Published in final edited form as:

Biol Blood Marrow Transplant. 2019 December ; 25(12): 2398–2407. doi:10.1016/j.bbmt.2019.08.012.

Comparison of high doses of total body irradiation in myeloablative conditioning prior to hematopoietic cell transplantation

Mitchell Sabloff[1], **Saurabh Chhabra**[2,3,*], **Tao Wang**[2,4], **Caitrin Fretham**[5], **Natasha Kekre**[11], **Allistair Abraham**[6], **Kehinde Adekola**[7], **Jeffery J Auletta**[8], **Christopher Barker**[9], **Amer M. Beitinjaneh**[10], **Christopher Bredeson**[11], **Jean-Yves Cahn**[12], **Miguel Angel Diaz**[13], **Cesar Freytes**[14], **Robert Peter Gale**[15], **Siddhartha Ganguly**[16], **Usama Gergis**[17], **Eva Guinan**[18], **Betty Hamilton**[19], **Shahrukh Hashmi**[20,21], **Peiman Hematti**[22], **Gerhard Hildebrandt**[23], **Leona Holmberg**[24], **Sanghee Hong**[25], **Hillard M. Lazarus**[26], **Rodrigo Martino**[27], **Lori Muffly**[28], **Taiga Nishihori**[29], **Miguel-Angel Perales**[30], **Jean Yared**[31], **Shin Mineishi**[32], **Edward A Stadtmauer**[33], **Marcelo C. Pasquini**[2], **Alison W. Loren**[34]

[1]Division of Hematology, Department of Medicine, University of Ottawa and Ottawa Hospital Research Institute, Ottawa, Canada

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

[3]Division of Hematology/Oncology, Department of Medicine, Medical College of Wisconsin, Milwaukee, WI

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

[5]CIBMTR® (Center for International Blood and Marrow Transplant Research), National Marrow Donor Program/Be the Match®, Minneapolis, MN

[6]Division of Blood and Marrow Transplantation, Center for Cancer and Blood Disorders, Children's National Medical Center, Washington, DC

[7]Division of Hematology/Oncology, Department of Medicine and Robert H. Lurie Comprehensive Cancer Center, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA

[8]Blood and Marrow Transplant Program and Host Defense Program, Divisions of Hematology/Oncology/Bone Marrow Transplant and Infectious Diseases, Nationwide Children's Hospital, Columbus, OH

[9]Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center

[*]**CORRESPONDING AUTHOR** Saurabh Chhabra, MD MS, Associate Professor of Medicine, Division of Hematology/Oncology, Department of Medicine, Medical College of Wisconsin, Milwaukee, WI, Scientific Director, Regimen-Related Toxicity Working Committee, CIBMTR, Milwaukee, WI.

[10]University of Miami, Miami, FL

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

[12]Department of Hematology, CHU Grenoble Alpes, Grenoble, France

[13]Department of Hematology/Oncology, Hospital Infantil Universitario Nino Jesus, Madrid, Spain

[14]Texas Transplant Institute, San Antonio, TX

[15]Hematology Research Centre, Division of Experimental Medicine, Department of Medicine, Imperial College London, London, United Kingdom

[16]Division of Hematological Malignancy and Cellular Therapeutics, University of Kansas Health System, Kansas City, KS

[17]Hematolgic Malignancies & Bone Marrow Transplant, Department of Medical Oncology, New York Presbyterian Hospital/Weill Cornell Medical Center, New York, NY

[18]Department of Pediatric Oncology, Dana-Farber Cancer Institute, Boston, MA

[19]Blood & Marrow Transplant Program, Cleveland Clinic Taussig Cancer Institute, Cleveland, Ohio

[20]Department of Internal Medicine, Mayo Clinic, MN

[21]Oncology Center, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia

[22]Division of Hematology/Oncology/Bone Marrow Transplantation, Department of Medicine, University of Wisconsin, Madison, WI

[23]Markey Cancer Center, University of Kentucky, Lexington, KY

[24]Fred Hutchinson Cancer Research Center

[25]Cleveland Clinic Taussig Cancer Center, Cleveland OH

[26]Case Western Reserve University, Cleveland, OH

[27]Divison of Clinical Hematology, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

[28]Division of Blood and Marrow Transplantation, Stanford University, Stanford, CA

[29]Department of Blood and Marrow Transplantation, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL

[30]Adult Bone Marrow Transplant Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY

[31]Blood & Marrow Transplantation Program, Division of Hematology/Oncology, Department of Medicine, Greenebaum Comprehensive Cancer Center, University of Maryland, Baltimore, MD

[32]Penn State Hershey Medical Center, Hershey, PA

[33]Abramson Cancer Center University of Pennsylvania Medical Center

[34]Division of Hematology/Oncology, Department of Medicine, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

Abstract

Malignancy relapse is the most common cause of treatment failure among recipients of hematopoietic cell transplantation (HCT). Conditioning dose intensity can reduce disease relapse, but it is offset by toxicities. Improvements in radiotherapy techniques and supportive care may translate to better outcomes with higher irradiation doses in the modern era. This study compares outcomes of recipients of increasing doses of high dose total body irradiation (TBI) divided into intermediate high dose (IH 13–13.75 Gy) and high dose (HD 14 Gy) to standard dose (SD 12Gy) with cyclophosphamide (Cy). A total of 2,721 patients ages of 18 to 60 with hematologic malignancies receiving HCT from 2001 to 2013 were included. Cumulative incidence of non-relapse mortality (NRM) at 5 years was 28% (95% Cumulative Incidence [CI] 25–30%), 32% (95%CI 29–36%) and 34% (95%CI 28–39%) for SD, IH and HD, respectively (p=0.02). Patients receiving IH-TBI had a 25% higher risk of NRM compared to SD-TBI (12 Gy) (p=0.007). Corresponding cumulative incidence of relapse was 36% (95%CI 34–38%), 32% (95%CI 29–36%) and 26% (95%CI 21–31%) (p=0.001). Hazard ratio for mortality compared to SD were 1.06 (95% 0.94–1.19, p=0.36) for IH and 0.89 (95% CI 0.76–1.05, p=0.17) for HD. The study demonstrates that despite improvements in supportive care, myeloablative conditioning using higher doses of TBI (with Cy) leads to worse non-relapse mortality and offers no survival benefit over SD, despite reducing disease relapse.

