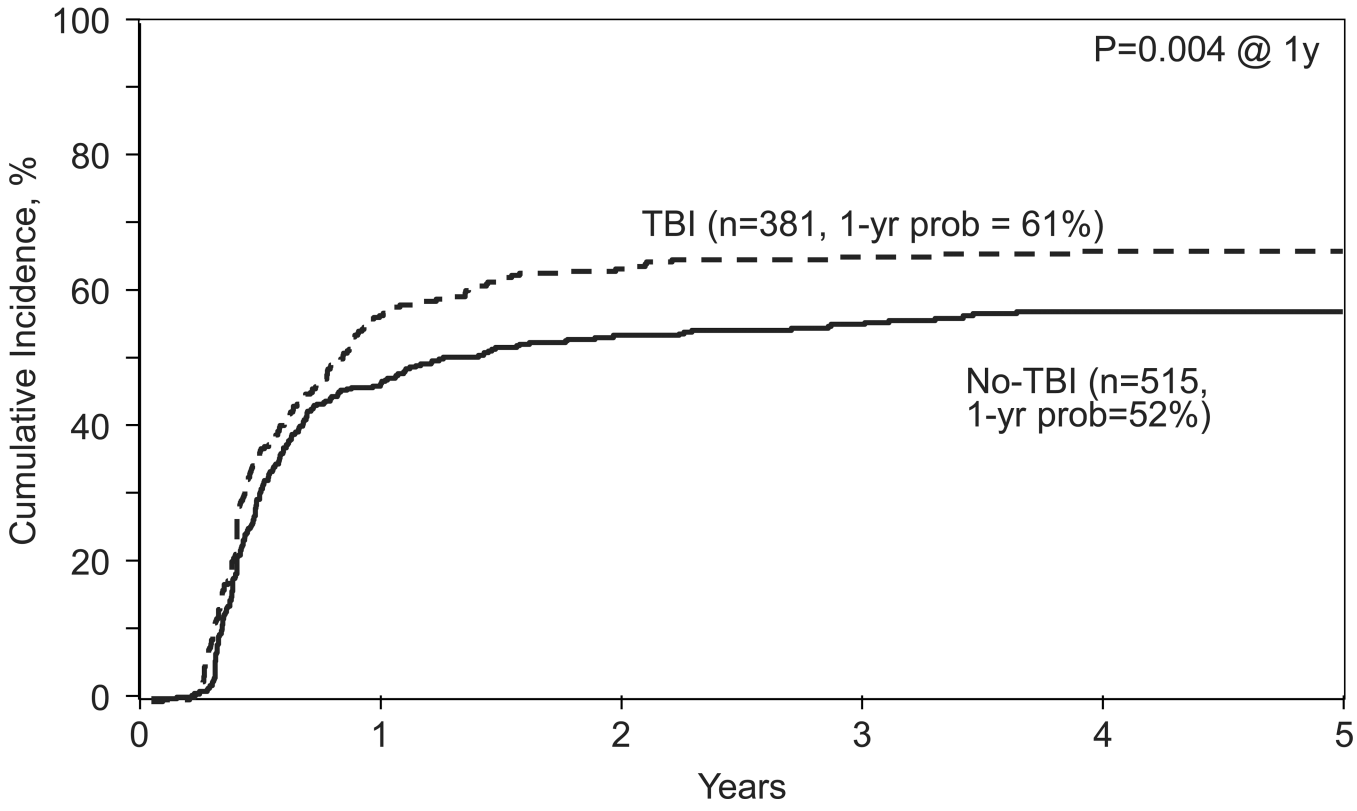
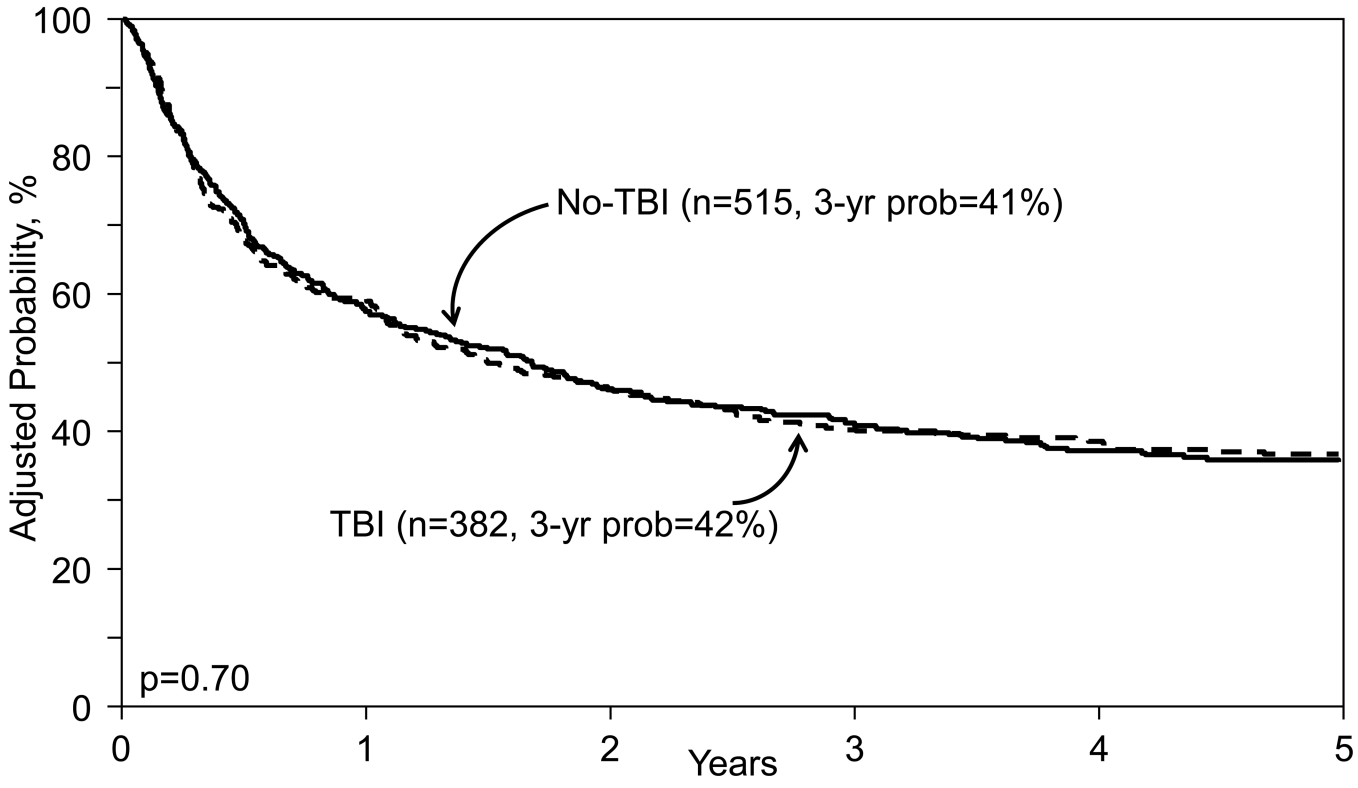
a. Acute GVHD, grade II-IV



