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Effect of the Thiotepa dose in the TBF Conditioning regimen in Patients Undergoing Allogeneic Stem-Cell Transplantation for Acute Myeloid Leukemia in complete remission: A report from the EBMT Acute Leukemia Working Party

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Microabstract:

We conducted a multicenter retrospective analysis of 639 patients to evaluate the optimal dose of thiotepa, administered as part of thiotepa-busulfan-fludarabine (TBF) conditioning regimen for allogeneic stem cell transplantation in adults with acute myeloid leukemia (AML) in complete remission (CR). This study suggested that a lower dose-intensity of thiotepa and busulfan (5 mg/kg thiotepa and 2 days of iv busulfan at 6.4 mg/kg (T1B2F)) in the TBF regimen may yield better outcomes.

Abstract

Background

Allogeneic hematopoietic cell transplantation (allo-SCT) is a potentially curative therapy for patients with acute myeloid leukemia (AML) after achieving complete remission (CR). The aim of this study is to evaluate the optimal dose of thiotepa, administered as part of thiotepa-busulfan-fludarabine (TBF) conditioning regimen for allogeneic stem cell transplantation (allo-SCT) in adults with AML in CR.

Methods

In a retrospective multicenter analysis, we identified 639 patients allotransplanted from matched related or unrelated donors or T replete haplo-identical donors. We compared the transplantation outcomes of patients who received 5 mg/kg thiotepa and 2 days of iv busulfan at 6.4 mg/kg (T1B2F) versus those who received 10 mg/kg thiotepa with 2 days of iv busulfan at 6.4 mg/kg (T2B2F) or 3 days of iv busulfan at 9.6 mg/kg (T2B3F). The median follow-up was 20 months.

Results

On multivariate analysis, our results showed that acute graft versus host disease (GVHD) was higher for patients receiving T2B2F (p=0.01; HR 2.25) or T2B3F (p=0.02; HR 2.05) as well as for patients receiving a transplant from a haploidentical donor or peripheral blood stem cells (PBSC). Non-relapse mortality (NRM) was higher in older patients (p=0.001; HR 1.56), patients receiving T2B3F (p=0.008; HR 2.28) and haploidentical transplant (p=0.009; HR 2.2). Importantly, overall survival (OS) was lower for older patients (p=0.001; HR 1.4) as well as for patients receiving T2B3F (p=0.004; HR 2.09).

Conclusion

T2B2F is associated with a higher incidence of acute GVHD compared to T1B1F whereas T2B3F is associated with a higher NRM, a higher incidence of acute GVHD and a lower OS compared to

T1B1F. These results suggest that a lower dose-intensity of thiotepa and busulfan in the TBF regimen may yield better results in AML patients in complete remission.

Introduction:

Allogeneic stem-cell transplantation (allo-SCT) is a well-established treatment modality for patients with high-risk acute myeloid leukemia (AML). [1] Even though standard myeloablative conditioning regimens are associated with a decreased incidence of relapse, they are associated with an increased risk of toxicity, graft-versus-host disease (GVHD), and non-relapse mortality (NRM). [2] Reduced-toxicity conditioning (RTC) has recently emerged as a possible and attractive solution to this problem as it combines the favorable antitumor effect of myeloablation with the benefit of lower NRM of reduced-intensity conditioning (RIC). [2] The optimal intensity of myeloablation with a RTC regimen to decrease relapse rate after allo-SCT without increasing NRM has not been well established.

The conditioning regimen must be sufficiently immunosuppressive to ensure engraftment and prevent relapse post-transplant. [3] A broad spectrum of regimens has been studied in the past, including various chemotherapeutic agents and total body irradiation (TBI). To date, no winner has been selected for the optimal outcome of allo-SCT. The development of RTC has led to the excessive adoption of platforms including busulfan and fludarabine. [4]

Thiotepa is an alkylating agent with antineoplastic activity and immunosuppressive properties, as well as the ability to penetrate the blood brain barrier. It has become an integral part of the thiotepa-busulfan-fludarabine (TBF) conditioning regimen, which is being used with increasing frequency, particularly for haploidentical and cord-blood transplants. [5, 6] However, few studies have focused on analyzing the effect of the thiotepa dose in TBF conditioning. [7] In an attempt to assess the optimal dose of thiotepa, we retrospectively compared the effect of the dose intensity of thiotepa on the outcome of a homogeneous population. We chose to study patients undergoing allo-SCT for AML after achieving complete remission (CR).

