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# The Sequence of Cyclophosphamide and Myeloablative Total Body Irradiation in Hematopoietic Cell Transplant for Patients with Acute Leukemia

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## Abstract

Limited clinical data are available to assess whether the sequencing of cyclophosphamide (Cy) and total body irradiation (TBI) changes outcomes. We evaluated the sequence in 1769 (CyTBI N=948, TBICy N=821) recipients of related or unrelated hematopoietic cell transplantation (HCT) who received TBI (1200-1500cGY) for acute leukemia from 2003 to 2010. The two cohorts were comparable for median age, performance score, type of leukemia, first complete remission, Ph+ ALL, HLA matched siblings, stem cell source, anti-thymocyte globulin use, TBI dose, and type of graft-versus-host disease (GVHD) prophylaxis. The sequence of TBI did not significantly affect TRM (24% vs. 23% at 3y, p=0.67; relative risk [RR] 1.01, p=0.91), leukemia relapse (27% vs. 29% at 3y, p=0.34; RR 0.89, p=0.18), leukemia-free survival (49% vs. 48% at3y, p=0.27; RR 0.93, p=0.29), chronic GVHD (45% vs. 47% at 1y, p=0.39; RR 0.9, p=0.11) or overall survival (53% vs. 52% at 3y, p=0.62; RR 0.96, p=0.57) for CyTBI and TBICy respectively. Corresponding cumulative incidences of sinusoidal obstruction syndrome were 4% and 6% at 100 days (p=0.08). This study demonstrates that the sequence of Cy and TBI does not impact transplant outcomes and complications in patients with acute leukemia undergoing HCT with myeloablative conditioning.

### Keywords

Allogeneic transplant; total body irradiation; Leukemia

## Introduction

Controversy concerning the optimal conditioning regimen and sequence of modalities for patients with hematologic malignancies still persists. The optimal regimen would maximize tumor cell kill and minimize toxicities. Cyclophosphamide (Cy) and total body irradiation (TBI) have been used in combination as a preparative regimen for high risk hematologic malignancies for several decades. Animal preclinical data in the early 1990's showed that Cy given 24 hours after TBI (TBICy) caused less lung damage but more bone marrow damage in the murine model.[1-2] Lowenthal et al. showed that the reverse, or CyTBI, offers an improved anti-leukemic effect as compared to TBICy in mice with B cell leukemia/lymphoma.[3] The optimal sequence of these agents in the preparative regimen and the associated impact on clinical outcomes, such as transplant related mortality (TRM) and leukemia relapse has not been systematically studied to date.

Synergism between chemotherapy and radiation therapy exists. In early studies, TBI was used solely as the conditioning regimen.[4] The goal of TBI is to obliterate the host marrow, deplete residual leukemia and allow for donor marrow cells to repopulate through immune-

ablation. TBI has high efficacy, however, there is controversy over the optimal dose, as higher doses have been related to increased incidence of graft-versus-host disease (GVHD) and mortality, thought to be triggered by radiation-related tissue damage.[5] TBI-only regimen was less effective at lower doses of TBI and more toxic at higher doses of TBI (1,400 to 2000 cGy). [6] Cy was later added to the regimen permitting lower TBI doses to be used, thereby decreasing the incidence of pulmonary toxicity while maintaining stable rates of leukemia relapse and immune-ablation.[7] The standard regimen for adults used for disease ablation and immunosuppression in patients with leukemia was established in the early 1970's, and is Cy 60 mg/kg/day for 2 days for adults (4 days for children) followed by 3-4 days of TBI.[7] A number of modifications to this regimen have been introduced to improve the rates of engraftment and reduce the relapse rate and radiation complications[8-9]. Another rationale for changing the sequence in the conditioning regimens was related to Cy induced emesis, which could affect the scheduling of subsequent TBI. Despite evidence that CyTBI is a good choice of myeloablative regimen, no overall consensus on timing of TBI and Cy has been investigated in large series.

This is a common clinical question in cases of conflicting schedules of irradiation treatment days and arrival or availability of a stem cell product for transplantation. The goal of this study was to compare CyTBI to TBICy in terms of the incidence of GVHD, leukemia relapse and incidence of sinusoidal obstruction syndrome (SOS).

## Methods

### Data Source

The Center for International Blood and Marrow Transplant Research (CIBMTR) is a voluntary working group of more than 450 transplantation centers worldwide that contribute detailed data on consecutive HSCTs to a Statistical Center located at the Medical College of Wisconsin in Milwaukee and the National Marrow Donor Program (NMDP) Coordinating Center in Minneapolis. Participating centers are required to report all transplantations consecutively; compliance is monitored by onsite audits. The CIMBTR maintains an extensive database of detailed patient-, transplant-, and disease-related information, and prospectively collects data longitudinally with yearly follow-ups. Observational studies conducted by the CIBMTR are performed in compliance with HIPAA regulations as a public health authority and also in compliance with all applicable federal regulations pertaining to the protection of human research participants, as determined by a continuous review by the Institutional Review Boards of NMDP and the Medical College of Wisconsin.[10]

### Patients

Patients were younger than 60 years who received HCT with Cy and TBI with myeloablative doses of 1200-1500cGY for treatment of acute leukemia in first or second complete morphologic remission from 2003 to 2010 and reported to the CIBMTR. Patients who received umbilical cord blood grafts, haploidentical or other HLA mismatched donors, or ex vivo T-cell depletion were excluded. Median follow up of cohort was 56 months and the completeness index[11] (the observed/the expected follow up) for a 3 year analysis was

88%. Eligible patients were separated according to the sequence of agents into CyTBI and TBICy groups based on the reported dates of administration of Cy and TBI.