b. Chronic GVHD



c. Progression-free Survival



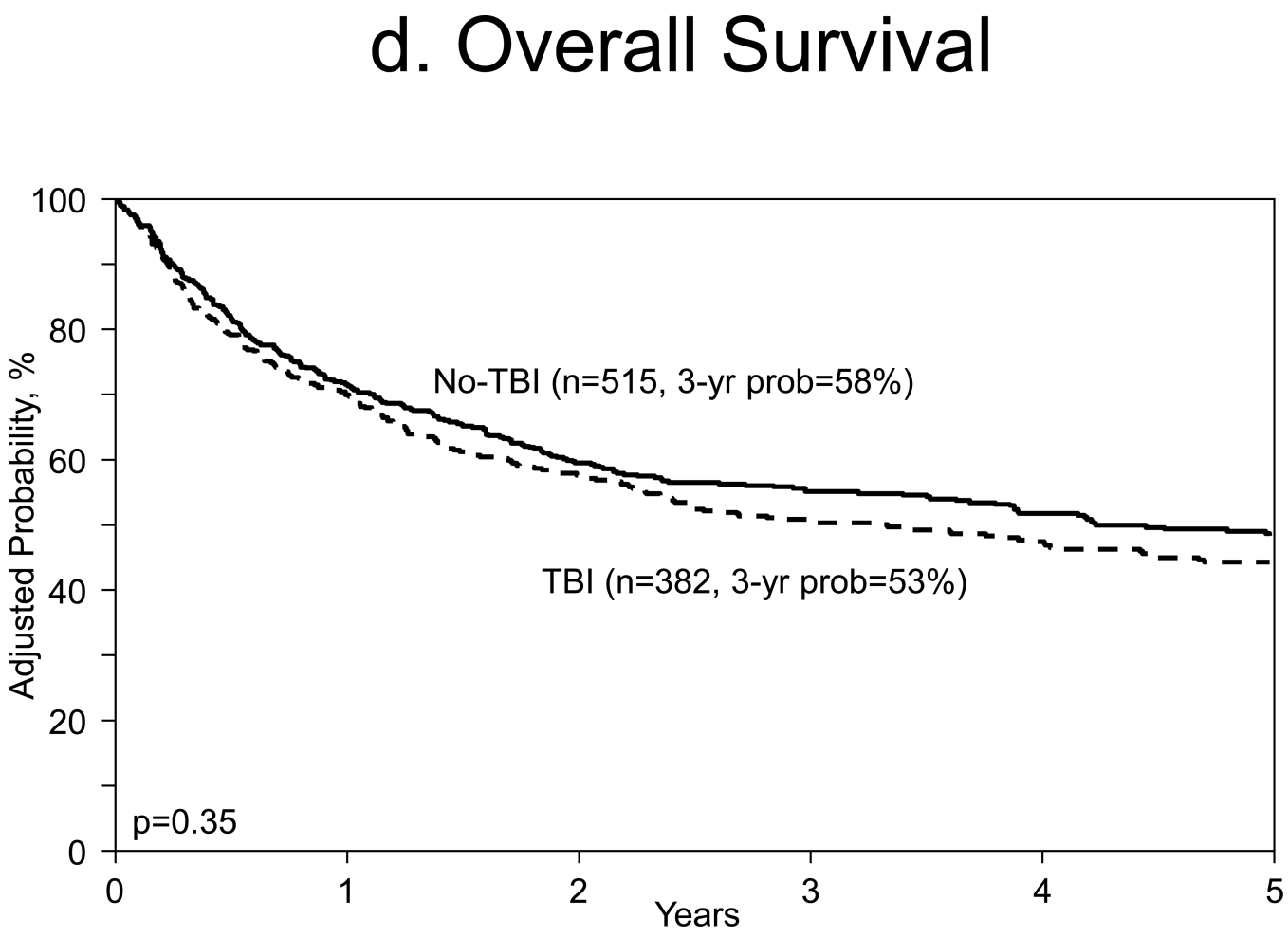


Figure 1.

