original research report

Cyclophosphamide plus total body irradiation compared with busulfan plus cyclophosphamide as a conditioning regimen prior to hematopoietic stem cell transplantation in patients with leukemia: a systematic review and meta-analysis

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BACKGROUND AND OBJECTIVES: Cyclophosphamide plus total body irradiation (CYTBI) and oral busulfan plus cyclophosphamide (BUCY) are commonly used conditioning regimens prior to allogeneic hematopoietic stem cell transplantation (HSCT) in patients with leukemia. However, there is conflicting data on the superiority of one regimen over the other. Our aim was to critically appraise and synthesize available evidence regarding the efficacy and safety of CYTBI compared to BUCY as a conditioning regimen.

DESIGN AND SETTING: Systematic review and meta-analysis of randomized, controlled trials (RCTs) comparing BUCY with CYTBI.

METHODS: We did a systematic search of the indexed medical literature using appropriate keywords to identify potentially relevant articles. The primary outcome of interest was efficacy measured by overall survival (OS) and disease-free survival (DFS). Acute and late toxicity were secondary endpoints. Meta-analysis was attempted only on RCTs. A relative risk or risk ratio (RR) and 95% confidence interval (CI) was calculated for each outcome in the meta-analysis.

RESULTS: Fifteen non-randomized comparative studies involving 6280 patients were included in a narrative review without attempting a pooled analysis, in view of the potential for significant bias. Outcome data from seven RCTs involving 730 patients randomly assigned to either CYTBI or BUCY was pooled using meta-analytic methods. CYTBI was associated with a modest but non-significant reduction in all cause mortality (RR=0.82, 95%CI: 0.64-1.05; *P*=.12) and relapse of leukemia (RR=0.89, 95%CI: 0.72-1.10; *P*=.28). Transplant-related mortality (TRM) was significantly lesser with CYTBI compared to oral BUCY (RR-0.53, 95%CI: 0.31-0.90; *P*=.02). The cumulative incidence of major complications was not significantly different between the two regimens, but specific complications varied according to the conditioning regimen. TBI-based regimens were associated with more severe late effects on growth and development in children.

CONCLUSION: This analysis represents the largest comparative analyses of CYTBI with BUCY as a conditioning regimen prior to HSCT in the indexed medical literature. Conditioning regimen and disease (type and setting) can significantly affect outcomes. TRM is significantly lesser with CYTBI, but this does not translate into a significant survival benefit. There remain valid concerns regarding the late effects of TBI, particularly in children. Although not overly superior, the weight of evidence favors CYTBI over BUCY as a first choice-conditioning regimen in patients with leukemia.

Hematopoetic stem cell transplantation (HSCT) is being increasingly utilized worldwide in contemporary hematology-oncology practice.[1] One of the commonest indications for allogeneic HSCT is leukemia,[1,2] in an upfront setting for primary refractory disease, after first remission for high-risk disease, or at relapse after achieving another remission with high-dose salvage chemotherapy. The anti-neoplastic activity of allogeneic HSCT is mediated by the high-intensity of the conditioning regimen as well as the immune-mediated graft-versus-disease reaction.[2,3] The two most commonly used conditioning regimens have been cyclophosphamide (CY) plus fractionated total body irradiation (TBI), known as CYTBI[4,5] or oral busulfan (BU) plus cyclophosphamide, known as BUCY.[6,7] There are inherent advantages[8] of TBI-based regimens such as adequate treatment of sanctuary sites, dose deposition regardless of vascular supply, no cross-resistance with chemotherapy, and a potential for shielding or boosting of specific sites. However, there have been concerns regarding late sequelae including cataracts, second malignancies, growth retardation, neuro-endocrine and neuro-psychologic dysfunction, particularly in children[9] prompting the use of chemotherapy-alone regimens as an alternative to TBI-based conditioning. There is inconclusive evidence on the superiority of one regimen over the other, both in terms of efficacy as well as toxicity. Retrospective comparative studies including reports from international transplant registries, prospective randomized controlled trials (RCTs), as well as previously attempted pooled analyses have yielded conflicting results and the most optimal conditioning regimen prior to transplantation in leukemia remains to be defined. The objective of this systematic review was to critically appraise all the available evidence and attempt a meta-analysis of RCTs comparing BUCY with CYTBI as a conditioning regimen prior to HSCT in patients with leukemia.