Keywords

total body irradiation; allogeneic hematopoietic cell transplantation; myeloablative conditioning; hematologic malignancies

INTRODUCTION

Relapse of the underlying disease is the most frequent cause of treatment failure after allogeneic HCT for hematologic malignancies[1]. Non-relapse mortality (NRM) accounts for the bulk of the remainder of deaths (20–30%)[2–5]. One of the strategies to reduce relapse risk is to intensify the pre-transplant conditioning regimen. Several studies have demonstrated that increasing the intensity of the conditioning regimen can reduce relapse risk [6–9]. Indeed, a prospective randomized trial of myeloablative (MAC) versus reduced intensity conditioning (RIC) for adults with acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) in first remission confirmed that greater conditioning intensity resulted in significantly lower relapse risk and improved relapse-free survival[10]. The outcomes after MAC regimens of cyclophosphamide (Cy) with total body irradiation (Cy/TBI) and busulfan with Cy (Bu/Cy) after allogeneic HCT for acute and chronic leukemia have been compared in a prospective study[11] which demonstrated that the adjusted 3-year overall survival (OS) was higher with Cy/TBI (vs. Bu/Cy; oral busulfan), although there was no difference in relapse-free survival between the cohorts. More recently, however, a few observational studies have reported that Bu/Cy (using intravenous busulfan) may offer a survival advantage over Cy/TBI in patients with AML[12–14], whereas for acute lymphoblastic leukemia (ALL) patients, TBI was associated with a lower relapse rate and favorable event-free survival, compared to oral busulfan when combined with Cy[15]. Attempts to further

optimize conditioning regimens have not improved outcomes except in small, single-center studies[16–20].

Radiation is highly lethal to leukemic cells in a dose-dependent fashion[21,22]. This observation led investigators, over three decades ago, to attempt to escalate radiation doses given as conditioning prior to transplant. The use of higher doses of TBI (>12 Grays [Gy]), in combination with chemotherapy, has been reported in small, single-institution studies[23–26]. The upper limit of TBI dose of 16 Gy was established in combination with Cy and of 14.4 Gy when used in combination with etoposide. A study comparing 12 Gy to 15.75 Gy established that the maximum tolerable dose of TBI with Cy was fractionated TBI at a dose of 12 Gy[27]. Although higher doses of radiation were indeed associated with lower relapse risk, this benefit was negated by increased NRM, and there was no difference in OS. However, in the last two decades, advances in the delivery of radiation therapy as well as substantial improvements in supportive care raise the question of whether, in the current era, higher doses of TBI (>12 Gy) result in improved non-relapse mortality and lower relapse rate and therefore, improved OS outcomes following allogeneic HCT, respectively[28–30]. We queried the Center for International Blood and Marrow Transplant Research (CIBMTR)'s registry to understand whether high dose TBI would translate into improved survival outcomes; we hypothesized that advances in supportive care and radiation delivery would reduce toxicity and NRM, thus yielding an OS advantage to higher doses of TBI.

METHODS

Data Source

The CIBMTR is a research collaboration between the Medical College of Wisconsin and the National Marrow Donor Program. The CIBMTR comprises a network of more than 450 transplantation centers worldwide that contribute data on allogeneic and autologous HCTs to a centralized statistical center for observational studies[31]. Health information is collected and maintained in the CIBMTR's capacity as a public health authority under the Health Insurance Portability and Accountability Act privacy rules.

Patients

The study included 2721 adults with AML, ALL, MDS, and chronic myeloid leukemia (CML) receiving Cy/TBI, with TBI at varying doses, as conditioning in anticipation of a first allogeneic HCT from a well-matched sibling or unrelated donor between 2001–2013. Either matched siblings or well- or partially- (7/8-) matched unrelated donors were included. Patients with inherited syndromes predisposing to acute leukemia, those with central nervous system involvement with disease, and those who received prior radiation for any reason were excluded. We defined three TBI dose groups: patients receiving standard dose (12 Gy) (SD-TBI), intermediate high dose (13–13.75 Gy) (IH-TBI), and high dose (14 Gy) (HD-TBI).

Study Endpoints

The primary endpoint of the study was non-relapse mortality (NRM). NRM was defined as death from any cause in continuous remission or death within the first 28 days of transplant

from any cause and was summarized by cumulative incidence estimate with relapse as competing risk. Secondary endpoints included OS, defined as time from transplant to death from any cause, with surviving patients censored at time of last contact, and disease-free survival (DFS), in which events were defined as death or relapse. Relapse was summarized by cumulative incidence estimate with NRM as the competing risk. We also sought to evaluate the incidence of other forms of toxicity and morbidity after allogeneic HCT including acute and chronic graft-versus-host disease (GVHD), veno-occlusive disease (VOD)/sinusoidal obstruction syndrome (SOS) of the liver[32,33], and idiopathic pneumonia syndrome (IPS)[34], all diagnosed on the basis of established criteria. Grading of acute and chronic GVHD was based on previously defined consensus criteria[35,36].