Outcomes

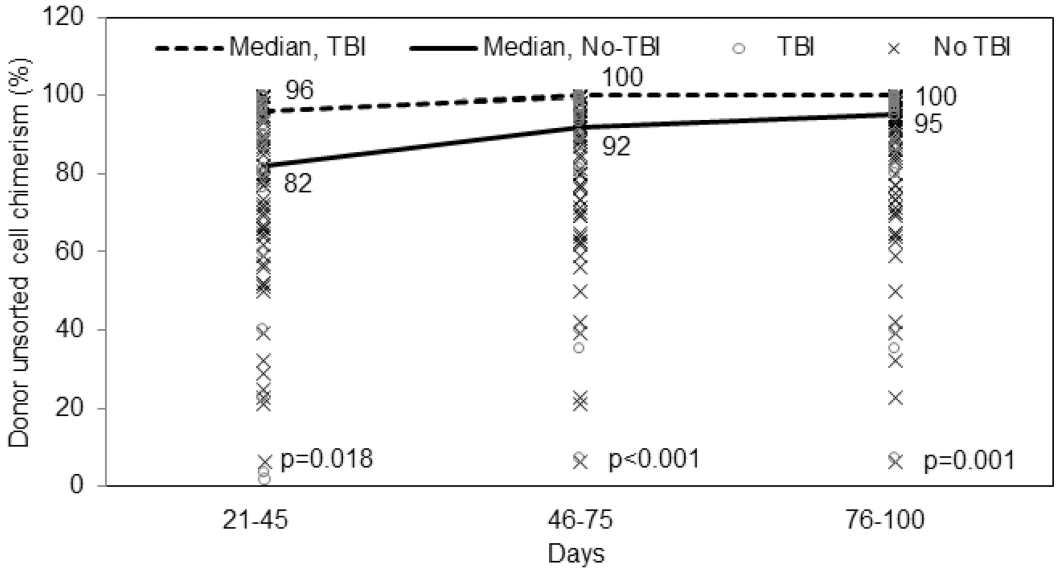
a. Acute GVHD, grades II–IV

b. Chronic GVHD

c. Adjusted progression free survival

d. Adjusted overall survival

a.



b.