METHODS

Inclusion and exclusion criteria for study selection

All reports comparing BUCY with CYTBI as full-intensity (myeloablative) conditioning regimens prior to HSCT in patients with acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML) or chronic myeloid leukemia (CML) were considered eligible for inclusion. Non-randomized comparisons from retrospective studies and international transplant registries were also included. All reports from clinical trials randomly assigning patients to either TBI-based regimen or BUCY, and published as full text were considered for pooling in the meta-analysis. Trials comparing different doses of TBI or different chemotherapy regimens only were not considered for inclusion. Studies on autoimmune diseases and non-myeloablative or reduced-intensity conditioning were also not considered.

Literature search strategy

A systematic search of PubMed was done from 1965 until June 2010 to identify all relevant and appropriate studies. Different keywords including Medical Subject Heading (MeSH) terms were combined using Boolean operations 'AND' and 'OR', such as "total body irradiation" OR "whole-body irradiation" [Mesh] AND ("bone marrow transplantation" [Mesh] OR "peripheral blood stem cell transplantation" [Mesh]) OR "transplantation" [MeSH] OR "leukemia" [Mesh] AND "busulfan" AND "cyclophosphamide". The Cochrane Library including the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews was also searched to identify potentially relevant trials and review articles respectively. Cross-references from selected articles were also used for retrieving relevant studies.

Outcome measures

The primary outcome of interest was efficacy as measured by overall survival (OS) and disease-free survival (DFS) (leukemia-free survival). Secondary outcomes included toxicity parameters like transplant-related mortality (TRM), acute graft-versus-host-disease (aGVHD), chronic GVHD (cGVHD), interstitial pneumonitis (IP), and veno-occlusive disease (VOD). Data extraction for the purpose of the meta-analysis was done by two reviewers jointly and later verified by the third reviewer independently. Any discrepancy was resolved by consensus.

Statistical methods

Non-randomized comparative studies were restricted to a narrative systematic review, as it was considered inappropriate to pool them for attempting a meta-analysis due to potential imbalances and biases inherent to retrospective analyses. Outcome data from all included RCTs were pooled for meta-analysis. Meta-analysis for any outcome of interest was attempted only if relevant data could be extracted from five or more trials. All meta-analyses were performed using the random effects model (assuming the existence of heterogeneity) to provide a more conservative yet robust estimate of effect. Review Manager (RevMan version 5.0, Copenhagen, The Nordic Cochrane Centre, The Cochrane Collaboration 2008) was used for performing the meta-analyses. Relative risk or risk ratio (RR)