### Outcome

The conditioning regimen sequence was compared according to overall survival (OS), leukemia free survival (LFS), transplant related mortality (TRM), leukemia relapse, graft versus host disease (GVHD), and sinusoidal obstruction syndrome (SOS). Events of GVHD and SOS were defined by transplant centers. GVHD data included date of onset, organ involvement and maximum grade. SOS data includes differential diagnosis, supporting clinical and diagnostic information. OS was defined as death by any cause and patients were censored at time of last follow up. Leukemia relapse or death was recorded as the event for the LFS outcome. TRM was defined as any death in the absence of prior leukemia relapse. GVHD was analyzed as grades IIIIV and II-IV acute (aGVHD) according to modified Gluksberg[12] and chronic GVHD (cGVHD).

### Statistical Analysis

Eligible patients were separated into two cohorts according to the sequence of TBI and Cy (CyTBI and TBICy) defined according to date of initiation of each component of the conditioning regimen. Selected variables were described for both cohorts, continuous variables were compared by Kruskall Wallis test and categorical variables by Chi-Square test to assess significant differences (defined as p-value<0.05).

Survival outcomes including OS and LFS were computed using Kaplan Meier and comparison was done with log rank test. For leukemia relapse, TRM and GVHD outcomes, SOS incidence, cumulative incidence was used to account for competing risks. Cox proportional hazards regression models for overall mortality, treatment failure (inverse of leukemia free survival), relapse and TRM were built using a forward selection approach forcing the main effect covariates (TBICy vs. CyTBI) on all outcomes. The covariates analyzed include: age, gender, performance score, donor-recipient gender, disease and disease status, cytogenetic risk stratification (for AML according to the SWOG/ECOG classification[13]: favorable, intermediate, poor or unknown; for ALL: presence of Philadelphia chromosome [Ph+], Ph negative and Ph status unknown) , year of transplant, donor type (sibling, well matched and partially matched unrelated donor)[14], dose of TBI (12Gy vs. 13Gy), donor recipient CMV status, graft source, in vivo T-cell depletion. Disease status and cytogenetic assessments were performed at the transplant center and reported to the CIBMTR. The final model included all covariates significantly associated with the outcome (p<0.05) and the main effect. Test for proportional hazards was included in case of non-proportional hazards during the study period and test for interactions was done between the main effect covariates and all significant covariates in each model.

## Results

### Demographics

A total of 948 patients received CyTBI and 821 received TBICy. The two cohorts were comparable for patient-, disease- and transplant-related characteristics (Table 1) with the

exception of age and Cy dose. The median age was 33 in the CyTBI group and 35 in the TBICy group (p<0.01). The median Cy dose was 108 mg/kg in the Cy TBI group and 115 mg/kg in the TBICy group (p=0.01). The median interval between starting TBI and Cy was 2 and 4 days for CyTBI and TBICy, respectively.

### Graft versus Host Disease

Cumulative incidences of grade II-IV aGVHD at day 100 were 39% (95% Cumulative Incidence [CI], 35-42%) and 45% (95% CI, 41-48%, p=0.01), and of grades III-IV aGVHD were 16% (95% CI, 13-18%) and 15% (95% CI, 12-17%, p=0.6) for CyTBI and TBICy, respectively (Figure 1). Multivariate analysis comparing CyTBI to TBICy demonstrated a relative risk for grades II-IV aGVHD of 0.87 (95% CI, 0.75-1.00, p=0.05) and for grades III-IV aGVHD of 1.09 (95% CI, 0.86-1.38, p=0.5). Other covariates associated with grades II-IV aGVHD were donor-recipient gender combinations, donor type and graft source (Appendix Table A). Donor type and year of transplant were associated with grades III-IV aGVHD.

Cumulative incidence of cGVHD at 1 year were 45% (95% CI, 41-48%) and 47% (95% CI, 43-50, p=0.39) (Figure 1). Multivariate analysis of cGVHD the RR of CyTBI was 0.9 (95% CI, 0.79-1.03, p=0.11). Other covariates associated with cGVHD were donor recipient gender match, donor type and graft source.

### Leukemia Relapse and TRM

Cumulative incidence of leukemia relapse at 3 years were 27% (95% CI, 24-30%) and 29% (95% CI, 26-33%, p=0. 34) for CyTBI and TBICy, respectively. Corresponding cumulative incidences for TRM at 3 years were 24% (95% CI, 21-27%) and 23% (95% CI, 20-26%, p=0.67). Multivariate analyses for leukemia relapse and TRM with associated covariates are shown in Table 2.

### Sinusoidal Obstruction Syndrome

Cumulative incidences for SOS at 100 days were 4% (95% CI, 3-6%) and 6% (95% CI, 4-8%, p=0.08) with CyTBI and TBICy, respectively.

### Leukemia-free and Overall Survival

Three-year probabilities of leukemia-free survival were 49% (95% CI, 46-52%) and 48% (95% CI, 44-51%, 0.34) for CyTBI and TBICy, respectively. Corresponding three-year probabilities of overall survival were 53% (95% CI, 50-57%) and 52% (95% CI, 49-56%, 0.48). Multivariate analyses for treatment failure (1-LFS) and overall mortality with associated covariates are shown in Table 2. Overall survival by different subset of children, adults, patients with acute lymphoid leukemia and acute myeloid leukemia are shown in Figure 3.

### Causes of Death

There was a wide range of causes of death for patients in each group, with the most common causes being leukemia relapse, infection, GVHD and pulmonary failure. Causes of death were comparable between both treatment groups (Appendix Table B).