Statistical Analysis

Patient-, disease-, and transplant-related characteristics were compared among the TBI dose groups using the chi-square test for categorical variables and the Kruskal-Wallis test for continuous variables. Outcomes of three TBI dose groups were compared using log-rank and Gray's test. NRM was described using the cumulative incidence function, with relapse as a competing risk, according to the method of Fine and Gray[37]. Cumulative incidence of GVHD, VOD/SOS, and IPS were evaluated by Fine and Gray's method of competing risks as well, with death as competing risk. Disease relapse was also reported using the cumulative incidence function, with NRM as the competing risk. Survival probabilities of OS and DFS were calculated using the Kaplan-Meier estimator and compared using the log-rank test. Multivariate analysis was performed using Cox proportional hazards regression models for OS, DFS, acute GVHD, chronic GVHD, VOD/SOS, and IPS; while Fine and Gray subdistribution hazards models[37] were used for relapse and NRM. The following variables were included in the analysis: recipient age, disease, disease status at HCT, donor type, *in vivo* T cell depletion, GVHD prophylaxis, Karnofsky performance score, donor-recipient sex match, year of transplant. All clinical variables were tested first for the affirmation of the proportional hazards assumption. Factors violating the proportional hazards assumption were adjusted through stratification. Then a stepwise, forward-backward procedure was performed to select the adjusted clinical variables (with a threshold of 0.05 for both entry and stay in the model) and to build the multivariate models. To account for multiple comparisons, $p<0.01$ was used as the significance level for the main effect. Analysis was also conducted to evaluate center-effect. All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

RESULTS

Patient and transplant characteristics

The characteristics of the patients across the three TBI groups in the study cohort (n=2721) are shown in Table 1. The patients in the three groups received TBI dose of 12 Gy (SD-TBI; n=1745), 13–13.75 Gy (IH-TBI; n=648), and 14 Gy (HD-TBI; n=328). The completeness index at 5 years post-alloHCT was excellent (92–96%). The HD-TBI group were older and had lower Karnofsky performance scores (KPS). AML was the most common indication for allogeneic HCT across the cohort and was more frequent indication in the HD-TBI group compared to the SD-TBI patients (60% vs 48%, respectively). ALL, in contrast, was less

common in the HD-TBI versus SD-TBI group (15 vs. 37%, respectively). HD-TBI-based HCTs were reported from 13 centers, compared to SD-TBI recipients from 155 centers and IH-TBI recipients from 49 centers. Median follow-up of survivors was similar across the groups at 67–73 months post-alloHCT.

Transplant characteristics are presented in Table 2. Fractionated TBI was administered to patients in all three groups: IH-TBI group received a median of 8 fractions with a median dose of 165 cGy per fraction, compared to a median of 6 and 7 fractions (with median doses of 200 cGy per fraction) in SD-TBI and HD-TBI groups, respectively (p<0.001). The HD-TBI group received a lower dose of Cy (median, 90 mg/kg vs 120 mg/kg in the other two groups, p<0.001). SD-TBI groups had a higher proportion of patients with a matched sibling donor (43% vs. 33% in the other two groups, p<0.001). Approximately 17% of patients in all three groups received allogeneic HCT using 7/8-matched unrelated donor. With respect to GVHD prophylaxis, most patients (>98%) received a calcineurin inhibitor (CNI), and most did not receive *in vivo* T-cell depletion. Peripheral blood grafts were used more commonly in HD-TBI group (76%) compared to both SD-TBI (71%) and IH-TBI (65%) groups.

Impact of conditioning TBI dose on post-transplant outcomes

Non-relapse mortality—Univariate analysis revealed that at 5 years post-HCT, NRM was 28% (95% Confidence Interval [CI], 25–30%) for the SD-TBI group, 32% (95%CI, 29–36%) for the IH-TBI group and 34% (95%CI, 28–39%) for the HD-TBI group (p=0.02) (Table 3). Multivariate modelling using Fine and Gray's method accounting for competing risks confirmed that TBI dose was statistically significantly associated with NRM (p=0.009) (Table 4) (Figure 1). Patients receiving IH-TBI (13–13.75 Gy) had a 25% higher risk of NRM compared to SD-TBI (12 Gy) (p=0.007). HD-TBI group (14 Gy), however, did not have a significantly increased NRM risk compared to SD-TBI (p=0.03) or IH-TBI (p=0.96) groups. Multivariate analysis also showed older patients (>30 years vs. <20 years), those with MDS and ALL (vs. AML), with unrelated donor (vs. matched sibling donor) and those who received CNI/MMF (vs. CNI/MTX) had a higher NRM risk (Supplemental Table S3). In addition, NRM risk improved with each time period (2011–2013 vs. 2001–2003; HR 0.46, p<0.0001) over the years.

Overall survival

OS after allogeneic HCT was similar across the three TBI dose groups on univariate analysis: 5-year OS was 42% (95%CI, 39–44%), 40% (95%CI, 36–44%) and 45% (95%CI, 39–50%) in SD-TBI, IH-TBI and HD-TBI groups, respectively (p=0.39) (Table 3). The multivariate analysis also showed no significant association between the TBI dose and OS (p=0.18) (Table 4) (Figure 4). The analysis also demonstrated that younger patients (<20 years vs. >40 years), those with CML (vs. AML), with matched sibling donor (vs. unrelated donor), and those receiving CNI/MTX (vs. CNI/MMF), with KPS ≥90 (vs. <90) had significantly improved OS (Supplemental Table S1). OS also improved significantly with each time interval (e.g., 2011–2013 vs. 2001–2003, HR 0.6, p<0.0001).

Disease-free survival

Univariate analysis demonstrated that the 5-year probability of DFS did not differ significantly among TBI dose groups and was 37% (95%CI, 34–39%), 35% (95%CI, 32–39%) and 40% (95%CI, 35–46%) in SD-TBI, IH-TBI and HD-TBI groups, respectively (p= 0.36) (Table 3). There was no significant difference in DFS among the three TBI dose groups on multivariate analysis (Table 4) (Figure 3).

Relapse

The risk of disease relapse post-HCT differed significantly among the TBI dose groups on univariate analysis: 5-year cumulative incidence of relapse was 36% (95%CI, 34–38%) in SD-TBI group, 32% (95%CI, 29–36%) in IH-TBI and 26% (95%CI, 21–31%) in HD-TBI group (p<0.001) (Table 3). Multivariate analysis showed that HD-TBI recipients had a significantly lower relapse risk compared to SD-TBI group (hazards ratio [HR] 0.69, p=0.002) (Table 4) (Figure 2). Patients with MDS (vs. AML) and early (vs. intermediate or advanced) disease and with matched sibling donor (vs. unrelated) had a lower risk of relapse (Supplemental Table S4).