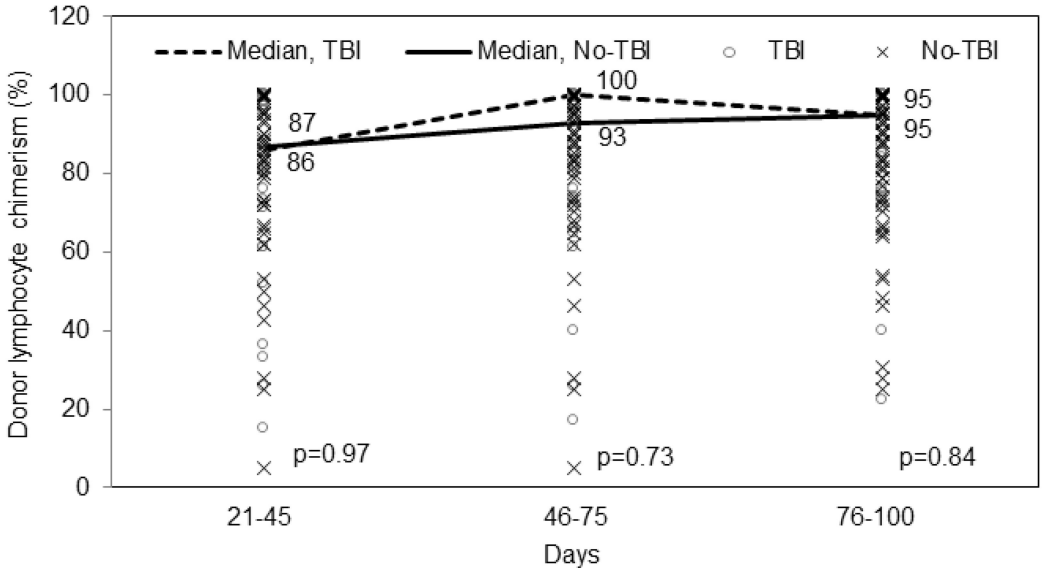


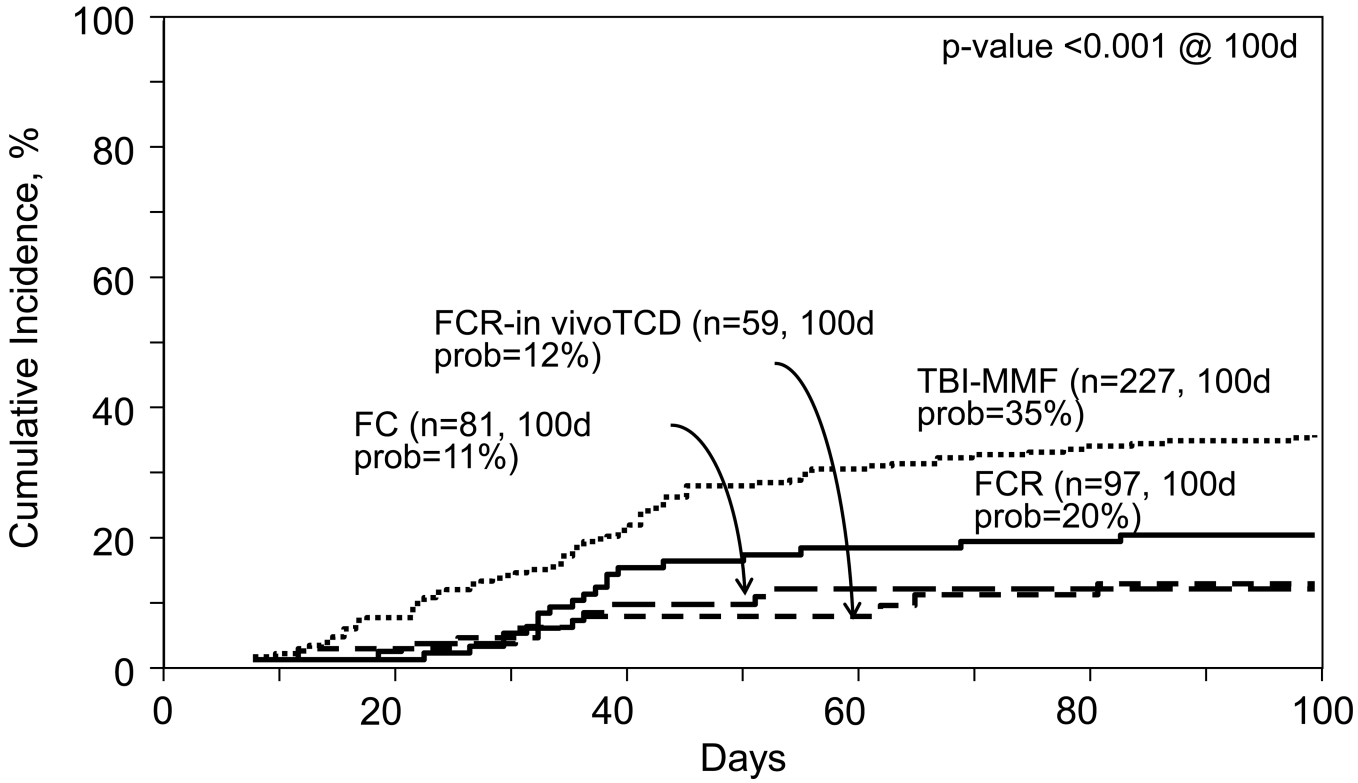
Figure 2.