## Discussion

This large retrospective analysis study compared the sequence of TBI and Cy in the myeloablative conditioning intensity setting for acute leukemia. Transplant outcomes were generally similar regardless of the sequence of TBI with exception of grades II-IV aGVHD. All the outcomes were **similar** when separating the cohort by disease (AML and ALL) and by patient populations (children and adults).

A study by McDonald et al linked circulating cyclophosphamide metabolites to liver dysfunction during TBI based transplantation.[15] The metabolism of cyclophosphamide was found to be highly variable; and increased levels of one of the metabolites, carboxyethyl–phosphoramide mustard (CEPM) was correlated with higher rates of SOS and nonrelapse mortality.[15] Subsequently, a phase II trial investigating the effect of a personalized dosing scheme for each patient according to Cy pharmacokinetics.[16] The trial concluded that a personalized dosing system led to lower peak bilirubin levels and acute kidney injury; however, non-relapse and overall survival rates were similar to controls.[16] These studies demonstrate a variability of Cy exposure using a standard regimen and a common protocol. Altering the sequence of specific agents may increase the variability of Cy metabolism and deserves to be specifically tested.

The exact timing between each component of the conditioning regimen may also influence toxicity and transplant outcomes. Hassan et al compared outcomes according to time between the last dose of busulfan and Cy and demonstrated that shorter intervals (<24hrs) were associated to higher exposure to Cy and consequently more toxicities.[17] In preclinical studies, shorter intervals between irradiation and chemotherapy were also associated with higher irradiation-induced tissue damage.[18-19] The present study could only address the sequence of agents, as only the date of initiation of each agent was available. The interval of initiation of each agent was different between the groups, since usually TBI is administered over a three-day period and Cy over a two-day period. Additionally, the interval distribution in both groups was narrow, thus the interval between the first days of each agent is closely related to the sequence of agents.

Enhanced toxicity from TBI exposure to Cy metabolites could also theoretically contribute to acute GVHD. When analyzing the incidence of acute GVHD in both groups, we found that Grade II-IV GVHD at 100 days post-transplant was significantly less in the CyTBI group. This should be interpreted with caution because the multivariate analysis showed borderline effect and there was no difference between the two approaches on grades III-IV aGVHD. Additionally, the dose of TBI was evaluated and it was not associated with the development of GVHD or any other outcomes analyzed.

We also show that the specific type of acute leukemia is not a factor in choosing a conditioning sequence. Previous studies have shown that differences exist in the preparative regimens for AML vs ALL. The optimal exact dosing of TBI has not been established; however, total doses of >13 Gy were associated with improved leukemia-free survival, relapse and mortality in ALL patients in CR2.[20] In contrast, Clift et al. were able to show

decreased relapse but increased mortality in AML patients treated with higher doses of TBI.[5]

Because our analysis is retrospective, it does have limitations, including the reason why one conditioning regimen sequence was chosen over the other. The specific sequence was not restricted to a number of transplant centers and the majority of centers reported both sequences. This observation likely reflects practice, as changes in the sequence of agents are done to accommodate transplant schedule and other activities during the timing of transplant. While ideally, this question of the timing of preparative components would be answered in a randomized prospective trial, our data would support equipoise for these decisions at this juncture.

This large cohort study demonstrates that the sequence of cyclophosphamide and TBI does not impact transplant outcomes and survival in patients with acute leukemia undergoing myeloablative transplantation in terms of toxicity or anti-leukemia benefit. TBICy may offer an advantage for a shorter hospitalization due to possible TBI delivery in the outpatient setting. This could potentially reduce the psychological distress associated with prolonged hospitalization. Furthermore, the apparent lack of difference in outcomes on an exact sequence of these two conditioning regimen agents provides flexibility for transplant planning.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgements

# Appendix

**Table A**

Multivariate analysis for grades II—IV and III-IV acute GVHD and chronic GVHD testing the sequence of TBI and cyclophosphamide as part of a myeloablative conditioning regimen hematopoietic cell transplantation for acute leukemia.

| Parameter | N | RR (95% CI) | p-value |
|---|---|---|---|
| Grade II-IV Acute GVHD | | | |
| Main effect | | | 0.052 * |
|    TBI/Cy | 816 | 1.00 | -- |
|    Cy/TBI | 942 | 0.87 (0.75-1.00) | 0.052 |
| | | | |
| Other covariates | | | |
| Donor-recipient sex match | | | 0.029 * |
|    M-M | 622 | 1.00 | -- |
|    F-M | 342 | 1.29 (1.06-1.57) | 0.012 |
|    M-F | 431 | 1.01 (0.84-1.22) | 0.90 |
|    F-F | 352 | 1.04 (0.85-1.27) | 0.70 |
| | | | |
| Donor type | | | <0.0001 * |
|    HLA-identical sibling | 604 | 1.00 | -- |
|    Well-matched URD | 791 | 1.82 (1.52-2.17) | <0.0001 |
|    Partially-matched URD | 261 | 2.39 (1.92-2.97) | <0.0001 |
|    URD-HLA match missing | 102 | 1.66 (1.29-2.30) | 0.0025 |
| | | | |
| Graft type | | | 0.024 * |
|    Bone marrow | 621 | 1.00 | -- |
|    Peripheral blood | 1137 | 1.19 (1.02-1.39) | 0.024 |
| Grade III-IV Acute GVHD | | | |
|    Main effect | | | 0.50 * |
|    TBI/Cy | 818 | 1.00 | -- |
| Cy/TBI | 947 | 1.09 (0.86-1.38) | 0.50 |
| | | | |
| Other covariates | | | |
| Donor type | | | <0.0001 * |
|    HLA-identical sibling | 608 | 1.00 | -- |
|    Well-matched URD | 794 | 1.62 (1.20-2.19) | 0.0018 |
|    Partially-matched URD | 261 | 3.08 (2.20-4.32) | <0.0001 |
|    URD-HLA match missing | 102 | 1.35 (0.70-2.62) | 0.37 |
| | | | |
| Year of transplant | | | 0.0023 * |
|    2003-2006 | 1009 | 1.00 | -- |
|    2007-2010 | 756 | 0.67 (0.51-0.87) | 0.0023 |
| Chronic GVHD | | | |