Acute GVHD

Univariate analysis revealed 1-year cumulative incidence of grade II-IV acute GVHD in the IH-TBI group was 49% (95%CI, 45–53%) compared to 43% in the SD-TBI group (95%CI, 40–45%) and 42% in HD-TBI group (95%CI, 37–47%) (p=0.02) (Table 3). On multivariate analysis, TBI dose was not associated with grade II-IV acute GVHD (p=0.01), or grade III-IV acute GVHD (p=0.21) (Table 4).

Chronic GVHD

On univariate analysis, 5-year cumulative incidence of chronic GVHD was not significantly different among the three groups: 52% (95%CI, 49–54%) in SD-TBI group, 50% (95%CI, 46–54%) in IH-TBI group and 53% (95%CI, 48–59%) in HD-TBI group (p=0.68) (Table 3). However, multivariate analysis suggested that the risk of chronic GVHD among the three cohorts was time-dependent: TBI was significantly associated with chronic GVHD in the first 8 months post-HCT (p=0.0001), but not beyond 8 months after HCT (p=0.02) (Table 4). HD-TBI conferred a lower risk of chronic GVHD compared to SD group (HR 0.64, p=0.0001) early on after allogeneic HCT.

TBI-associated post-transplant organ dysfunction

On univariate analysis, the 100-day cumulative incidence of VOD/SOS following allogeneic HCT was 5% (95%CI, 4–6%), 6% (95%CI, 4–7%) and 9% (95%CI, 6–12%) in SD-TBI, IH-TBI and HD-TBI groups, respectively (Table 3). Multivariate analysis showed TBI dose was not significantly associated with risk of VOD/SOS (p=0.03) (Table 4). TBI dose also had no significant association with IPS after allogeneic HCT, which carried a 2-year cumulative incidence of 8–9% in the three cohorts (Tables 3–4).

Causes of death

Relapse of primary disease was the most common cause of death in all three groups (Table 5). However, there were more relapse-related deaths with SD-TBI (55%) compared to the other two groups (47% in IH-TBI and 40% in HD-TBI group). The proportion of deaths due to organ failure increased with higher doses of TBI (19% in HD-TBI and 9% in SD-TBI group). Respiratory and multi-organ failure were most common, followed by heart failure and hepatic dysfunction (Table 5a).

DISCUSSION

This contemporary observational study compared MAC regimens containing Cy combined with three TBI dose groups in allogeneic HCT recipients with AML, ALL, CML and MDS. HD-TBI group had a more frequent use of peripheral blood graft, unrelated donors, had fewer patients with KPS>90 and had a higher median age: all variables were included in multivariate modelling to account for the baseline differences. Compared to 12 Gy TBI, we observed increased NRM with intermediate TBI dose of 13–13.75 Gy and lower relapse with high TBI dose (14 Gy). While the analysis showed significant difference in NRM risk between SD-TBI and IH-TBI groups, there was no significant difference in the risk of NRM between HD-TBI and other two groups. However, the impact on NRM seemed to be equal once the TBI dose increased beyond SD-TBI: comparing the NRM risk between HD-TBI and SD-TBI groups in the multivariate model showed HR for death was 1.25 (the same as HR with IH compared to SD group). It is likely that the statistical significance was not reached given the small sample size population in the HD group hindering power to detect a difference; a larger population may have shown significant results. With regards to the relapse model, there is a linear relationship with increments on the TBI dose: HR (for death) of 1.0 for SD-TBI, 0.92 for IH-TBI and 0.69 for HD-TBI, though not statistically significant. With the potentially opposing effects of TBI dose on relapse and NRM, there was no significant difference observed in OS and DFS among the TBI dose groups in the study.

There was no statistically significant difference in the risk of grade II-IV or III-IV acute GVHD. Furthermore, no association of TBI dose with the risk of IPS was found. The risk of chronic GVHD (in the early post-HCT period) was lower in patients receiving HD-TBI, an unexpected finding, particularly given the absence of significant difference in acute GVHD risk. While there is no good explanation for having increased risk chronic GVHD after SD TBI compared to the higher doses; one possibility is that SD-TBI patients received early interventions to prevent or treat relapse, such as withdrawal of immunosuppression or donor leukocyte infusions, which would then be expected to result in increased risk of early onset chronic GVHD. However, we did not have access to the post-transplant data to support this hypothesis. There is also a possibility of residual confounding by other variables that were not included in the analysis such as post-transplant therapeutic interventions. The study demonstrated no significant association between the TBI dose and the risk of IPS after allogeneic HCT. While the incidence of VOD/SOS of liver was higher with higher doses of TBI, this observation did not meet statistical significance.

Radiation is a potent anti-tumor therapy that is not dependent on cell cycle, growth or metabolism, and is not affected by common methods of chemotherapy resistance such as P-

glycoprotein pumps[38–40] and so chemotherapy-resistant clones may still be radio-sensitive[41]. Furthermore, radiation is directly toxic to hematopoietic stem cells[21,22], and can reach potential sanctuary sites such as testis and brain[41], making TBI an important component of the conditioning regimens before allogeneic HCT for treatment of hematologic malignancies. TBI has traditionally been a part of MAC regimens with the objective of eradicating malignant cells and also providing the immunosuppression needed to prevent rejection of donor hematopoietic cells[41]. Dose escalation of TBI in MAC has been investigated and demonstrated to be feasible with acceptable non-relapse mortality in several single-center studies[23,24,26]. Myeloablative TBI dose cohorts have been compared in a few studies and have shown reduced relapse risk of AML[27,42], CML[43] and ALL[44] with higher dose TBI in the conditioning. A randomized study by Clift et al. published in 1990s evaluated a conditioning regimen of Cy 120 mg/kg in combination with TBI 15.75 Gy with 7 consecutive daily fractions of 2.25 Gy (n=37), and demonstrated a lower relapse risk compared with TBI 12 Gy with 6 consecutive daily fractions of 2 Gy (n=34) in patients with AML in first complete remission[42]. The 3-year probabilities of relapse were 35% for the 12 Gy group and 12% for the 15.75 Gy group (p=0.06). However, the 3-year NRM was 12% and 32% for the two respective groups (p=0.04). In essence, the increased dose of TBI significantly reduced the probability of relapse but did not improve OS because of increased NRM.