Achievement of donor chimersim

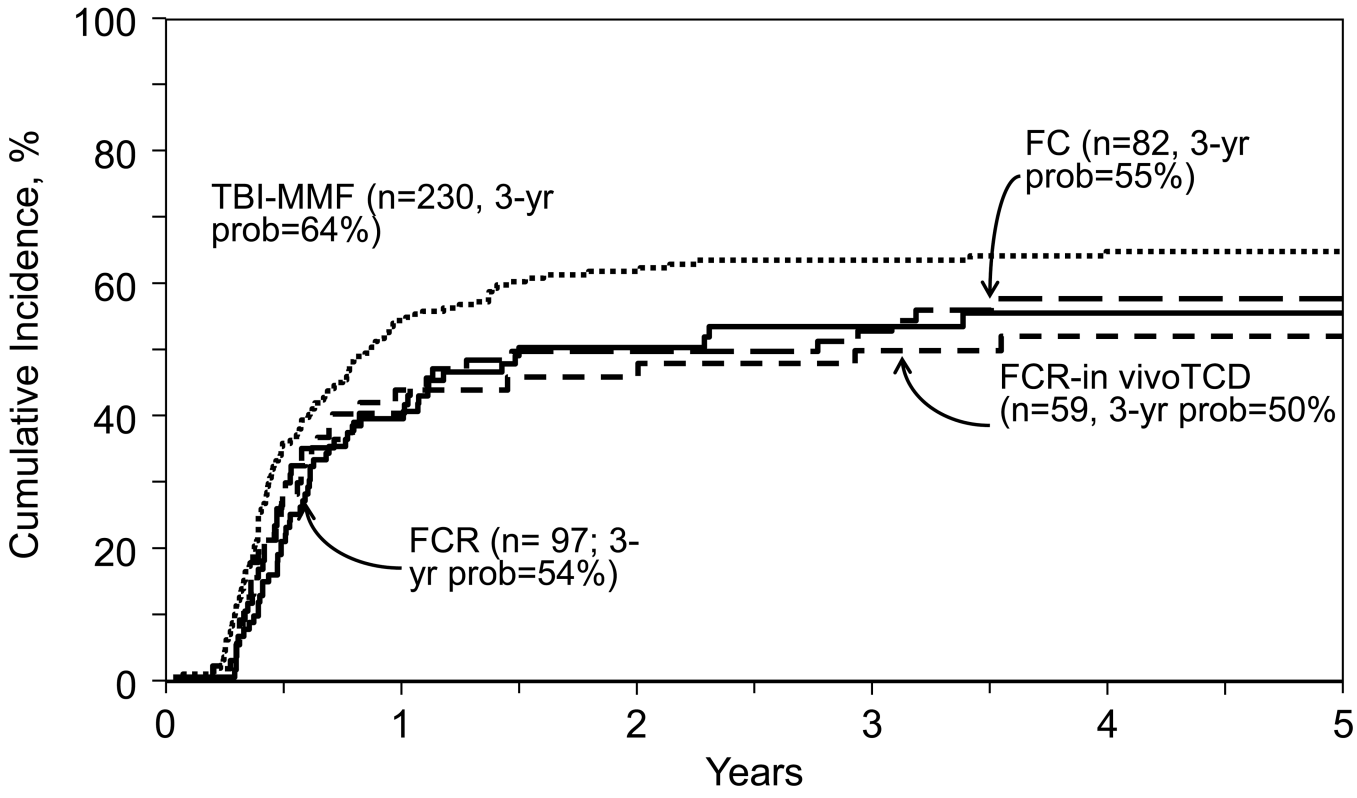
a. Unsorted chimerism

b. Sorted lymphocyte chimerism

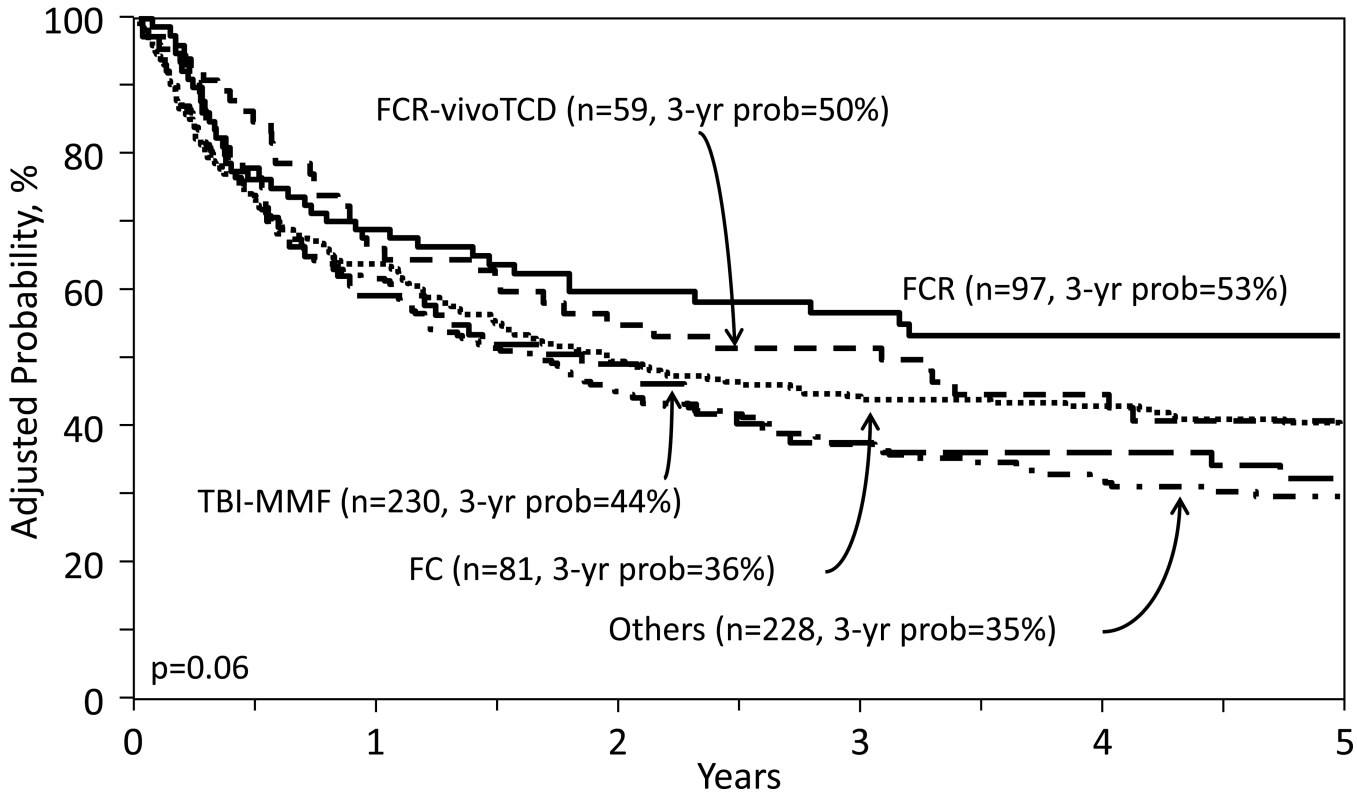
a. Acute GVHD, grade II-IV



b. Chronic GVHD



c. Progression-free Survival