Patients and Methods:

Study population

In this retrospective multicenter analysis, we used the European Society for Blood and Marrow Transplantation (EBMT) registry to identify patients with a diagnosis of AML who received allo-SCT between 2009 and 2018. Data were provided by the acute leukemia working party (ALWP) of the EBMT registry. The EBMT registry is a voluntary working group of more than 600 transplant centers that are required to report annually, all consecutive stem cell transplantations and follow-ups. Audits are routinely performed to determine the accuracy of the data. All patients who proceeded to transplantation provided written informed consent for the use of their data for clinical research, in accordance with the local ethics committee and the modified Declaration of Helsinki. The study was approved by the ALWP of the EBMT.

The aim of this study was to evaluate the optimal dose of thiotepa, administered as part of a TBF conditioning regimen for allo-SCT in adults with AML transplanted after achieving CR. We compared the transplant outcomes of patients who received thiotepa (5 mg/kg/day) and 2 days of busulfan (6.4 mg/kg) (T1B2F) versus those who received 10 mg/kg thiotepa (5mg/kg x 2 days) with 2 days of busulfan (6.4 mg/kg) (T2B2F) or 3 days of busulfan (9.6 mg/kg) (T2B3F), using a large dataset from the EBMT registry.

We included all adult patients (aged >18 years) from 2009 to 2018 at EBMT centers, who underwent allo-SCT with TBF conditioning for AML, regardless of the type of donor (full-matched related donor (MRD), full-matched unrelated donor (MUD), haplo-identical related donor (HRD)) and who were in first or second complete remission (CR1 or CR2), excluding all refractory patients. Patient and transplant characteristics are shown in Table 1.

Definition of Endpoints

The aim of this study was to compare dose intensity of thiotepa in TBF conditioning. The primary endpoints were relapse incidence (RI), NRM, progression free survival (PFS) and overall survival (OS). The secondary endpoints included engraftment, graft versus host disease (GVHD), and GVHD- and relapse-free survival (GRFS). OS was defined as the time from allo-SCT to death, regardless of the cause. PFS was defined as survival with no evidence of relapse or progression; NRM, as death without evidence of relapse or progression; and GRFS, as being alive without grade III-IV acute GVHD, severe chronic GVHD, or disease relapse. Acute and chronic GVHD were diagnosed and graded according to standard criteria. [8, 9] Engraftment or neutrophil recovery was defined as the first of 3 days with neutrophil count >500/mm^3.

Statistical analysis

Standard demographic and transplant-related characteristics are summarized using the median, range and interquartile range (IQR) for continuous variables and counts and percentages for categorical variables. Patient, disease, and transplant-related characteristics for the three-thiotepa groups were compared using the χ^2 statistic for categorical variables and the Kruskal-Wallis test for continuous variables.

Probabilities of OS, PFS, and GRFS were calculated using the Kaplan–Meier method. Cumulative incidence was used to estimate the endpoints of NRM, RI, acute and chronic GVHD to accommodate for competing risks. To study acute and chronic GVHD, we considered relapse and death to be competing events. Univariate analyses were done using the Gray's test for cumulative incidence functions and the log rank test for OS, GRFS, and PFS. A Cox proportional hazards model was used for multivariate regression. All variables differing significantly between the 3 groups, or factors associated with one outcome on univariate analysis were included in the Cox model. In order to test for a centre effect, we introduced a random effect or frailty for each centre into the model. [10] Results were expressed as the hazard ratio (HR) with a 95% confidence interval (95% CI). Proportional hazards assumptions were checked systematically for all proposed models using the Grambsch-Therneau residual-based test. All tests were 2-sided. The type I error rate was fixed at 0.05 for the determination of factors associated with time-to-event outcomes. Statistical analyses were performed with SPSS 24.0 (SPSS Inc, Chicago, IL, USA) and R 3.4.0 (R Core Team (2017). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/.)

Results:

We identified 639 AML patients allotransplanted between January 2009 and June 2018 from MRDs or MUDs or T replete haplo-identical donors. Overall, 127 patients (20%) received T1B2F; 113 patients (18%) received T2B2F; the remaining 399 patients (62%) received T2B3F. Median follow-up was 20 months (IQR: 9-37). Outcomes are summarized in Table 2. Engraftment was

similar across the three groups. At day 30, cumulative incidences were 96%, 95% and 97% in T1B2F, T2B2F and T2B3F, respectively (results not shown).