Baseline demographics show the HD-TBI recipients were older, with poorer KPS: this suggests the possibility of selection bias by clinicians to target a higher risk patient population with increased TBI dose. However, multivariate analysis should account for these differences. Similarly, the analysis accounted for the higher proportion of AML patients in the HD-TBI group. The analysis demonstrated significantly better OS in CML patients (vs. AML; HR 0.8, p=0.006); MDS patients experienced higher NRM (vs. AML; HR 1.82, p=0.0001) and lower relapse risk (vs. AML; HR 0.45, p<0.0001) on multivariate analysis. With regards to donor-recipient HLA matching, since the proportion of 7/8 matched unrelated donors was similar across all three groups, and our multivariate analysis adjusted for degree of HLA matching, this small group of patients is unlikely to have altered our results. It is worth noting that we tested for interaction between the TBI dose and disease type, disease risk and all other variables, for each endpoint, and found none. The study covered a period of 14 years and as expected, the patients receiving allogeneic HCT in more recent years experienced significantly less NRM (36% better in 2008–2010 and 54% improvement in 2011–2013, as compared to 2001–03, respectively) and OS (23% and 40% improvement over 2001–03, respectively) (Supplemental Tables S1 and S3). The lack of significant interaction between the TBI dose and the categorical variable of year of HCT indicates that the improvement in NRM over time has been observed in all TBI-based MAC allogeneic HCTs regardless of the TBI dose. Stated differently, the results suggest that despite the improvement in supportive care over the years, which may allow for a higher dose of TBI, NRM continues to be higher with HD-TBI.

This study has many limitations, including those inherent with the retrospective nature of the study arising from non-random assignment to the TBI groups, institutional variability in TBI dosing and fractionation, as well as variation in Cy dosing (HD group that had a lower median Cy dose to allow a higher TBI dose) (Table 2). It is important to point out that the

reason for selecting the doses of TBI is not known; the TBI doses were most likely decided by the institutions as a matter of preference and were likely not based on the disease risk category, as evident from Table 1. Nonetheless, we cannot exclude potential selection bias in the higher dose TBI groups and residual confounding that could not be addressed by the analysis. The much smaller number of HD-TBI conditioned transplant in the recent time periods (6% in 2011–13 vs. 12% in 2001–05 vs. 13% in 2006–10) may indicate that this bias is present (Table 1). From a radiobiologic perspective, a major shortcoming of this analysis is anchoring the analysis on total TBI dose; we were unable to incorporate dose rate and/or protractionation. These fundamental variables are known to be associated with the biological consequences of ionizing radiation exposure and interpreting the data in the absence of these variables can be difficult. This variability in clinical practice with regards to the use of TBI among centers is exemplified by the study by European Group for Blood and Marrow Transplantation that surveyed 56 centers from 23 countries and demonstrated significant differences in the treatment technique, dose per fraction, in the organs shielded and the maximum accepted total delivered dose to those organs[45]. Furthermore, we did not evaluate TBI dose in combination with chemotherapy agents other than Cy such as etoposide, melphalan or fludarabine and this limits the generalizability of the study findings. The question of optimal TBI dose for other types of allogeneic transplant, such as umbilical cord blood and haploidentical transplants in the myeloablative setting, remains unanswered.

In conclusion, TBI dose of over 12Gy was demonstrated to reduce relapse risk, but this advantage was hampered by the increase in NRM, and that likely translated into no significant impact on OS. The study results suggest that Cy/TBI 12 Gy, therefore, should be considered the optimal conditioning regimen for patients with AML, ALL, MDS, and CML undergoing MAC allogeneic HCT. Higher TBI dosing may be associated with greater morbidity, as evidenced by the higher incidence of organ failure as the cause of death (Table 5a). We can speculate that young adults (<40 years), with robust performance status (KPS ≥90), advanced disease (myeloid malignancy) and a matched sibling donor may derive greater survival benefit from HD-TBI (compared to <14 Gy TBI; Supplemental Table S1). Future research should focus on novel strategies to protect patients against the adverse effects of high dose TBI. Its potency in disease control is clear; reducing TBI's toxicity and NRM may therefore help overcome relapse, the most significant barrier to long-term survival after allogeneic HCT. Developing safer methods to deliver radiation, sparing sensitive organs, continues to be an important area of research to maximize the effectiveness of high dose TBI in allogeneic HCT recipients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors thank Jennifer Motl for editorial support in accordance with Good Publication Practice (GPP3) guidelines (http://www.ismpp.org/gpp3). Funding: The CIBMTR is supported primarily by Public Health Service Grant/Cooperative Agreement 5U24CA076518 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 1U24HL138660 from NHLBI and NCI; a contract HHSH250201700006C with Health Resources and Services Administration (HRSA/DHHS); Grants N00014 1712388, N000141712850 and

N000141812045 from the Office of Naval Research HHSH250201700006C; and grants from Adaptive Biotechnologies; *Amgen, Inc.; Anonymous donation to the Medical College of Wisconsin; Astellas Pharma US; Atara Biotherapeutics, Inc.; Be the Match Foundation; *bluebird bio, Inc.; *Bristol Myers Squibb Oncology; *Celgene Corporation; *Chimerix, Inc.; *CytoSen Therapeutics, Inc.; Fred Hutchinson Cancer Research Center; Gamida Cell Ltd.; Gilead Sciences, Inc.; HistoGenetics, Inc.; Immucor; *Incyte Corporation; Janssen Scientific Affairs, LLC; *Jazz Pharmaceuticals, Inc.; Karius, Inc.; Karyopharm Therapeutics, Inc.; *Kite Pharma, Inc.; Medac, GmbH; *Mediware; The Medical College of Wisconsin; *Merck & Co, Inc.; *Mesoblast; MesoScale Diagnostics, Inc.; Millennium, the Takeda Oncology Co.; *Miltenyi Biotec, Inc.; Mundipharma EDO; National Marrow Donor Program; Novartis Pharmaceuticals Corporation; PCORI; *Pfizer, Inc; *Pharmacyclics, LLC; PIRCHE AG; *Sanofi Genzyme; *Seattle Genetics; Shire; Spectrum Pharmaceuticals, Inc.; St. Baldrick's Foundation; Swedish Orphan Biovitrum, Inc.; *Takeda Oncology; and University of Minnesota. 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.