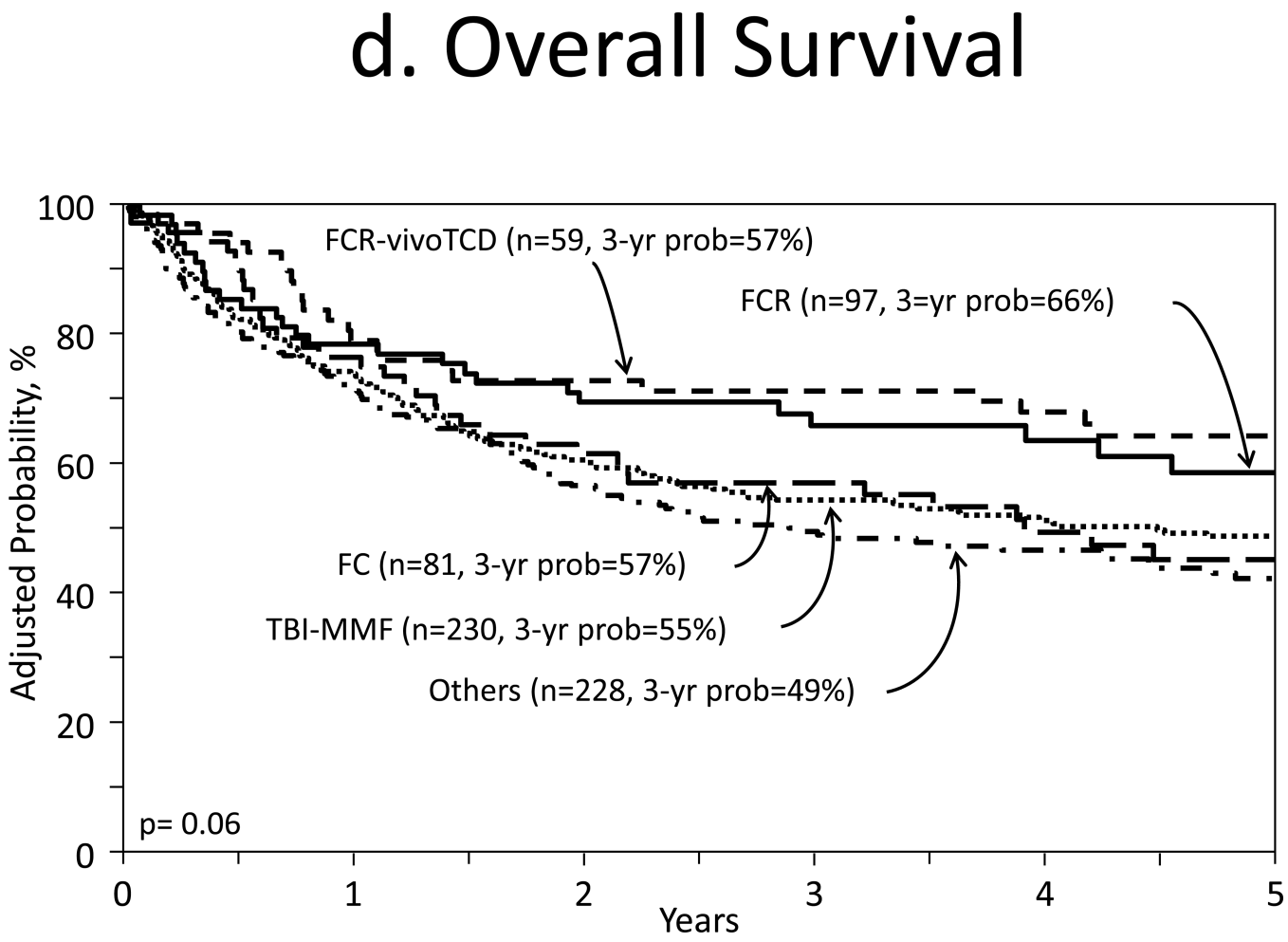


Figure 3.

Outcomes of regimen-GVHD prophylaxis combinations

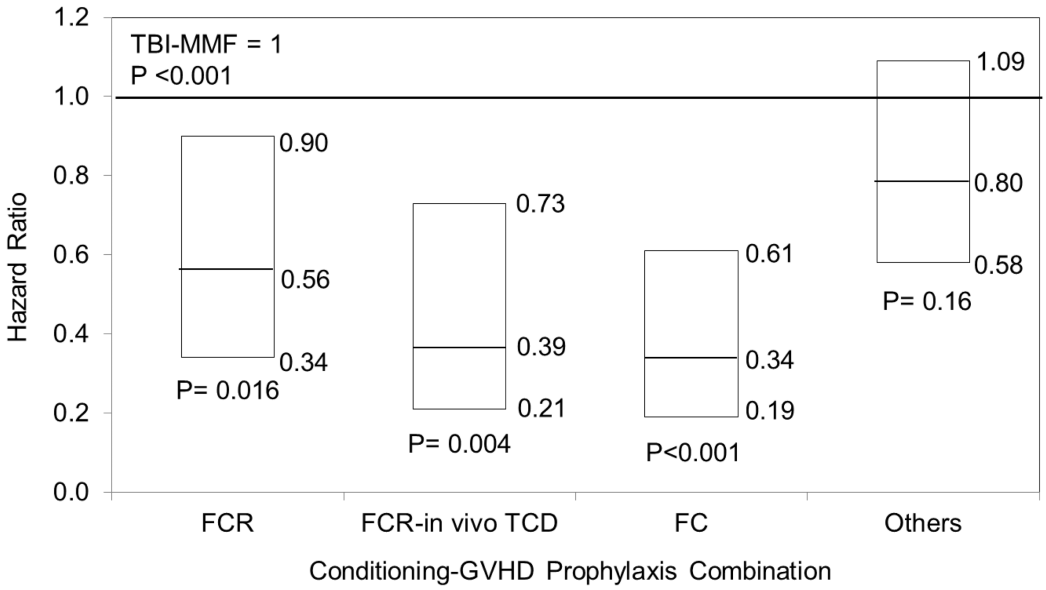
a. Acute GVHD, grades II–IV

b. Chronic GVHD

c. Adjusted progression free survival

d. Adjusted overall survival

a.



b.