On univariate analysis, the incidence of acute GVHD grade II-IV was 15-19% and was not significantly different between the 3 groups (T1B2F 15.1%, T2B2F 19%, T2B3F 17.1%) (Table 2). We did not find a significant difference with respect to chronic GVHD between the 3 groups (31%, 34% and 28% p=0.14) respectively, Table 2. On multivariate analysis, the incidence of acute GVHD was significantly higher in T2B2F and T2B3F compared to T1B2F (HR 2.25; 95% CI: 1.19-4.27; p=0.013 and HR 2.05; 95% CI: 1.14-3.69; p=0.016; respectively).

OS, PFS, NRM

With a median follow-up of 20 months (IQR, 9-37), 182 patients (28%) were dead at last follow up: 38 death were attributed to disease progression while 144 attributed to NRM. Causes of death were infection in 29%, 50% and 4% and GVHD in 19%, 21% and 4% in the T1B2F, T2B2F and T2B3F group respectively. The 2-year NRM was 22%, 25% and 21% in the T1B2F, T2B2F and T2B3F groups respectively.

At 2 years, the PFS and OS were 60% and 67%, respectively in the T1B2F group. They were 56% and 62% respectively in the T2B2F group. They were 63% and 67% respectively in the T2B3F group. On multivariate analysis, there was no significant difference between the 3 groups for PFS, but T2B3F was associated with a lower OS compared to T1B2F (HR 2.09; 95% CI: 1.26-3.45; p=0.004). The only other factor associated with PFS and OS was patient age and correlation was insignificant: HR 1.25; 95% CI:1.09-1.44; p=0.002 for PFS and HR 1.4; 95% CI:1.2-1.64; p<10^-3 for OS.

The 2-year GRFS however, varied significantly with 50%, 43%, and 55% in the 3 TBF groups respectively, p=0.02. On multivariate analysis (results not shown), acute GVHD was higher for patients receiving T2B2F (p=0.01; HR 2.25) or T2B3F (p=0.02; HR 2.05) as well as for patients receiving transplant from a haploidentical donor or PBSC, whereas NRM was higher for older patients (p=0.001; HR 1.56), patients receiving T2B3F (p=0.008; HR 2.28) or haploidentical transplant (p=0.009; HR 2.2). The comparison between the three groups was adjusted according to other prognostic factors such as stem cell source, donor type, age, cytogenetics and other

comorbidities especially when differing in distribution between the three groups. Consequently, it is important to focus on the comparison between the outcomes related to the difference in conditioning regimen intensity and not confounding prognostic factors, which were only used for adjustment. Importantly, OS was lower for older patients (p=0.001; HR 1.4 95% CI 1.2-1.64) or for patients receiving T2B3F (p=0.004; HR 2.09 95% CI 1.26-3.45).

Discussion:

In 1996, Bacigalupo et al. suggested that a thiotepa-cyclophosphamide conditioning regimen is well tolerated in patients with advanced leukemia and is highly efficient due to the myeloablative properties of thiotepa. [11] They reported a 2-year OS of 57% and a NRM of 29%. Thiotepa was later included in RIC regimens in an effort to intensify the antileukemic effect and reduce the relapse rates, which were higher after RIC compared to myeloablative regimens. [12] Recently, we published a study proving the superiority of thiotepa at 10mg/kg in the TBF conditioning regimen for patients undergoing allo-SCT for hematologic malignancies compared to thiotepa at 5 mg/kg. [7] Engraftment was observed in all cases, suggesting a sufficient immunosuppressive activity of both doses of thiotepa with fludarabine in combination with intermediate doses of busulfan and anti-thymocyte globulin (ATG). The incidence of acute GVHD was comparable between the two groups of patients receiving thiotepa at 5mg/kg and at 10mg/kg. However, the aforementioned study was unicentric, unlike the current one. It also included patients with various hematologic malignancies including lymphoid and myeloid disease, rendering their population heterogeneous. A recent registry study performed by the ALWP of the EBMT compared thiotepa based conditioning to standard myeloablative conditioning with cyclophosphamide and TBI in patients with AML in CR, which showed a comparable outcome between the two groups. Acute GVHD was observed in 25%, chronic GVHD in 40%, and NRM in 24%, with a relapse rate of 17% after a thiotepa-based regimen. [13] However, the impact of thiotepa dose on outcome was not investigated and our study uses the same ALWP-EBMT database to compare these differences.