| | | | |
|---|---|---|---|
| Main effect | | | 0.11[*] |
| TBI/Cy | 812 | 1.00 | -- |
| Cy/TBI | 937 | 0.90 (0.79-1.03) | 0.11 |
| | | | |
| Other covariates | | | |
| Donor-recipient sex match | | | <0.0001[*] |
| M-M | 622 | | -- |
| F-M | 341 | 1.43 (1.19-1.72) | 0.0001 |
| M-F | 428 | 0.80 (0.67-0.96) | 0.014 |
| F-F | 348 | 1.25 (1.04-1.50) | 0.019 |
| | | | |
| Donor type | | | <0.0001[*] |
| HLA-identical sibling | 596 | 1.00 | -- |
| Well-matched URD | 792 | 1.42 (1.22-1.66) | <0.0001 |
| Partially-matched URD | 260 | 1.55 (1.26-1.92) | <0.0001 |
| URD-HLA match missing | 101 | 1.90 (1.44-2.50) | <0.0001 |
| | | | |
| Graft type | | | <0.0001[*] |
| Bone marrow | 618 | 1.00 | -- |
| Peripheral blood | 1131 | 1.86 (1.60-2. | <0.0001 |

[*] Overall p-value

**Table B**

Causes of death according to the sequence of cyclophosphamide and total body irradiation.

| Cause of death | TBICy N=419 (%) | CyTBI N=467 (%) |
|---|---|---|
| Primary disease | 45 | 41 |
| Infection | 15 | 13 |
| GVHD | 13 | 16 |
| Pulmonary Failure | 9 | 12 |
| Liver failure | 2 | 2 |
| Other Organ Failure | 5 | 4 |
| New malignancy | 1 | 1 |
| Others | 6 | 10 |
| Unknown | 4 | 1 |

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**Additional we include the "Highlights" as requested**

1. The sequence of cyclophosphamide and myeloablative doses of total body irradiation does not affect post-transplant survival in acute leukemia.