* Corporate Members

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HIGHLIGHTS

- Total body irradiation (TBI) is an important component of myeloablative conditioning regimens for allogeneic hematopoietic cell transplantation. Long-term disease control appears to be dose-dependent, but doses >12 Gray (Gy) have previously been associated with excess toxicity and higher non-relapse mortality (NRM).
- In the current era, TBI doses higher than 12 Gy offer no survival advantage over standard dose TBI (12 Gy) when used in combination with cyclophosphamide as conditioning for allogeneic transplant, as a decrease in relapse risk is offset by increased risk of NRM. The study supports the recommendation for fractionated TBI 12 Gy in myeloablative conditioning for hematologic malignancies.

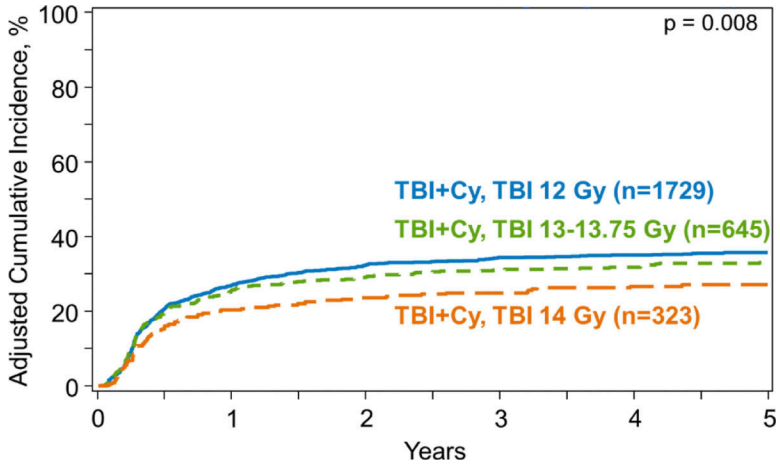

Figure 1.
Cumulative incidence function of non-relapse mortality by dose of TBI

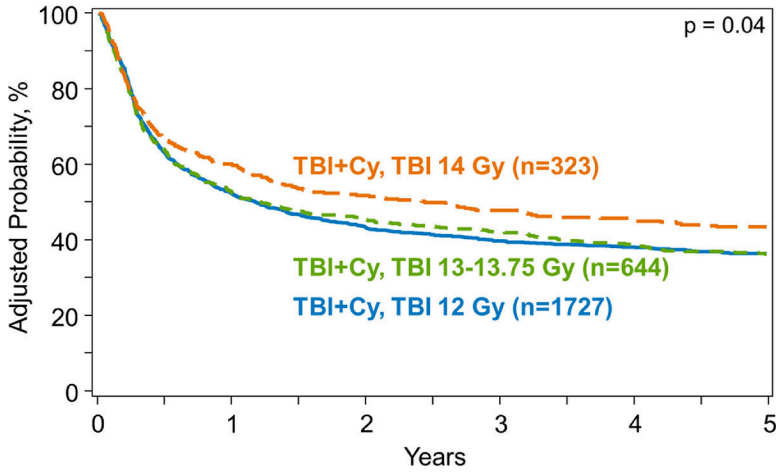

Figure 2.
Cumulative incidence function of relapse by dose of TBI

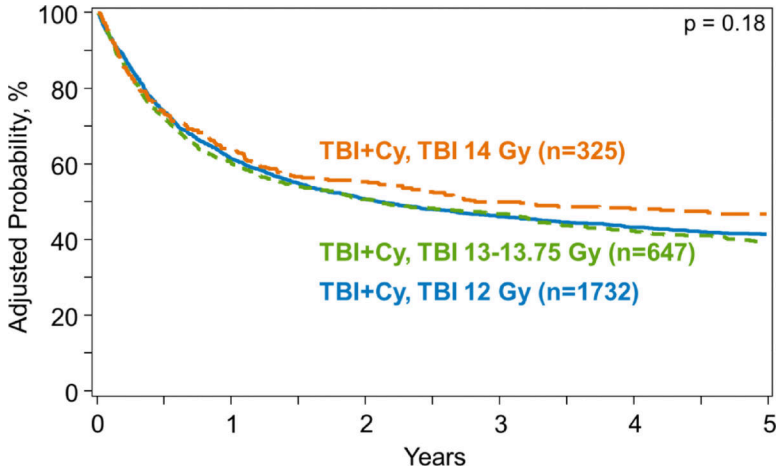

Figure 3.
Disease-free survival by dose of TBI

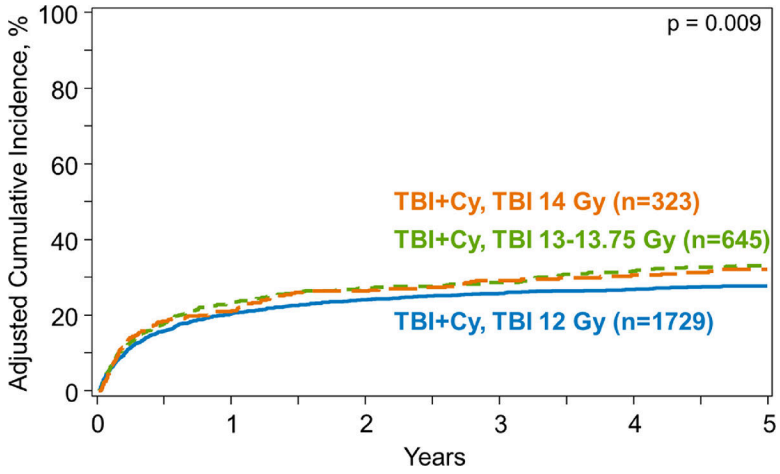

Figure 4.
Kaplan-meier curve of overall survival by dose of TBI

Table 1.