Another recent study by Pagliardini et al. studied the TBF conditioning in the specific setting of pre-haploidentical SCT with post-transplant cyclophosphamide in 100 AML patients in different stages of disease (advanced and CR). Seventy-seven patients received RIC, (busulfan total dose $\leq$ 260 mg/m^2) and 23 patients received myeloablative conditioning, (busulfan total dose > 260

mg/m^2). [14] However, the groups were not compared to each other and not comparable to our groups because all patients received thiotepa (5 mg/kg/day for 1 day). Their bicentric study showed this TBF regimen to be a safe and effective alternative for patients who lack HLA-matched donors with high antileukemic activity in both CR1 and advanced disease groups. Although no excess of NRM was observed in CR1 patients, encouraging haploidentical SCT in CR1 AML, the TBF platform should be used with caution in patients with advanced AML, with a higher NRM counterbalancing the benefit in disease control.

The current study is the first large one to assess the optimal dose of thiotepa as part of the TBF conditioning for allo-SCT in adults with AML in CR, by comparing the transplantation outcomes. Our results show that the incidence of acute GVHD grade II-IV was higher with higher doses of thiotepa (T2B2F) or higher doses of busulfan (T2B3F). This result was also confirmed by multivariate analysis. The NRM and the RI were highest with the maximum dose of thiotepa (T2B2F) and the lowest with the maximum dose of busulfan (T2B3F). Interestingly, the PFS and the OS were the lowest with T2B2F. The OS with T1B2F was similar to that of T2B3F and the PFS in the T2B3F was slightly higher than in the T1B2F group. According to these findings, patients with AML in CR might not tolerate high-dose intensities of thiotepa or busulfan eventually, thus low-dose intensities of this conditioning regimen may have produced better transplantation and survival outcomes in this particular population. [15]

Although busulfan dose also differs between a considerable number of patients, there are no clear criteria for how the dose was selected. Furthermore, our study only focused on the comparison of outcomes according to thiotepa dose and not busulfan, which could be investigated in another study. In addition, the use of pharmacokinetic data for busulfan dose adjustment could improve the safety of this platform. [16] Moreover, post-transplant treatments such as hypomethylating agent, [17-19] tyrosine kinase inhibitors [20-22] and/or donor lymphocyte infusions [23, 24] could be helpful in partially overcoming the high risk of relapse in this advanced disease population when intensification of the conditioning regimen is not feasible. Based on the current study results, one can speculate that T1B2F is a better conditioning regimen than T2B2F or T2B3F, in patients with AML who are about to undergo allo-SCT. This is especially true when we use immunomodulatory therapeutics post-transplant, such as azacitidine, [25-27] to decrease relapse rates and improve outcomes. Our results, especially cause of death, highlight the frailty of our patients, which could be attributed to previous cumulative treatments. This again emphasizes the importance of caution

while using the TBF regimen, as the antitumor effect could be nullified by an increase in mortality, as well as the importance of perfecting strategies to better select patients for conditioning regimen optimization.

We recognize that a weakness of this study is its retrospective nature. Additionally, there are no clear criteria on how patients are to be selected to receive different doses of thiotepa but we concluded that different patients received different doses according to their physician's preference and the experience of their SCT group. On the contrary, the strength of our study is that it is a large, multicentric study with a considerable number of patients who are homogeneous in disease nature and course (AML patients in CR). It also includes very recent (2018) data.

Conclusion

This study demonstrated that T2B2F is associated with a higher incidence of acute GVHD compared to T1B1F, whereas T2B3F is associated with higher NRM, a higher incidence of acute GVHD and a lower OS as compared to T1B1F. With the limitation of the retrospective nature of registry data, these results suggest that a lower dose-intensity of thiotepa and busulfan in the TBF regimen may yield better outcomes in AML patients transplanted in complete remission.