2. Post-transplant complications are similar regardless of the sequence of cyclophosphamide and TBI in the conditioning.
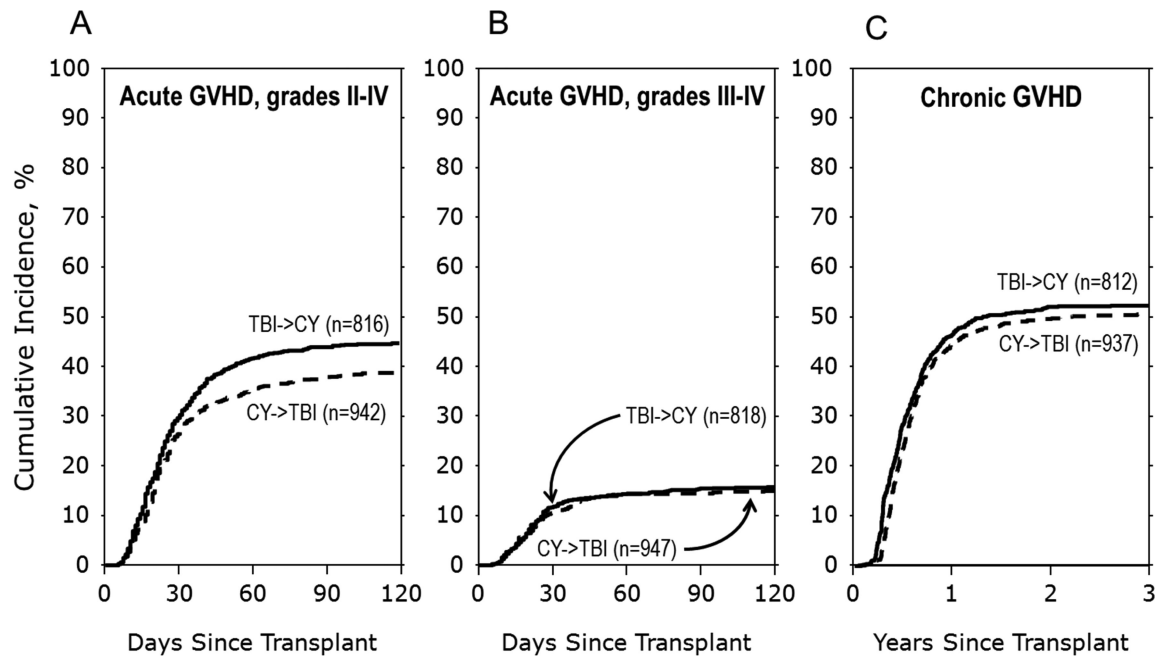
**Figure 1.**
Cumulative incidences of II-IV (A) and III-IV (B) acute GVHD, and chronic GVHD (C) comparing CyTBI to TBICy prior to allogeneic transplant for acute leukemia.
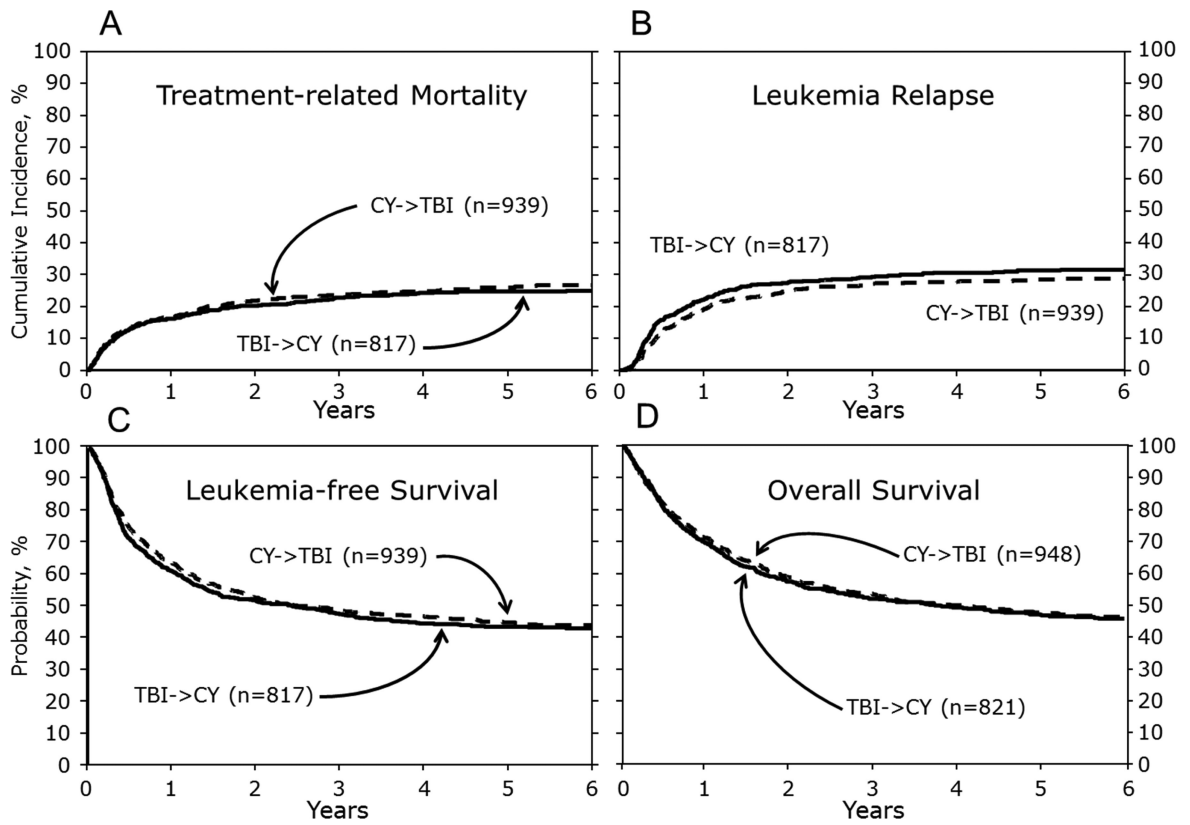
**Figure 2.**
Cumulative incidence of transplant-related mortality (A), cumulative incidence of leukemia relapse (B), probability of leukemia-free survival (C), and probability of overall survival (D) comparing CyTBI to TBICy prior to allogeneic transplant for leukemia.