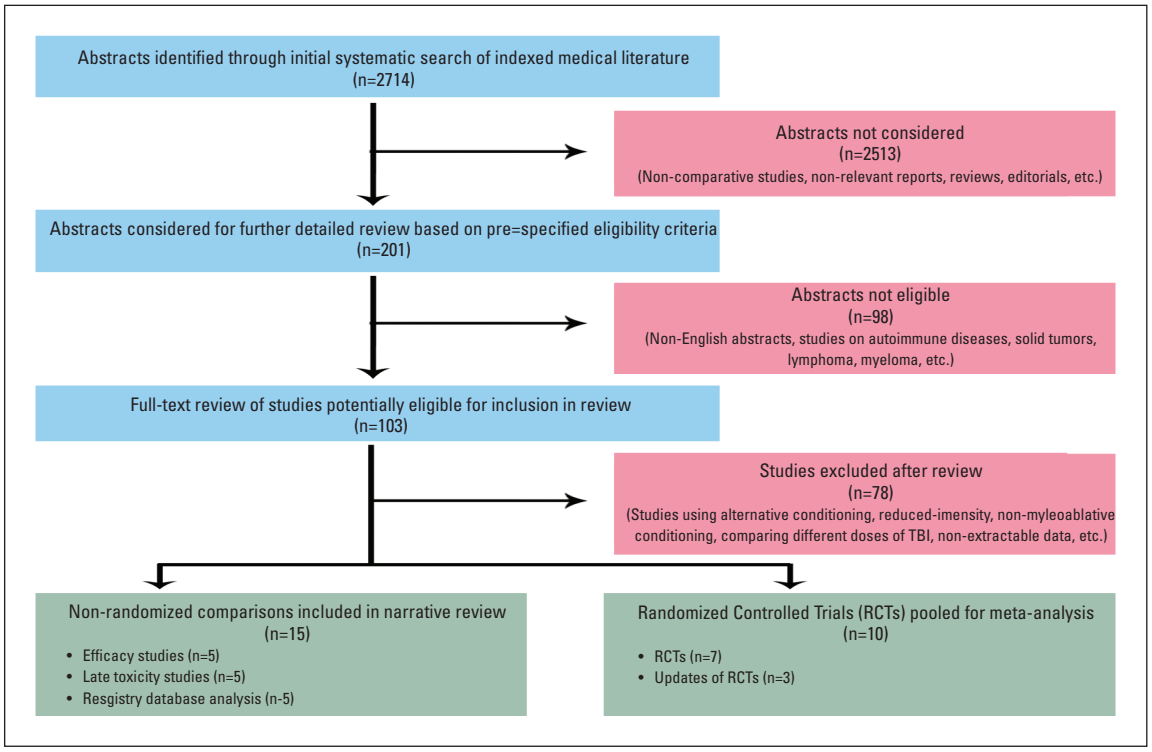

Figure 1. Flowchart of study selection in the systematic review and meta-analysis

and 95% confidence interval (CI) were calculated for each outcome and presented as forest plots after pooling. The pooled RR, symbolized by a solid diamond at the bottom of the forest plot (the width of which represents the 95%CI) is the best estimate of the pooled outcome. Sensitivity or influence analysis was carried out to assess the influence of each study on the overall summary effect.

RESULTS

Figure 1 is a flowchart showing selection and exclusion of studies using the pre-specified search strategy. An unrestricted search of the indexed medical literature yielded a total of 2714 potential abstracts. Of these, 201 abstracts were considered for further review based on pre-specified eligibility criteria. The search was further refined to yield 103 abstracts by limiting to 'controlled clinical trials', and the 'English' language. After a review of full-text articles of all eligible abstracts, 15 non-randomized comparative studies and 11 RCTs comparing a TBI-based conditioning regimen with BUCY were identified. One randomized trial[10] comparing two doses of melphalan with or without TBI in multiple myeloma was excluded. All 15 non-randomized studies involving 6280 patients were included, but restricted to a narrative systematic review without pooled analysis. Amongst the ten included articles identified as randomized trials, three were updates of previous RCTs and not separate trials. However, data extraction was done from both the original publication as well as the updated publication for the purpose of the meta-analysis. Thus seven trials reported in ten publications including three long-term mature updated results involving a total of 730 patients randomly comparing CYTBI with BUCY comprised the dataset for the meta-analysis.

Review of non-randomized comparative studies

The CYTBI regimen was first used successfully as a conditioning regimen in the 1970s.[4,5] However, due to concerns regarding long-term sequelae, non-TBI regimens were investigated by substituting it with oral busulfan[6,7] in an attempt to reduce toxicity. There have been several retrospective comparisons (**Table 1**) of these two conditioning regimens, both in terms of efficacy[11-15] and safety including late toxicity.[16-20]

Comparison of efficacy

Michel et al[11] analyzed the French experience with BUCY as a conditioning regimen used as either BUCY120 (120 mg cyclophosphamide) (n=23) or BUCY200 (120 mg cyclophosphamide) (n=19) and compared it with CYTBI (n=32) in children with AML

Table 1. Non-randomized comparative studies of efficacy and safety of CYTBI compared with BUCY as a conditioning regimen.

Author, year (reference)	CYTBI (N)	BUCY (N)	Diagnosis	Age range (median, y)	Median follow-up (y)	Conclusions
Comparison of efficacy						
Michel, 1994[11]	32	42	AML	≤16	3	BUCY120 inferior to BUCY200 & CYTBI
Granados, 2000[12]	114	42	ALL	1-59	6	CYTBI better than BUCY for ALL
Kim, 2001[13]	26	27	CML	17-50 (32)	3.5	BUCY acceptable alternative to CYTBI
Kroger, 2001[14]	25	25	CML	16-52 (36)	3	Similar efficacy, but, higher toxicity with BUCY
Lahteenmaki, 2004[15]	26	18	ALL, AML, misc	<7	5	CYTBI better for high risk groups
Comparison of late toxicity						
Wingard, 1992[16]	23	24	ALL, AML	1-12 (6.5)	2	Growth impairment similar in both regimens
Hartsell, 1995[17]	79	65	ALL, AML, misc	2-57 (28)	4.4	cGVHD, prior bleomycin use had pulmonary toxicity
Michel, 1997[18]	19	26	AML	1-16 (8.5)	5.9	Late toxicities lesser with BUCY
Holmstrom, 2002[19]	21	24	AML, ALL, CML	≤17	5	Higher incidence (95%) of cataract in TBI
Smedler, 2008[20]	12	10	ALL, AML, CML	0.4-3.6 (2)	6.5	Favorable neuropsychological profile with BUCY