Clinical Practice Points

- Thiotepa-busulfan-fludarabine (TBF) conditioning regimen is a well-known regimen used in allogeneic stem cell transplantation (allo-SCT).
- To date, no studies had assessed the optimal dose of thiotepa in the TBF regimen.
- We conducted a multicenter retrospective analysis of 639 patient records to evaluate the optimal dose of thiotepa, administered as part of thiotepa-busulfan-fludarabine (TBF) conditioning regimen for allo-SCT in adults with acute myeloid leukemia (AML) in complete remission (CR).
- Our study population was sampled from the European Society for Blood and Marrow Transplantation (EBMT) registry.
- At 2 years, the PFS and OS were 60% and 67%, respectively in the T1B2F group. They were 56% and 62% respectively in the T2B2F group. They were 63% and 67% respectively in the T2B3F group.
- OS was lower for older patients (p=0.001; HR 1.4 95% CI 1.2-1.64) or for patients receiving T2B3F (p=0.004; HR 2.09 95% CI 1.26-3.45).
- This study demonstrated that a lower dose-intensity of thiotepa and busulfan (5 mg/kg thiotepa and 2 days of iv busulfan at 6.4 mg/kg (T1B2F)) in the TBF regimen may yield better outcomes.
- Our study presents evidence on the optimal dosage of thiotepa and busulfan and effects on outcomes that will help with the choice of conditioning regimens.

Compliance with ethical standards

Conflicts of interest

All authors have no potential conflicts of interests to declare.

Ethical approval

The study was approved by the Acute Leukemia Working Party (ALWP) of the EBMT registry. All patients who proceeded to transplantation provided written informed consent for the use of

their data for clinical research, in accordance with the local ethics committee and the modified Declaration of Helsinki.

Funding Support

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Figure legends

Table 1

Patient and transplant characteristics

Abbreviations: VOD, veno-occlusive disease; IP, interstitial pneumonia; GVHD, graft-versus-host disease; NRM, non-relapse mortality

Table 2

Results at 2 years

Figure 1

Adjusted NRM for T1B2F, T2B2F and T2B3F groups

Figure 2

Adjusted acute GVHD II-IV for T1B2F, T2B2F and T2B3F groups

Figure 3

Adjusted OS for T1B2F, T2B2F and T2B3F groups

Table 1 Patient and transplant characteristics:

	T1B2F	T2B2F	T2B3F	Test p-value
N (%)	127 (20%)	113 (18%)	399 (62%)	
Follow-up (mo) median (range)	15.5 (4-31)	15.3 (5-30)	24.4 (11.7-40.8)	<10-3
Patient age HSCT median (range) [QR]	62.3 (29.3-72.2) [58.3-65.9]	60.0 (18.7-70.2) [54-63.4]	45.0 (18.2-67.9) [35.5 - 53.9]	<10-3
Year HSCT median (range) [QR]	2016 (2009-2018) [2015-2016]	2015 (2011-2018) [2014-2016]	2015 (2009-2018) [2014-2016]	0.012
Time diag-HSCT (mo) median (range) [QR]	6.1 (3-174.8) [4.6-12.3]	5.1 (1.8 -41.4) [4.2-8.7]	6.3 (0.1-189.7) [4.8-9.7]	0.012
Status at HSCT				
CR1	92 (72.4%)	87 (76.9%)	296 (74.2%)	0.718
CR2	35 (27.6%)	26 (23%)	103 (25.8%)	
Donor				
MSD	33 (25.9%)	38 (33.6%)	78 (19.6%)	0.008
UD 10/9	19 (14.9%)	13 (11.5%)	85 (21.3%)	
TR Haplo	75 (59.1%)	62 (54.9%)	236 (59.2%)	
Source of SC				
BM	43 (33.9%)	52 (46%)	243 (60.9%)	<0.0001
PB	84 (66.1%)	61 (53.9%)	156 (39.1%)	
Patient sex				
Male	81 (64.3%)	62 (54.9%)	198 (49.6%)	0.015
Female	45 (35.7%)	51 (45.13%)	201 (50.4%)	
Missing	1	0		
GVHD Prophylaxis				
CSA+MTX	36 (28.8%)	31 (27.9%)	138 (34.9%)	NA
CSA+MMF	7 (5.6%)	6 (5.4%)	15 (3.8%)	
TACRO+MMF	0 (0%)	3 (2.7%)	4 (1%)	
CSA+MMF+MTX	19 (15.2%)	0 (0%)	31 (7.9%)	
PT-CY	49 (39.2%)	58 (52.3%)	194 (49.1%)	
OTHER	14 (11.2%)	13 (11.7%)	13 (3.3%)	
Missing	2	2	4	
acute GVHD				
Grade 0-I	97 (80.2%)	72 (67.9%)	286 (73.9%)	NA
Grade II	17 (14.1%)	23 (21.7%)	64 (16.5%)	