## A: Pediatric patients
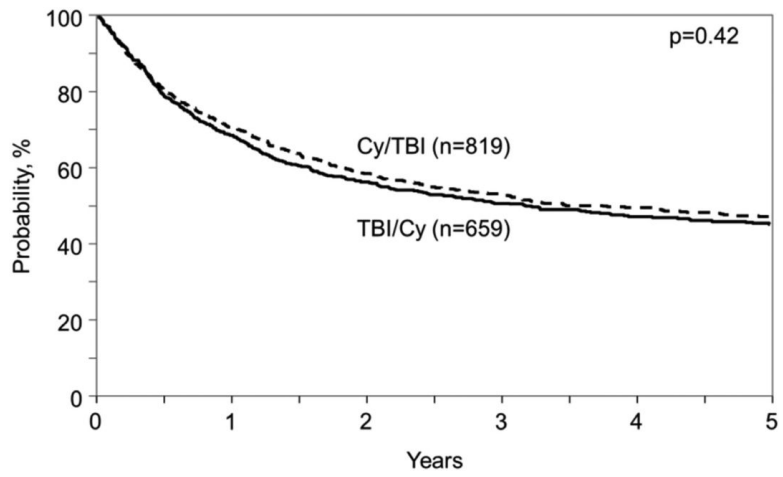


## B: Adult Patients
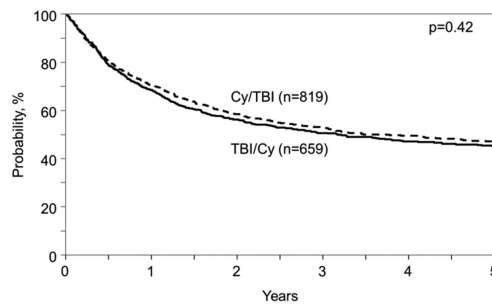


## C: Patients with Acute Lymphocytic Leukemia
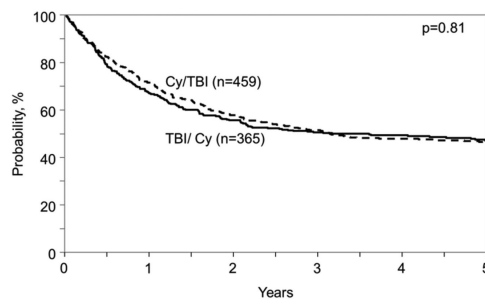
## D: Patients with Acute Myeloid Leukemia
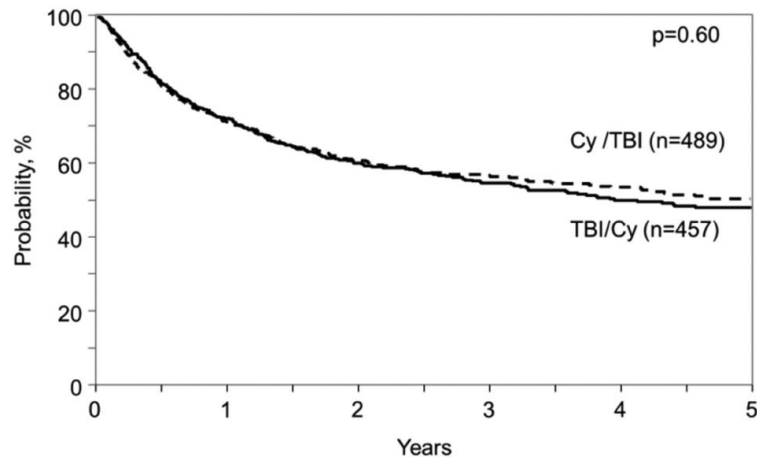


**Figure 3.**
Overall survival among (A) adults patients, (B) children, (C) patients with acute lymphoid leukemia and (D) with acute myeloid leukemia according to the sequence of cyclophosphamide and total body irradiation as part of a myeloablative conditioning prior to allogeneic hematopoietic cell transplant.

**Table 1**

Characteristic of AML and ALL patients who received allogeneic hematopoietic cell transplantation with total body irradiation and cyclophosphamide conditioning regimen between 2003 and 2010 according to the sequence of administered.

| Characteristics of patients | TBICy | CyTBI | p-value |
|---|---|---|---|
| Number of patients | 821 | 948 | |
| Number of centers | 100 | 114 | |
| Age, median (range), years | 33 (2 - 60) | 35 (2 - 60) | <0.01 |
| 0-9 | 64 ( 8) | 61 ( 6) | <0.01 |
| 10-19 | 147 (18) | 114 (12) | |
| 20-29 | 157 (19) | 212 (22) | |
| 30-39 | 168 (20) | 172 (18) | |
| 40-49 | 180 (22) | 224 (24) | |
| 50-59 | 105 (13) | 165 (17) | |
| Sex | | | 0.63 |
| Male | 458 (56) | 518 (55) | |
| Female | 363 (44) | 430 (45) | |
| Race | | | 0.01 |
| Caucasian | 663 (81) | 827 (87) | |
| African-American | 30 ( 4) | 31 ( 3) | |
| Asian | 76 ( 9) | 49 ( 5) | |
| Pacific islander | 2 (<1) | 1 (<1) | |
| Native American | 5 (<1) | 4 (<1) | |
| Other | 20 ( 2) | 14 ( 1) | |
| Unknown | 25 ( 3) | 22 ( 2) | |
| Performance score | | | 0.08 |
| <90% | 164 (20) | 223 (24) | |
| #x2265; 90% | 608 (74) | 656 (69) | |
| Unknown | 49 ( 6) | 69 ( 7) | |
| Disease | | | 0.09 |
| AML | 456 (56) | 489 (52) | |
| ALL | 365 (44) | 459 (48) | |
| AML/ALL disease status prior to transplant | | | 0.82 |
| 1st CR | 529 (64) | 606 (64) | |
| 2nd CR | 292 (36) | 342 (36) | |
| AML Cytogenetics | | | 0.55 |
| Favorable | 36 ( 8) | 44 ( 9) | |
| Intermediate | 187 (41) | 187 (38) | |
| Poor | 105 (23) | 129(26) | |
| Unknown | 128 (28) | 129 (26) | |

| Characteristics of patients | TBICy | CyTBI | p-value |
|---|---|---|---|
| ALL Ph+ | | | 0.77 |
| No | 131 (36) | 154 (34) | |
| Yes | 90 (25) | 115 (25) | |
| Unknown | 144 (39) | 190 (41) | |
| Donor/recipient HLA match | | | 0.01 |
| HLA-identical sibling | 281 (34) | 329 (35) | |
| Well-matched URD | 346 (42) | 450 (47) | |
| Partially matched URD | 136 (17) | 125 (13) | |
| URD-HLA matching unavailable | 58 ( 7) | 44 ( 5) | |
| Graft type | | | 0.12 |
| BM | 305 (37) | 319 (34) | |
| PB | 516 (63) | 629 (66) | |
| Donor/recipient sex match | | | 0.62 |
| M-M | 291 (35) | 333 (35) | |
| F-M | 165 (20) | 180 (19) | |
| M-F | 194 (24) | 241 (25) | |
| F-F | 168 (20) | 186 (20) | |
| Unknown | 3 (<1) | 8 (<1) | |
| Donor-Recipient CMV status | | | 0.35 |
| +/+ | 224 (27) | 272 (29) | |
| +/- | 96 (12) | 122 (13) | |
| -/+ | 203 (25) | 250 (26) | |
| -/- | 266 (32) | 264 (28) | |
| Unknown | 32 ( 4) | 40 ( 4) | |
| Total Cy dose, median (range), mg/kg | 115 (<1 - 470) | 108 (<1 - 486) | 0.01 |
| <55 mg/kg | 33 ( 4) | 58 ( 6) | 0.02 |
| 55-96 mg/kg | 166 (20) | 234 (25) | |
| 97-120 mg/kg | 474 (58) | 482 (51) | |
| 121-135 mg/kg | 52 ( 6) | 70 ( 7) | |
| >135 mg/kg | 28 ( 3) | 39 ( 4) | |
| Unknown | 68 ( 8) | 65 ( 7) | |
| TBI dose | | | 0.51 |
| 1200-1300 cGy | 514 (63) | 579 (61) | |
| 1320-1500 cGy | 307 (37) | 369 (39) | |
| TBI fractionated | | | 0.21 |
| No | 1 (<1) | 4 (<1) | |
| Yes | 820 (99) | 942 (99) | |
| Unknown | 0 | 2 (<1) | |
| CNS boost given | | | 0.40 |