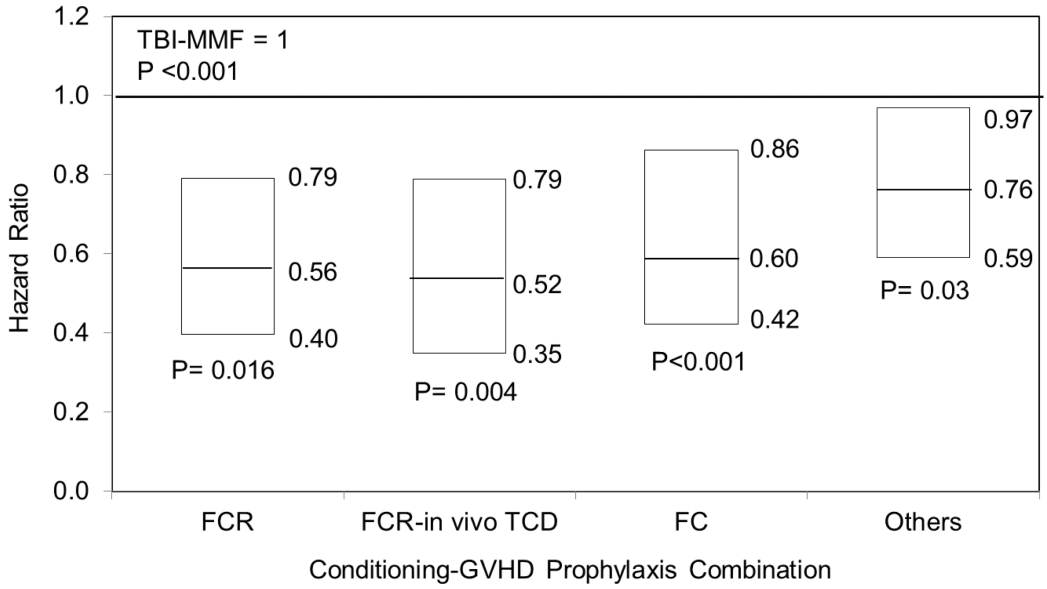


Figure 4.

Multivariate analysis of regimen-GVHD prophylaxis combinations

a. Acute GVHD, grades II–IV

b. Chronic GVHD

Table 1

Patient characteristics according to nomyeloablative conditioning with or without use of total body irradiation prior to hematopoietic cell transplantation for lymphoproliferative diseases.

Variable	TBI (%)	No-TBI (%)[1]	P-value
Number of patients	382	515	
Number of centers	53	80	
Age, years (Median, 95% CI)	57 (40–75)	56 (40–74)	0.13
Male	281 (74)	346 (67)	0.047
Disease group[2]			0.81
Low grade	219 (56)	297 (58)	
Intermediate grade	135 (35)	175 (34)	
Other	28 (7)	43 (8)	
Sensitive/ Resistant to therapy prior to transplant			<0.001
Sensitive	182 (48)	310 (60)	
Resistant	59 (15)	70 (14)	
Other/Unknown	141 (37)	145 (26)	
Disease at transplant			<0.001
CR-1	32 (8)	28 (5)	
PR-1	50 (13)	63 (12)	
=>CR2	67 (18)	133 (26)	
=>PR-2	36 (9)	49 (10)	
Relapse	104 (27)	159 (31)	
Stable disease	16 (4)	20 (4)	
Progressive disease	17 (4)	23 (4)	
CLL with unknown status	54 (14)	26 (5)	
Unknown status	6 (2)	14 (3)	
Time from diagnosis to transplant (month)	51 (2.5–413)	47 (2.2–325)	0.31
Year of transplant			<0.001
2001–2004	153 (40)	228 (45)	
2005–2008	194 (51)	219 (43)	
2009–2011	35 (9)	68 (13)	
Bone marrow graft source	14 (5)	57 (14)	<0.001
Donor			<0.001
HLA-identical sibling	121 (29)	253 (46)	
URD well-matched (8/8)	205 (49)	212 (38)	
URD partially matched (7/8)	56 (13)	50 (9)	
D-R CMV match status			0.003
Pos/pos	83 (22)	167 (32)	
Pos/neg	40 (10)	55 (11)	

Variable	TBI (%)	No-TBI (%)[1]	P-value
Neg/pos	131 (34)	137 (27)	
Neg/neg	122 (32)	142 (27)	
Unknown status	6 (2)	14 (3)	
Prior autologous transplant	96 (25)	71 (14)	<0.001
Conditioning regimen			<0.001
Flu + TBI <= 200 cGY dose	382	-	
Flu TBI (no Cy)	341 (89)	-	
Flu Cy TBI	41 (11)	-	
Flu + Cy	-	493 (96)	
Flu + others[3]	-	22 (4)	
Rituximab use	153 (40)	320 (62)	<0.001
During conditioning regimen	26 (7)	206 (40)	
GVHD prophylaxis			<0.001
CNI + MTX +/− other	24 (6)	335 (65)	
CNI + MMF +/− other	334 (87)	78 (15)	
CNI +/− other	10 (3)	96 (19)	
Other	14 (4)	6 (1)	
Median follow-up (range)	26 (<1–134)	26 (<1–145)	-

Abbreviations: CMV, cytomegalovirus serologic status; CR, complete remission; CNI, calcineurin inhibitor; Cy, cyclophosphamide; R-R; donor to recipient; Flu, fludarabine; MMF, mycophenolate mofetil; MTX, methotrexate; PR, partial remission, TBI, total body irradiation; URD, unrelated donor.