Grade III-IV	6 (4.9%)	11 (10.4%)	33 (8.5%)	
Grade unknown	1 (0.8%)	0 (0%)	4 (1%)	
Missing	6	7	12	

Cause of death (N)	**T1B2F**	**T2B2F**	**T2B3F**	**Test p-value**
Cardiac toxicity	0 (0%)	2 (5.9%)	1 (0.9%)	
Hemorrhage	1 (3.2%)	0 (0%)	1 (0.9%)	
VOD	1 (3.2%)	0 (0%)	1 (0.9%)	
Infection	9 (29%)	17 (50%)	4 (3.6%)	
IP	4 (12.9%)	0 (0%)	31 (28.2%)	
GVHD	6 (19.4%)	7 (20.6%)	4 (3.6%)	
Original disease	7 (22.6%)	6 (17.7%)	25 (22.7%)	
Second malignancy	1 (3.2%)	0 (0%)	31 (28.2%)	
Other NRM	2 (6.5%)	2 (5.9%)	3 (2.7%)	
Missing	2	0	9 (8.2%)	

Abbreviations: VOD, veno-occlusive disease; IP, interstitial pneumonia; GVHD, graft-versus-host disease; NRM, non-relapse mortality

Table 2 Results at 2 years:

	RI	NRM	PFS	OS	GRFS	acute GVHD II-IV	acute GVHD III-IV	chronic GVHD	ext. cGVHD
T1B2F (n=127)	18.1% (10.6-27.3)	21.9% (14-30.9)	60.3% (49.8-70.9)	67.2% (56.7-77.7)	50.4% (39.8-61)	15.1% (9.4-22.2)	4.2% (1.6-9)	31.4% (21.4-41.8)	15.5% (8.6-24.2)
T2B2F (n=113)	18.7% (11.3-27.4)	25.1% (16.3-34.9)	56.3% (45.5-67.1)	62.2% (51-73.4)	43.1% (32.6-53.6)	17% (10.6-24.8)	6.6% (2.9-12.4)	34% (23.4-44.8)	16.6% (9.1-26)
T2B3F (n=399)	16.7% (12.8-21)	20.7% (16.5-25.3)	62.6% (57.2-68)	67.1% (61.8-72.4)	55.3% (49.9-60.8)	19.1%(15.3-23.2)	8.1% (5.6-11.1)	28.4% (23.2-33.8)	9.5% (6.5-13.2)
P value	0.37	0.62	0.21	0.56	**0.02**	0.13	0.31	0.14	0.1