Patient characteristics in the observational study of allogeneic transplant patients receiving myeloablative conditioning regimen of cyclophosphamide and total body radiation (TBI) with different doses of TBI between 2001 and 2013.

Characteristics	**12 Gy (n=1745) n (%)**	**13–13.75 Gy (n=648) n (%)**	**14 Gy (n=328) n (%)**	***P-value***
Number of patients	1745	648	328	
Number of centers	155	49	13	
Age, median (range), years	39 (18–60)	39 (18–60)	43 (18–60)	***<0.001***
Male sex	959 (55)	344 (53)	169 (52)	*0.436*
KPS 90–100%	1197 (69)	405 (63)	190 (58)	***<0.001***
Disease				***<0.001***
Acute myelogenous leukemia	836 (48)	352 (54)	198 (60)	
Acute lymphoblastic leukemia	647 (37)	175 (27)	49 (15)	
Chronic myelogenous leukemia	202 (12)	89 (14)	50 (15)	
Myelodysplastic syndrome	60 (3)	32 (5)	31 (9)	
Disease status prior to transplant				*0.50*
Early	912 (52)	331 (51)	157 (48)	
Intermediate	421 (24)	164 (25)	78 (24)	
Advanced	407 (23)	153 (24)	90 (27)	
Not reported	5 (<1)	0	3 (<1)	
BMI, median (range), kg/m^2	25 (16 – 49)	24 (17 – 49)	27 (17 – 49)	***<0.001***

Table 2.

Transplant characteristics in the observational study of allogeneic transplant patients receiving myeloablative conditioning regimen of cyclophosphamide and total body radiation (TBI) at different doses between 2001 and 2013.

Characteristics	**12 Gy (n=1745) n (%)**	**13–13.75 Gy (n=648) n (%)**	**14 Gy (n=328) n (%)**	***P-value***
Time from diagnosis to transplant, median (range), months	7 (1–252)	7 (2–310)	6 (1–222)	*0.44*
Number of fractions, median (range)	6 (2–12)	8 (3–12)	7 (2–8)	***<0.001***
TBI dose per fraction, median (range), cGy	200 (100–600)	165 (108–440)	200 (175–700)	***<0.001***
Cy dose, median (range), mg/kg	120 (34–240)	120 (36–239)	90 (33–206)	***<0.001***
Donor type				***<0.001***
HLA-identical sibling	746 (43)	216 (33)	109 (33)	
Matched unrelated (8/8)	694 (40)	313 (48)	164 (50)	
Partially matched unrelated (7/8)	305 (17)	119 (18)	55 (17)	
Graft source				***<0.001***
Bone marrow	504 (29)	228 (35)	79 (24)	
Peripheral blood	1241 (71)	420 (65)	249 (76)	
Donor–Recipient sex match				*0.37*
Male–Male	606 (35)	218 (34)	114 (35)	
Male–Female	446 (26)	176 (27)	78 (24)	
Female–Male	347 (20)	125 (19)	55 (17)	
Female–Female	338 (19)	128 (20)	81 (25)	
Not reported	8 (<1)	1 (<1)	0	
Donor–Recipient cytomegalovirus status				*0.02*
−/−	510 (29)	157 (24)	99 (30)	
−/+	429 (25)	183 (28)	96 (29)	
+/−	193 (11)	63 (10)	38 (12)	
+/+	527 (30)	207 (32)	76 (23)	
Not reported	86 (5)	38 (6)	19 (6)	
Unrelated donor age, median (range), years	33 (19–61)	33 (18–58)	32 (19–60)	*0.95*
Year of transplant				***0.005***
2001–2005	809 (46)	267 (41)	149 (45)	
2006–2010	749 (43)	308 (48)	161 (49)	
2011–2013	187 (11)	73 (11)	18 (5)	
Inpatient days, median (range)	29 (<1–123)	32 (<1–175)	26 (<1–100)	
Median follow-up of survivors, range, months	72 (3 – 167)	67 (4 – 148)	72 (5 – 144)	

Abbreviations: Cy, cyclophosphamide; HLA, human leukocyte antigen; TBI, total-body irradiation

Table 3.

Unadjusted clinical outcomes after myeloablative conditioning allogeneic transplant using matched sibling and unrelated donor by dose of total body irradiation (TBI) (2001–2013)

Outcomes	12 Gy (n=1745) Probability (95% CI)	13–13.75 Gy (n=648) Probability (95% CI)	14 Gy (n=328) Probability (95% CI)	*P-value*
Veno-occlusive disease/sinusoidal obstruction syndrome				
100-day	5% (4–6)	6% (4–7)	9% (6–12)	*0.09*
Idiopathic pneumonia syndrome				
2-year	8% (6–9)	8% (6–11)	9% (6–13)	*0.57*
Grade II-IV acute graft-vs-host disease				
1-year	43% (40–45)	49% (45–53)	42% (37–47)	*0.02*
Grade III-IV acute graft-vs-host disease				
1-year	19% (17–21)	23% (20–26)	20% (16–25)	*0.10*
Chronic graft-vs-host disease				
5-year	52% (49–54)	50% (46–54)	53% (48–59)	*0.68*
Relapse				
1-year	27% (25–29)	25% (22–28)	20% (16–24)	*0.01*
5-year	36% (34–38)	32% (29–36)	26% (21–31)	***<0.001***[a]
Non-relapse mortality				
5-year	28% (25–30)	32% (29–36)	34% (28–39)	*0.02*
Disease-free survival				
5-year	37% (34–39)	35% (32–39)	40% (35–46)	*0.29*
Overall survival				
5-year	42% (39–44)	40% (36–44)	45% (39–50)	*0.39*

Abbreviations: CI, confidence interval; Gy, Gray.