N= number of patients, y= years

Table 2. Comparative studies of CYTBI with BUCY from international transplant registries.

Author, year (reference)	CYTBI (N)	BUCY (N)	Diagnosis	Age range (median, y)	Median follow-up (y)	Conclusions
Ringden,1996[21]	921	921	ALL, AML	All ages	2	CYTBI has better outcomes in medium risk ALL
Davies, 2000[22]	451	176	ALL	1-20 (12)	3	CYTBI is the superior regimen in ALL
Litzow, 2002[23]	200	381	AML	20-57 (35)	5	CYTBI reduces relapse without improving survival
Kanda, 2005[24]	714	243	ALL, AML, CML	33 (16-63)	5	CYTBI first choice regimen in unrelated HSCT
Uberti, 2010[25]	1275	318	AML, CML	1-58 (37)	8	Equivalent efficacy & safety of both regimens

N= number of patients, y= years

in first complete remission. The probability of relapse was significantly higher in BUCY120 (54%), but was similar in the BUCY200 (13%) and TBI (10%) arms. The 3-year event-free survival (EFS) was 46% (95%CI: 22-70%), 82% (95%CI: 64-100%), and 80% (95%CI: 66-94%), respectively, in the three groups. Multivariate analysis identified conditioning with BUCY120 and delayed transplantation (>120 days from diagnosis) as independent negative prognostic factors.

Granados et al[12] retrospectively compared outcomes in 156 consecutive patients with ALL conditioned with CYTBI (n=114) or BUCY (n=42). At a median follow-up of 6 years, EFS was 43% (95%CI: 35-51%) in the CYTBI versus 22% (95%CI: 10-34%) in the BUCY cohort (P=.01). TRM was 22% and 17% in the BUCY and CYTBI groups, respectively (P=.24). The actuarial

Table 3. Randomized controlled trials comparing CYTBI with BUCY as conditioning regimen in leukemia.

Author, year (reference)	CYTBI (N)	BUCY (N)	Diagnosis	Age range (median, y)	Median Follow-up (y)	Conclusions
Blaise, 1992[26] Blaise†, 2001[27]	50	51	AML	32 (mean)	2 10.8	BUCY inferior to CYTBI Confirms inferiority of BUCY
Blume, 1993[28]	61	61	AML, ALL, CML	2-48	2.5	No difference in safety or efficacy of both regimens
Clift, 1994[29] Clift†, 1999[30]	69	73	CML	6-55 (37)	1 (minimum) 7.7	BUCY compares favorably to CYTBI in CML Confirms better tolerability, similar efficacy of BUCY
Ringden, 1994[31] Ringden†, 1999[32]	79	88	CML	1-55 (34)	2.1 7	CYTBI regimen of choice, for high-risk disease Confirms higher late toxicity, lower efficacy of BUCY
Dusenbery, 1995[33]	18	17	AML	1.6-56	2.6	CYTBI equivalent or better than BUCY
Devergie, 1995[34]	55	65	CML	10-54 (36)	3.5	Similar outcomes with both regimens
Bunin, 2003[35]	22	21	ALL	0.5-20 (8)	3.6	BUCY is inferior to CYTBI in pediatric ALL

† long-term update of previous trial

probability of relapse at 3-years was significantly higher in the BUCY group (71% versus 47%; *P*=.01), leading to the conclusion that TBI-based regimen should remain the standard preparative method in ALL.