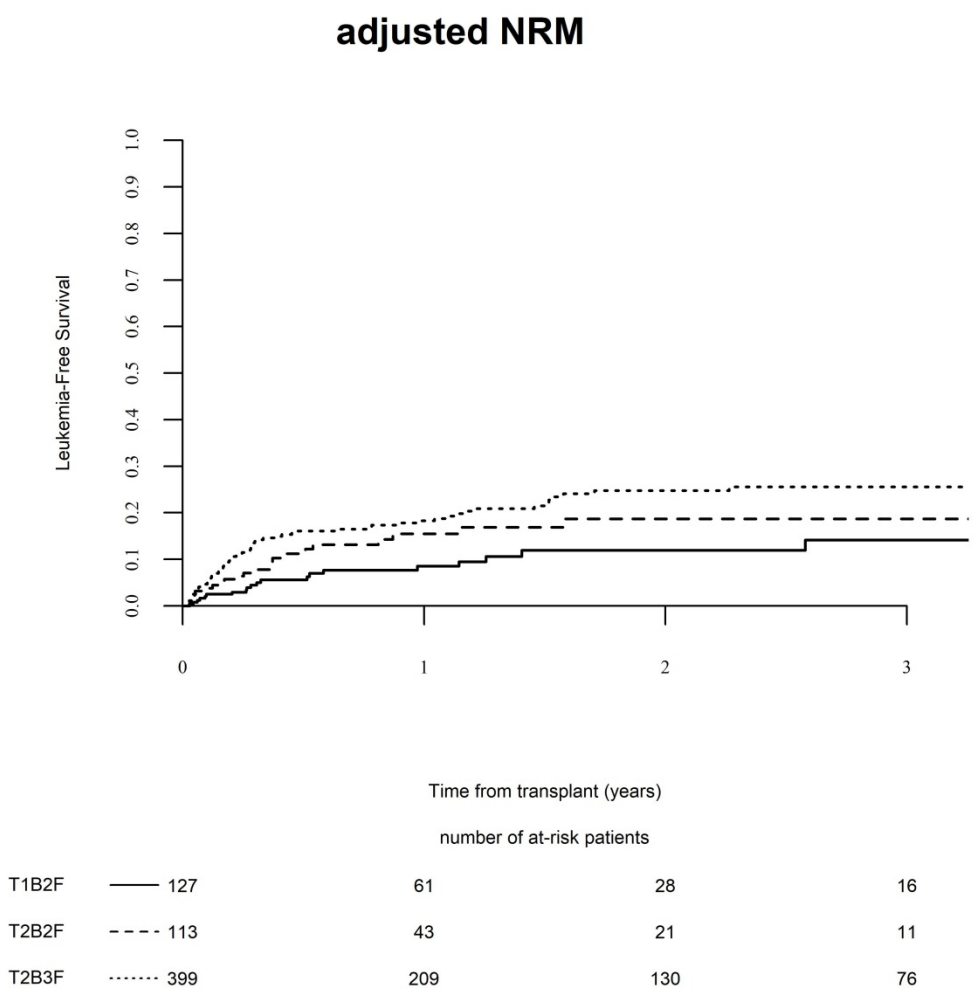

Figure 1: Adjusted NRM for T1B2F, T2B2F and T2B3F groups

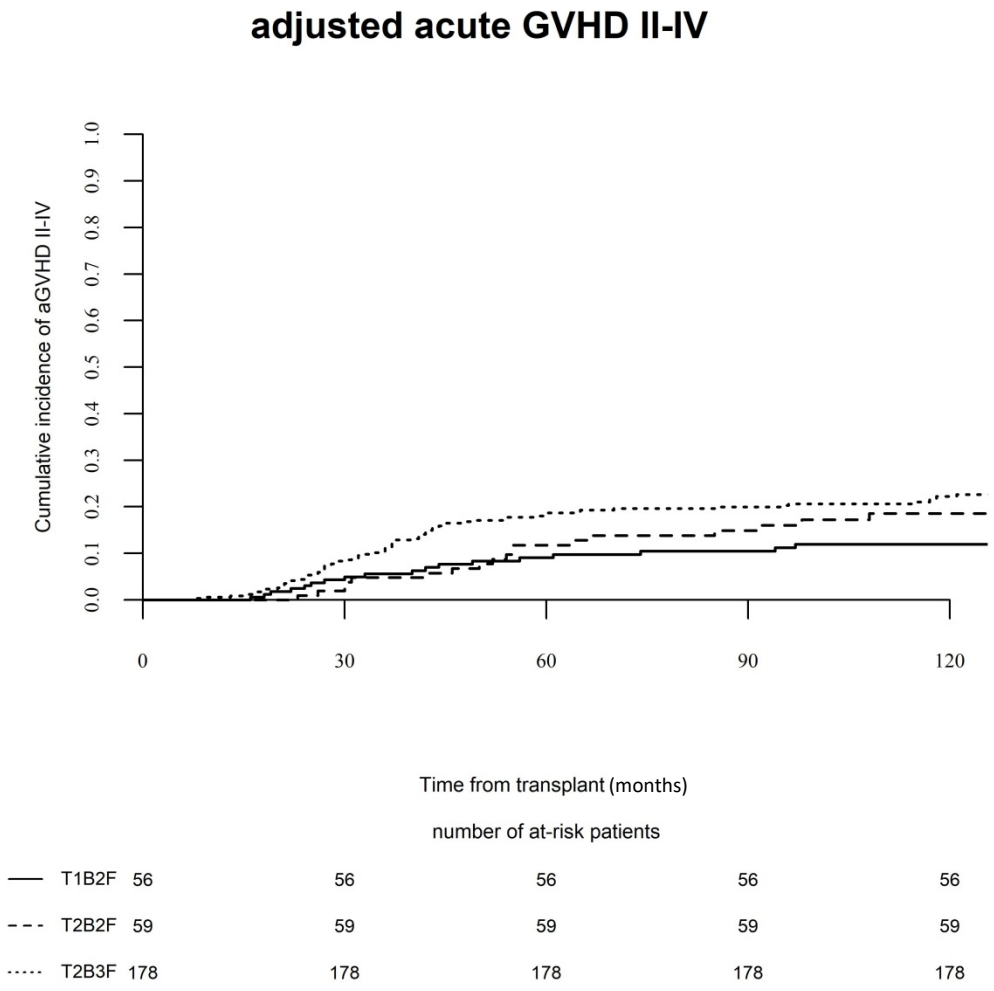

Figure 2: Adjusted acute GVHD II-IV for