[a]Significant at $p < 0.01$ level

Table 4.

Total body irradiation (TBI) dose in multivariate models of treatment with cyclophosphamide plus TBI as myeloablative conditioning regimen for allogeneic transplant using matched sibling and unrelated donor (2001–2013).

Outcome	n	Events	HR	Upper	Lower	*P-value*
Overall Survival						
TBI dose						*0.18*
12 Gy	1732	1024	1.0			
13–13.75 Gy	647	394	1.06	0.94	1.19	*0.36*
14 Gy	325	190	0.89	0.76	1.05	*0.17*
14 Gy vs. TBI 13–13.75 Gy (Ref.)			0.85	0.71	1.01	*0.06*
Disease-Free Survival						
TBI dose						*0.04*
12 Gy	1727	1098	1.0			
13–13.75 Gy	644	423	1.01	0.90	1.13	*0.90*
14 Gy	323	199	0.83	0.71	0.97	*0.02*
14 Gy vs. TBI 13–13.75 Gy (Ref.)			0.82	0.69	0.97	*0.02*
Non-Relapse Mortality						
TBI dose						***0.009***[a]
12 Gy	1734	486	1.0			
13–13.75 Gy	645	215	1.25	1.06	1.48	***0.007***
14 Gy	326	117	1.25	1.02	1.53	*0.03*
14 Gy vs. TBI 13–13.75 Gy (Ref.)			0.99	0.79	1.25	*0.96*
Relapse						
TBI dose						***0.008***[a]
12 Gy	1737	618	1.0			
13–13.75 Gy	646	209	0.92	0.78	1.08	*0.29*
14 Gy	323	84	0.69	0.55	0.88	***0.002***[a]
14 Gy vs. TBI 13–13.75 Gy (Ref.)			0.76	0.59	0.98	*0.03*
Acute GVHD Grade II-IV						
TBI dose[b]	.	.	.	.	.	*0.01*
12 Gy	1724	739	1.0	.	.	.
13–13.75 Gy	640	313	1.15	1.00	1.31	*0.05*
14 Gy	326	137	0.85	0.71	1.03	*0.09*
14 Gy vs. TBI 13–13.75 Gy (Ref.)			0.74	0.61	0.91	*0.004*
Acute GVHD Grade III-IV						
TBI dose						*0.21*
12 Gy	1728	329	1.0			
13–13.75 Gy	641	148	1.18	0.97	1.44	*0.10*

Outcome	n	Events	HR	Upper	Lower	*P-value*
14 Gy	324	66	0.96	0.73	1.27	*0.79*
14 Gy vs. TBI 13–13.75 Gy (Ref.)			0.82	0.61	1.10	*0.18*
Chronic GVHD						
TBI dose (<=8 months)						***0.0001***[c]
12 Gy	1127	622	1.0			
13–13.75 Gy	401	205	0.83	0.71	0.97	*0.02*
14 Gy	193	96	0.64	0.52	0.80	***0.0001***[a]
14 Gy vs. TBI 13–13.75 Gy (Ref.)			0.78	0.61	1.00	*0.05*
TBI dose (>8 months)						*0.02*
12 Gy	588	217	1.0			
13–13.75 Gy	239	102	1.10	0.98	1.24	*0.12*
14 Gy	133	75	1.00	0.62	1.62	*0.99*
14 Gy vs. TBI 13–13.75 Gy (Ref.)			0.91	0.51	1.63	*0.75*
VOD/SOS						
TBI dose						*0.03*
12 Gy	1737	88	1.0			
13–13.75 Gy	648	36	1.16	0.78	1.71	*0.46*
14 Gy	322	30	1.77	1.17	2.69	*0.007*
14 Gy vs. TBI 13–13.75 Gy (Ref.)			1.53	0.94	2.49	*0.08*
IPS						
TBI dose						*0.80*
12 Gy	1715	131	1.0			
13–13.75 Gy	634	53	1.08	0.78	1.49	*0.63*
14 Gy	318	30	1.12	0.75	1.67	*0.57*
14 Gy vs. TBI 13–13.75 Gy (Ref.)			1.04	0.66	1.63	*0.87*

Abbreviations: GVHD, graft-versus-host disease; Gy, Gray; HR, hazard ratio; IPS, interstitial pneumonia syndrome; TBI, total body irradiation; VOD, veno-occlusive disease.

[a] Significant at p<0.01 level

[b] All patients received cyclophosphamide with TBI

[c] Significant at p < 0.01 level

Table 5.

Causes of death after myeloablative conditioning allogeneic transplant using cyclophosphamide and total body irradiation (TBI) as conditioning, by dose of TBI (2001–2013).

Cause of death	12 Gy (n=1034) n (%)	13–13.75 Gy (n=395) n (%)	14 Gy (n=192) n (%)
Primary disease	564 (55)	184 (47)	77 (40)
New malignancy	9 (1)	4 (1)	3 (2)
Graft-versus-host disease	112 (11)	63 (16)	24 (13)
Interstitial pneumonitis	52 (5)	15 (4)	9 (5)
Infection	131 (13)	47 (12)	27 (14)
Organ failure	96 (9)	46 (12)	37 (19)
Other cause	62 (6)	29 (7)	13 (7)
Not reported	8 (1)	7 (2)	2 (1)

Table 5a.

Organ failure as cause of death following myeloablative conditioning allogeneic transplant using cyclophosphamide and total body irradiation (TBI) as conditioning, by dose of TBI (2001–2013).

Cause of death, n	12 Gy	13–13.75 Gy	14 Gy
Liver (n=21)	10	7	4
Veno-occlusive disease/SOS (n=14)	4	4	6
Cardiac (n=28)	17	8	3
Pulmonary (n=61)	36	10	15
Central nervous system (n=5)	3	2	0
Renal (n=6)	4	0	2
Multiple organ (n=39)	20	13	6
Other (n=4)	1	2	1