In a comparative analysis of the two regimens,[13] 53 patients with CML treated with HLA-identical sibling donor transplants were included. TRM was similar in both groups (19% in BUCY versus 12% in CYTBI). Grade II–IV acute GVHD was 9% in BUCY as compared to 52% with CYTBI. The overall incidence of chronic GVHD was similar (BUCY, 50% versus CYTBI, 52%). In patients with chronic phase, 5-year OS was 73% in the BUCY group compared with 87% in the CYTBI group (statistically non-significant). DFS was 75% in BUCY and 59% in the CYTBI group (statistically non-significant). The actuarial 5-year relapse rate was 15% after BUCY versus 34% after CYTBI (*P*=.46), suggesting that BUCY may be an acceptable alternative for patients with CML during human leukocyte antigen (HLA)-identical sibling allogeneic HSCT.

In another study[14] of 50 patients with CML treated with unrelated stem cell transplantation using either BUCY or CYTBI, there were no significant differences in efficacy between the two regimens. The incidence of grade II–IV GVHD was similar between the two groups (CYTBI, 40% and BUCY, 36%). The incidence of cGVHD at 1 year was higher in the BUCY group (65% versus 30%; *P*=.02). Hepatic toxicity and hemorrhagic cystitis was also significantly higher with BUCY. There were seven relapses in CYTBI group compared to no relapse in BUCY after a median follow up of 44 and 15 months, respectively. The estimated 3-year OS was 72% (95%CI: 55-98%) for CYTBI and 70% (95%CI: 52-98%) for BUCY (*P*=.7). Similar values for DFS were 58% (95%CI: 39-77%) and 70% (95%CI: 51-89%) respectively (*P*=.7), suggesting that the anti-leukemic activity of BUCY may be comparable to CYTBI in unrelated stem cell transplantation for CML.

Lahteenmaki and colleagues[15] retrospectively evaluated 44 children (<7 years) with hematologic malignancies conditioned with either single fraction TBI (n=26) plus cyclophosphamide or BUCY (n=18). The rates of neutrophil engraftment, aGVHD and cGVHD were similar in the two arms. The 5-year actuarial survival was 43.3% (95%CI: 23.3-63.3%) and 33.3% (95%CI: 7.9-58.7%) in the CYTBI and BUCY groups, respectively (*P*=.6). However, CYTBI was associated with a trend towards improved survival in the high-risk subgroup. Long-term overall survival was significantly better with the TBI-based regimen in ALL, while BUCY was superior for myeloid malignancies. Endocrinopathies, cognitive dysfunction and cataract were seen commonly in TBI whereas behavioral problems, deafness, seizures, and developmental problems were associated with BUCY.

Comparison of late toxicities

Wingard and colleagues[16] assessed growth during the first 2 years after transplant in children (age <12 years) treated with either BUCY (n=24) or CYTBI (n=23). Prior to transplant, their median height was 0.2 standard deviation (SD) below age- and sex-adjusted means (range: -2.5 to +3.0). Pre-transplant heights were comparable in the BUCY and CYTBI groups. Following transplant, median 1-and 2-year heights were 0.7 and 0.9 SD below normal, respectively. Growth rates were 2.2 SD and 1.4 SD below normal during the first and second years respectively. There was no significant difference in the growth rates between BUCY versus CYTBI [-2.5 versus -1.7 SD during the first year (P=.19) and -1.5 versus -1.1 SD during the second year (P=.61)].

Hartsell et al[17] retrospectively compared pulmonary complications in patients conditioned with CYTBI (n=79) and BUCY (n=65). The 1-year actuarial pulmonary complication rate was similar between the two groups (32.9% versus 29.5%; P=.61). The incidence of acute pulmonary complications such as acute respiratory distress syndrome, infective lobar pneumonia, interstitial pneumonia, or diffuse pulmonary infiltrates was similar between the two groups. However, late pulmonary events (occurring >45 days after transplant) such as interstitial pneumonia, obliterative bronchitis, lobar pneumonia, or asthma were significantly higher in the CYTBI compared to BUCY (n=15 versus 4; P=.04). Pulmonary complications were significantly associated with GVHD and prior bleomycin use.

Michel and colleagues[18] compared late effects of BUCY (n=26) and CYTBI (n=19) in a French cohort of AML patients transplanted in first remission and followed for a mean of 5.9 years. The mean cumulative changes in height SD score was -0.86 at 3-years and -1.56 at 5-years in the TBI group, which was inferior to -0.05 and -0.17 in the BUCY group (P<.01) at similar time points. The 6-year probability of hypothyroidism was 9% (95%CI: 1-17%) with BUCY compared to 43% (95%CI: 28-58%) with TBI (P<.02). The 6-year probability of cataract was 70% (95%CI: 57-83%) with TBI, while no child in the BUCY group developed cataract suggesting that BUCY has a better late toxicity profile as a cytoreductive conditioning regimen.