T1B2F, T2B2F and T2B3F groups

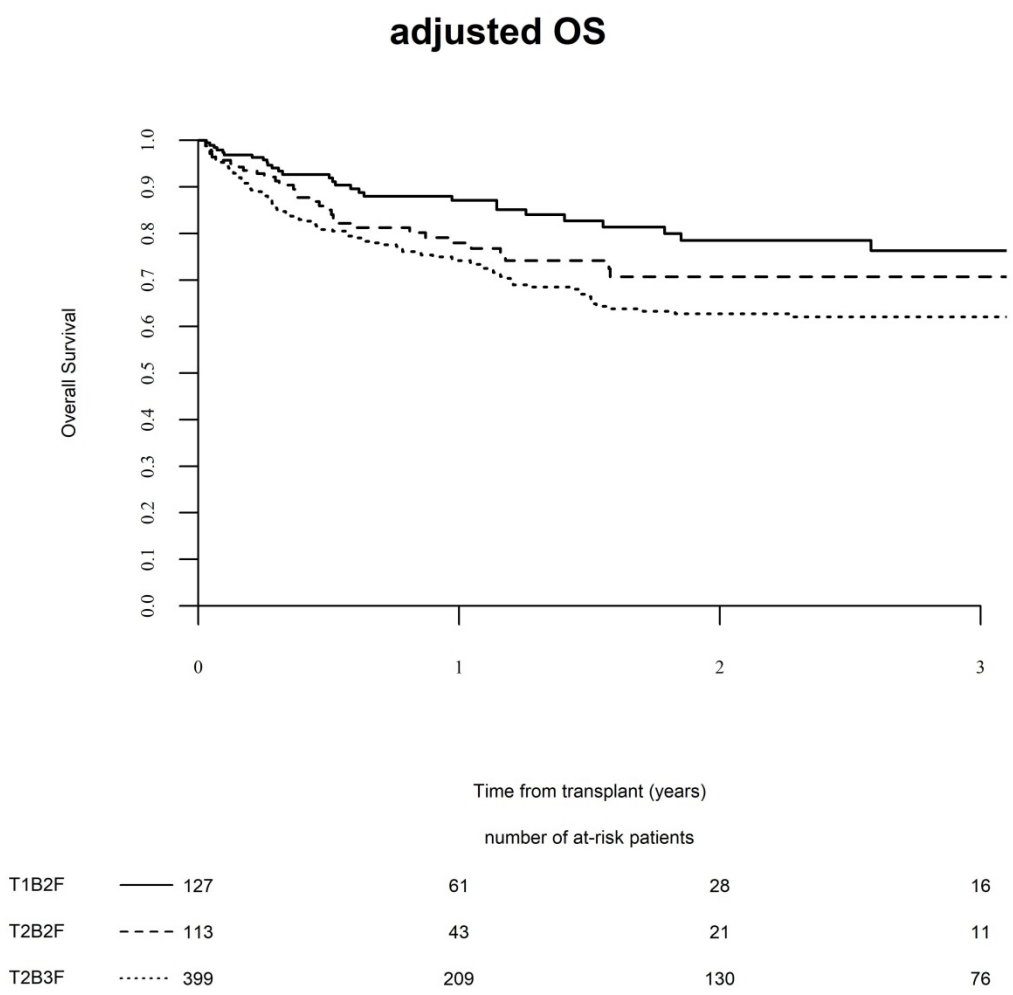

Figure 3: Adjusted OS for T1B2F, T2B2F and T2B3F groups

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