| Characteristics of patients | TBICy | CyTBI | p-value |
|---|---|---|---|
| No | 768 (94) | 891 (94) | |
| Yes | 52 ( 6) | 53 ( 6) | |
| Unknown | 1 (<1) | 4 (<1) | |
| Interval between TBI and Cy, days | 4 (2-7) | 2 (2-6) | <0.001 |
| Year of transplant | | | 0.08 |
| 2003 | 67 ( 8) | 78 ( 8) | |
| 2004 | 130 (16) | 167 (18) | |
| 2005 | 118 (14) | 173 (18) | |
| 2006 | 137 (17) | 142 (15) | |
| 2007 | 107 (13) | 110 (12) | |
| 2008 | 103 (13) | 84 ( 9) | |
| 2009 | 85 (10) | 98 (10) | |
| 2010 | 74 ( 9) | 96 (10) | |
| Use of ATG | | | 0.10 |
| ATG alone | 108 (13) | 101 (11) | |
| No ATG | 713 (87) | 847 (89) | |
| GVHD prophylaxis | | | 0.12 |
| Tacro + MMF ± others | 57 ( 7) | 70 ( 7) | |
| Tacro + MTX ± others | 371 (45) | 409 (43) | |
| Tacro ± others | 42 ( 5) | 76 ( 8) | |
| CSA + MMF± others | 11 ( 1) | 5 (<1) | |
| CSA + MTX ± others | 317 (39) | 364 (38) | |
| CSA ± others | 15 ( 2) | 13 ( 1) | |
| Other GVHD prophylaxis | 8 (<1) | 11 ( 1) | |
| Median follow-up of survivors, range, months | 57 (3 - 100) | 56 (3 - 100) | |

Abbreviations: ATG: anti-thymocyte globulins; BM: bone marrow; CR: complete remission; CMV: cytomegalovirus; CNS: central nervous system; Cy: cyclophosphamide; CSA: cyclosporine. GVHD: graft-versus-host disease; MMF: mycophenolate mofetil; MTX: methotrexate; PB: peripheral blood; Ph+: Philadephia chromosome positive Tacro: tacrolimus; TBI: total body radiation; URD: unrelated donor.

**Table 2**

Multivariate analysis of transplant related mortality (TRM), leukemia relapse, treatment failure and overall mortality comparing CyTBI to TBICy and additional covariates associated with each outcome.

| TRM | N | RR (95% CI) | p-value |
|---|---|---|---|
| Main effect | | | 0.91[*] |
| TBI/Cy | 817 | 1.00 | -- |
| Cy/TBI | 939 | 1.01 (0.84-1.23) | |
| | | | |
| Other covariates | | | |
| Age | | | <0.0001[*] |
| 0-9 | 124 | 1.00 | -- |
| 10-19 | 260 | 2.49 (1.21-5.14) | 0.013 |
| 20-29 | 364 | 3.02 (1.57-5.83) | 0.0010 |
| 30-39 | 337 | 4.27 (2.21-8.24) | <0.0001 |
| 40-49 | 401 | 5.01 (2.61-9.62) | <0.0001 |
| 50-59 | 270 | 6.09 (3.15-11.80) | <0.0001 |
| Donor-recipient sex match | | | <0.0001[*] |
| M-M | 621 | 1.00 | -- |
| F-M | 343 | 1.40 (1.09-1.80) | 0.0088 |
| M-F | 433 | 0.66 (0.50-0.87) | 0.0028 |
| F-F | 348 | 1.18 (0.91-1.51) | 0.21 |
| Performance score | | | 0.0025[*] |
| <90% | 383 | 1.00 | -- |
| 90-100% | 1256 | 0.70 (0.56-0.87) | 0.0012 |
| Unknown | 117 | 0.96 (0.65-1.43) | 0.85 |
| Donor type | | | <0.0001[*] |
| HLA-identical sibling | 607 | 1.00 | -- |
| Well-matched URD | 786 | 1.53 (1.22-1.94) | 0.0003 |
| Partially-matched URD | 261 | 2.62 (1.99-3.44) | <0.0001 |
| URD-HLA match missing | 102 | 1.13 (0.71-1.81) | 0.60 |
| **Leukemia Relapse** | | | |
| Main effect | | | 0.18[*] |
| TBI/Cy | 817 | 1.00 | -- |
| Cy/TBI | 939 | 0.89 (0.75-1.06) | 0.18 |
| | | | |
| Other covariates | | | |
| Cytogenetics | | | <0.0001[*] |
| AML Intermediate | 374 | 1.00 | -- |
| AML Favorable | 80 | 0.14 (0.05-0.31) | <0.0001 |
| AML Unfavorable | 234 | 1.61 (1.20-2.16) | 0.001 |