Researchers at the Karolinska Institute followed up children treated with BUCY (n=24) or CYTBI (n=21) conditioning for the development of lens opacities with annual ophthalmic evaluations for 10 years.[19] Cataracts developed in 20/21 (95%) children conditioned with TBI-based regimens as compared to only 5/24 (21%) children conditioned with busulphan. There was no relationship between cataract development and age at transplant or treatment with corticosteroids.

Long-term neuro-psychological outcomes were compared in very young children (age <3.6 years) treated with BUCY (n=10) or CYTBI (n=12), with extensive assessments done at an average of 6.5 years post-transplant.[20] The BUCY group performed at age level on verbal measures, but tended to score below age level in the executive and visuo-spatial domains (P<.01). In comparison, children treated with CYTBI had more pervasive neuro-psychological impairments, including motor deficits (P<.01) and varying degrees of perceptual (P<.05), executive and cognitive (P<.05) problems leading to the conclusion that BUCY was more favorable for neuro-psychological development for children transplanted at a very young age.

Analyses of registry database

The HSCT fraternity has set up several international registries, namely the European Cooperative Group Bone Marrow Transplantation (EBMT) registry, the International Bone Marrow Transplantation Registry (IBMTR), and the Centre for International Blood and Marrow Transplant Research (CIBMTR), where participating centres voluntarily contribute detailed data on demography, disease characteristics, transplant characteristics, and outcomes, both for autologous as well as allogeneic transplants (**Table 2**). The first such analysis reported by Ringden et al[21] compared the outcome of patients in the EBMT database transplanted for acute leukemia between 1987 until 1994, who had been treated with either BUCY or CYTBI as a conditioning regimen. Patients were matched for age, type of transplant (autologous versus allogeneic), type of leukemia (myeloid versus lymphoid), disease status (early versus intermediate), prevention of GVHD, and year of transplant. A total of 1842 patients (921 in each arm) were included in this matched-pair analysis. In patients treated with autologous transplant (530 matched pairs) in early stage acute leukemias and intermediate stage AML, transplant-related deaths, relapse incidence, and leukemia-free survival did not differ significantly between the two groups. However, in patients with intermediate stage ALL, the probability of relapse was significantly higher in BUCY (82%, 95%CI: 77-87% versus 62%, 95%CI: 56-68%; P=.002) compared to CYTBI. Similarly, the 2-year leukemia-free survival was significantly better with CYTBI (34%, 95%CI: 28-40% versus 14%, 95%CI: 10-18%; P=.002). In patients treated with allogeneic transplant from HLA-identical siblings (391 matched pairs), the relapse incidence, TRM and leukemia-free survival was similar in both groups with no significant differences. BUCY was associated with

higher incidence of VOD and hemorrhagic cystitis.

Outcomes data on children (age <20 years) with ALL treated with HLA-identical sibling transplants between 1988 and 1995 using either BUCY (n=176) or CYTBI (n=451) reported to the IBMTR were compared retrospectively.[22] Both groups were well balanced in terms of gender, immune phenotype, leukocyte count at diagnosis, chromosomal abnormalities, remission status and duration. With a median follow-up of 37 months, the 3-year estimate of OS was 55% (95%CI: 50-60%) in CYTBI and 40% (95%CI: 32-48%) in the BUCY group (*P*=.003). The 3-year probability of leukemia-free survival was 50% (95%CI: 45-55%) and 35% (95%CI: 28-43%), respectively (*P*=.005). All-cause mortality (RR-1.39; *P*=.17), TRM (RR-1.68; *P*=.12) and treatment failure (RR-1.42; *P*=.006) was significantly worse in the BUCY group on multivariate analysis leading to the conclusion that CYTBI was the superior conditioning regimen in HLA-identical sibling transplants in children with ALL.

Litzow et al[23] reported a similar comparison from the IBMTR database in patients with AML in first remission treated with HLA-identical sibling transplants between 1988 and 1996 using either CYTBI (n=200) or BUCY (n=381). BUCY was associated with a higher incidence of hepatic veno-occlusive disease (VOD) (13% versus 6%; *P*=.009). The risks of acute and chronic GVHD were similar between the two groups. The risk of relapse was higher in the BUCY group (RR-1.72, 95%CI: 1.05-2.81; *P*=.031). However, there were no significant differences in TRM, leukemia-free survival, and overall survival between the two groups.