[1]TBI dose=200 cGY.

[2]Low-grade diseases included CLL, low or intermediate grade follicular lymphoma, marginal zone lymphoma, and diffuse small cleaved cell lymphoma. Intermediate-grade diseases included high-grade follicular lymphoma, mantle cell lymphoma, diffuse large B-cell lymphoma, and T-cell lymphoma. Other diseases included Hodgkin lymphoma (HL), unknown grade follicular lymphoma, small lymphoplasmacytic lymphoma, mycosis fungoidies, and other non-Hodgkin lymphoma (NHL)

[3]Fludarabine + Others group consisted of 5 cases of fludarabine + ATG, 7 cases of fludarabine + campath, 3 cases of fludarabine + rituximab, 2 cases of fludarabine + anthracyclines, 1 case of fludarabine + melphalan, and 4 cases of fludarabine alone.

Table 2

Multivariate Analysis

Factor	Level	n	Hazard Ratio	95% Hazard Ratio Confidence Limits		P-value
Overall Mortality^		897				
Regimen	No-TBI	515	1			
	TBI	382	1.09	0.91	1.32	0.35
Age	40 – 49	217	1			<0.001*
	50 – 59	406	1.31	1.03	1.66	0.03
	≥ 60	274	1.66	1.28	2.15	<0.001
KPS	90 – 100	570	1			<0.001*
	< 90	234	1.49	1.21	1.83	<0.001
	Unknown	93	1.42	1.07	1.90	0.016
Donor type	HLA-identical sibling	374	1			<0.001*
	8/8 matched unrelated donors	417	1.28	1.04	1.58	0.021
	7/8 matched unrelated donors	106	1.94	1.46	2.59	<0.001
Treated-related mortality$		897				
Regimen	No-TBI	515	1			
	TBI	382	1.10	0.85	1.41	0.48
Age	40 – 49	217	1			0.012*
	50 – 59	406	1.11	0.80	1.55	0.54
	≥ 60	274	1.59	1.12	2.24	0.009
Donor type	HLA-identical sibling	374	1			<0.001*
	8/8 matched unrelated donors	417	1.42	1.06	1.92	0.021
	7/8 matched unrelated donors	106	2.63	1.79	3.87	<0.001
Progression/Relapse%		897				
Regimen	No-TBI	515	1			
	TBI	382	1.05	0.83	1.33	0.68*
KPS	90 – 100	570	1			0.011

Factor	Level	n	Hazard Ratio	95% Hazard Ratio Confidence Limits		P-value
	< 90	234	1.42	1.10	1.83	0.007
	Unknown	93	1.40	0.99	1.98	0.05
In vivo T-cell depletion	No use of in-vivo T-cell depletion	628	1			
	In-vivo T-cell depletion used	269	1.55	1.22	1.97	<0.001
Treatment failure[&]		897				
Regimen	No-TBI	515	1			
	TBI	382	0.97	0.81	1.15	0.70
KPS	90 – 100	570	1			0.005[*]
	< 90	234	1.34	1.10	1.62	0.003
	Missing	93	1.33	1.01	1.75	0.04
Donor type	HLA-identical sibling	374	1			<0.001[*]
	8/8 matched unrelated donors	417	1.21	1.00	1.47	0.05
	7/8 matched unrelated donors	106	1.79	1.36	2.34	<0.001
Acute GVHD Grade II–IV[^^]		896				
Regimen	No-TBI	515	1			
	TBI	382	1.54	1.19	2.00	0.001
KPS	90 – 100	570	1			0.016[*]
	< 90	234	1.45	1.09	1.92	0.010
	Missing	93	1.50	0.97	2.33	0.07
Sensitivity	Sensitive	492	1			<0.001[*]
	Resistant	129	2.01	1.35	2.99	<0.001
	Untreated/unknown/CLL	276	1.93	1.47	2.55	<0.001
History of prior autologous transplant	Previously received autologous transplant	167	1			
	No history of prior autologous transplant	730	12.11	4.95	29.63	<0.001
Chronic GVHD[$$]		896				
Regimen	No-TBI	514	1			
	TBI	382	1.32	1.10	1.59	0.003

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Factor	Level	n	Hazard Ratio	95% Hazard Ratio Confidence Limits		P-value
Donor type	HLA-identical sibling	373	1			0.003*
	8/8 matched unrelated donors	417	1.39	1.13	1.71	0.002
	7/8 matched unrelated donors	106	1.50	1.08	2.08	0.015
In vivo T-cell depletion	No use of in-vivo T-cell depletion	627	1			
	In-vivo T-cell depletion used	269	0.60	0.47	0.75	<0.001

* overall p-value

^ Model stratified by year of transplant and sensitivity. Other pair-wise contrasts: age (p-value= 0.024), donor type (p-value= 0.002)

$ Model stratified by year of transplant and sensitivity. Other pair-wise contrasts: age (p-value= 0.015), donor type (p-value <0.001)

% Model stratified by disease group and sensitivity.

& Model stratified by disease group, year of transplant, and sensitivity. Other pair-wise contrasts: donor type (p-value= 0.003)

^^ Other pair-wise contrasts: sensitivity (p-value= 0.84)

$$ Other pair-wise contrasts: donor type (p-value= 0.62)