| TRM | N | RR (95% CI) | p-value |
|---|---|---|---|
| AML Unknown | 256 | 1.08 (0.79-1.47) | 0.22 |
| ALL Ph-neg | 285 | 1.16(0.86-1.56) | 0.34 |
| ALL Ph+ | 205 | 1.20 (0.85-1.68) | 0.30 |
| ALL Ph- unknown | 334 | 1.31 (0.99-1.74) | 0.055 |
| Disease status prior to transplant | | | 0.0016[*] |
| 1st CR | 1125 | 1.00 | -- |
| 2nd CR | 631 | 1.34 (1.12-1.61) | 0.0016 |
| **Treatment Failure** | | | |
| Main effect | 817 | | 0.29[*] |
| TBI/Cy | 939 | 1.00 | -- |
| Cy/TBI | | 0.93 (0.82-1.06) | 0.29 |
| Other covariates | | | |
| Age | | | <0.0001[*] |
| 0-9 | 124 | 1.00 | -- |
| 10-19 | 260 | 1.52 (1.07-2.15) | 0.020 |
| 20-29 | 364 | 1.54 (1.12-2.11) | 0.0072 |
| 30-39 | 337 | 1.90 (1.37-2.62) | 0.0001 |
| 40-49 | 401 | 1.98 (1.43-2.74) | <0.0001 |
| 50-59 | 270 | 2.48 (1.78-3.47) | <0.0001 |
| Donor-recipient sex match | | | 0.0005[*] |
| M-M | 621 | 1.00 | -- |
| F-M | 343 | 1.14 (0.95-1.36) | 0.15 |
| M-F | 433 | 0.77 (0.65-0.92) | 0.0044 |
| F-F | 348 | 1.05 (0.88-1.25) | 0.62 |
| Performance score | | | 0.0007[*] |
| <90% | 383 | 1.00 | -- |
| 90-100% | 1256 | 0.78 (0.67-0.91) | 0.0015 |
| Unknown | 117 | 1.08 (0.82-1.40) | 0.60 |
| Cytogenetics | | | 0.0012 |
| AML Intermediate | 374 | 1.00 | -- |
| AML Favorable | 80 | 0.51 (0.34-0.79) | 0.002 |
| AML Unfavorable | 234 | 1.26 (1.01-1.58) | 0.04 |
| AML Unknown | 256 | 1.10 (0.88-1.37) | 0.40 |
| ALL Ph-neg | 285 | 1.20(0.96-1.51) | 0.10 |
| ALL Ph+ | 205 | 1.31 (1.03-1.67) | 0.03 |
| ALL Ph- unknown | 334 | 1.18 (0.96-1.47) | 0.12 |
| Disease status prior to transplant | | | 0.0081[*] |

| TRM | N | RR (95% CI) | p-value |
|---|---|---|---|
| 1st CR | 1125 | 1.00 | -- |
| 2nd CR | 631 | 1.22 (1.05-1.40) | 0.0081 |
| Donor type | | | 0.0007[*] |
| HLA-identical sibling | 607 | 1.00 | -- |
| Well-matched URD | 786 | 1.15 (0.99-1.35) | 0.070 |
| Partially-matched URD | 261 | 1.45 (1.89-1.76) | 0.0002 |
| URD-HLA match missing | 102 | 0.84 (0.60-1.69) | 0.29 |
| **Overall Mortality** | | | |
| Main effect | | | 0.57[*] |
| TBI/Cy | 821 | 1.00 | -- |
| Cy/TBI | 948 | 0.96 (0.84-1.10) | 0.57 |
| | | | |
| Other covariates | | | |
| Age | | | <0.0001[*] |
| 0-9 | 125 | 1.00 | -- |
| 10-19 | 261 | 1.51 (1.05-2.19) | 0.027 |
| 20-29 | 369 | 1.65 (1.19-2.28) | 0.0028 |
| 30-39 | 340 | 2.05 (1.46-2.87) | <0.0001 |
| 40-49 | 404 | 2.17 (1.54-3.04) | <0.0001 |
| 50-59 | 270 | 2.84 (2.01-4.02) | <0.0001 |
| Donor-recipient sex match | | | 0.0002[*] |
| M-M | 624 | 1.00 | -- |
| F-M | 345 | 1.16 (0.97-1.39) | 0.11 |
| M-F | 435 | 0.76 (0.63-0.91) | 0.0035 |
| F-F | 354 | 1.05 (0.87-1.26) | 0.61 |
| Performance score | | | 0.0011[*] |
| <90% | 387 | 1.00 | -- |
| 90-100% | 1264 | 0.76 (0.65-0.89) | 0.0008 |
| Unknown | 118 | 0.99 (0.75-1.31) | 0.97 |
| Disease status prior to transplant | | | 0.0022[*] |
| 1st CR | 1135 | 1.00 | -- |
| 2nd CR | 634 | 1.26 (1.09-1.46) | 0.0022 |
| Donor type | | | <0.0001[*] |
| HLA-identical sibling | 610 | 1.00 | -- |
| Well-matched URD | 796 | 1.13 (0.96-1.33) | 0.13 |
| Partially-matched URD | 261 | 1.57 (1.29-1.92) | <0.0001 |
| URD-HLA match missing | 102 | 0.83 (0.58-1.18) | 0.30 |
| Cytogenetics | | | 0.0023[*] |

| TRM | N | RR (95% CI) | p-value |
|---|---|---|---|
| AML Intermediate | 374 | 1.00 | -- |
| AML Favorable | 80 | 0.56 (0.37-0.86) | 0.009 |
| AML Unfavorable | 234 | 1.35 (1.07-1.71) | 0.012 |
| AML Unknown | 256 | 1.10 (0.87-1.38) | 0.44 |
| ALL Ph-neg | 285 | 1.26(1.00-1.59) | 0.048 |
| ALL Ph+ | 205 | 1.26 (0.98-1.63) | 0.068 |
| ALL Ph- unknown | 334 | 1.20 (0.96-1.51) | 0.10 |

[*]Overall p-value