Kanda et al[24] retrospectively compared outcomes in patients receiving transplantation from an unrelated donor between 1993 and 2002 registered in the Japan Marrow Donor Program. Standard dose CYTBI (n=714), intensified CYTBI (n=861), BUCY (n=243) and BUCY with total lymphoid irradiation (n=57) were compared using multivariate analysis. There were significant differences between the patient background characteristics at baseline in terms of age, diagnosis, risk-category, and GVHD prophylaxis. Standard CYTBI was significantly better than BUCY with regards to incidence of engraftment failure (OR-2.49; *P*=.046) and OS (RR-1.31; *P*=.50). Intensified CYTBI resulted in inferior OS probably due to larger number of poor-risk patients. BUCY with total lymphoid irradiation improved engraftment but increased non-relapse mortality. Secondary analysis of standard dose CYTBI with BUCY alone confirmed the inferiority of BUCY in terms of engraftment failure (OR-2.53, 95%CI: 1-6.39; *P*=.49) and overall survival (RR-1.32, 95%CI: 1-1.75; *P*=.53), leading to the conclusion that standard dose CYTBI remains the regimen of first-choice in patients with unrelated HSCT.

The most recent comparative analysis[25] of BUCY versus CYTBI in myeloid leukemia and myelodysplasia included 1593 patients treated with T-replete unrelated marrow donor transplantation from 1991 to 1999 and reported to the CIBMTR. The CYTBI group included patients with standard-dose TBI (1000-1260 cGy) or high-dose TBI (1320-1500 cGy). Neutrophil and platelet engraftment was better with standard-dose CYTBI (n=420) compared to BUCY (n=318) or high-dose CYTBI (n=855). The cumulative incidence of grades III-IV acute GVHD was similar in all three groups. At 6-months, the cumulative incidence of chronic GVHD was higher in the CYTBI-based regimens compared to BUCY (35% versus 23%; *P*=.001), which lost significance over time. At 5-years, there was no significant difference (*P*=.779) in overall survival between standard-dose CYTBI (35%, 95%CI: 30-40%), high-dose CYTBI (32%, 95%CI: 28-36), and BUCY (33%, 95%CI: 30-36%). Similarly there was no difference in disease-free survival (*P*=.464) or TRM (*P*=.37) between the three groups. On univariate analysis, the cumulative incidence of relapse was significantly higher at 1-year in the high-dose CYTBI group compared to standard-dose CYTBI or BUCY (*P*<.001). However, there was no difference in the risk of relapse between the three groups (*P*=.155) on multivariate analysis.

Meta-analysis of randomized controlled trials

Outcome data from seven randomized controlled trials (**Table 3**) reported in 10 publications[26-35] (including 3 updates) between 1992 and 2003 involving a total of 730 patients randomly assigned to either CYTBI or BUCY were pooled for meta-analysis. Baseline characteristics were well balanced in both arms in all these trials, reducing the potential for bias. The median follow-up though variable was generally robust across studies (ranging from 2 to 10.8 years).

Overall survival and disease-free survival

All RCTs provided data on overall survival and disease-free survival. The 4-year survival rate was used to calculate the number of events (deaths for overall survival and relapse of leukemia for disease-free survival) in each trial for both treatment groups. The use of CYTBI was associated with an 18% reduction in mortality at 4-years (RR-0.82, 95%CI: 0.64-1.05; *P*=.12) compared to BUCY (**Figure 2**) that was not statistically significant. CYTBI was also associated with a non-significant reduction (11%) in the risk of leukemia relapse (**Figure**

2) compared to the BUCY regimen (RR-0.89, 95%CI: 0.72-1.10; *P*=.28).

Transplant-related mortality

Six RCTs reported on deaths directly attributable to the transplant-related complications. The use of CYTBI as a conditioning regimen was associated with a 47% reduction in the relative risk of transplant-deaths (**Figure 3**) compared to BUCY regimen, that was statistically highly significant (RR-0.53, 95%CI: 0.31-0.90; *P*=.02). However, it may be pertinent to note that intravenous busulfan with its more predictable pharmacokinetics and better toxicity profile was not available at that time limiting these trials to its oral use.

Acute and chronic GVHD

Acute GVHD generally occurs within first 3 months of transplantation, while chronic GVHD occurs beyond 3-months. Data on the incidence of acute as well as chronic GVHD could be extracted from 5 trials that were pooled for meta-analysis. A modest but non-significant increase in the incidence of grade II-IV aGVHD (**Figure 4a**) was seen with CYTBI compared to BUCY (RR-1.16, 95%CI: 0.92-1.45; *P*=.22). However, the incidence of cGVHD was very similar (**Figure 4b**) in the two treatment groups (RR-0.96, 95%CI: 0.77-1.20; *P*=.72).

Other complications

Interstitial pneumonitis, an inflammatory complication involving the lung post-transplant was reported in six trials. CYTBI was associated with a moderate, though, non-significant increase in the risk of clinically significant pulmonary complications (**Figure 5a**) compared to BUCY (RR-1.22, 95%CI: 0.79-1.88; *P*=.37). In post-transplant setting, VOD generally affects the hepatic sinusoidal vessels leading to progressive liver dysfunction. CYTBI was associated with a 64% relative risk reduction in the incidence of VOD of the liver as compared to BUCY (RR-0.36, 95%CI: 0.15-0.86; *P*=.02), that was highly statistically significant (**Figure 5b**). There was lack of extractable data from these randomized trials on other late complications such as the incidence of cataract, growth retardation, endocrine dysfunction, fertility impairment, and neuropsychological dysfunction to attempt pooled analysis.

Sensitivity/influence analysis

Sensitivity analysis was also done for all outcome measures by dropping one study at a time to assess if any single study has a major influence on the overall summary effect. None of the studies seemed to influence the overall effect for any outcome.

DISCUSSION

The most optimal conditioning regimen prior to HSCT in patients with leukemia remains to be defined.[36] This analysis represents the largest systematic body of evidence involving over 7000 patients comparing the efficacy and safety of two of the most commonly used conditioning regimens i.e. CYTBI and BUCY. There have been previous attempts at a systematic review and meta-analysis addressing the same issue. Hartman et al[37] pooled individual study data from 5 RCTs comparing CYTBI with BUCY and computed the odds ratio (OR) using the random effects model with overall survival, disease-free survival, and toxicities as endpoints. Although survival (both overall as well as DFS) was superior with TBI-based regimens (OR-1.4, 95%CI: 0.9-2.2; *P*=.09 and OR-1.2, 95%CI: 0.7-2.1; *P*=.44, respectively), this difference was not statistically significant. However, a power analysis could not exclude a survival advantage for TBI-based regimens. A significantly greater incidence of VOD was associated with BUCY (OR-2.5, 95%CI: 1.2-5.2; *P*=.02). Other toxicities were similar between the two groups, supporting the notion that CYTBI was the better conditioning regimen. Since then, two newer RCTs have been published and data from four trials included in the Hartman meta-analysis has been updated. In the update[38] on patients in 4 randomized trials comparing BUCY with CYTBI, the projected 10-year overall survival was similar (65% and 63%, *P*=.73 respectively) for CML, but non-significantly inferior with BUCY (51% versus 63%, *P*=.068) for patients with AML. The incidence of long-term complications, general health status, and return to work was similar between the two regimens except for an increased risk of cataract in CYTBI and alopecia in BUCY.

Recently, Shi-Xia and colleagues[39] pooled data from all published comparative studies including retrospective and non-randomized comparisons. Eighteen reports involving 3172 patients were assessed. For patients with ALL and AML, CYTBI regimen was associated with lower rates of relapse (OR-0.65, 95%CI: 0.22-1.88; *P*=.42 and OR-0.69, 95%CI: 0.49-0.98; *P*=.04, respectively). However in patients with CML, the rate of leukemia relapse was significantly higher with CYTBI (OR-2.51, 95%CI: 1.29-4.89; *P*=.007). CYTBI also resulted in better DFS for acute leukemia, with an OR of 1.93 (95%CI: 1.42-2.64; *P*<.0001) for ALL and 1.49 (95%CI: 1.01-2.20; *P*=.04) for AML. However, there was no significant difference between the two regimens in DFS for patients with CML (OR-0.93, 95%CI: 0.44-1.98; *P*=.85). TRM was significantly improved with

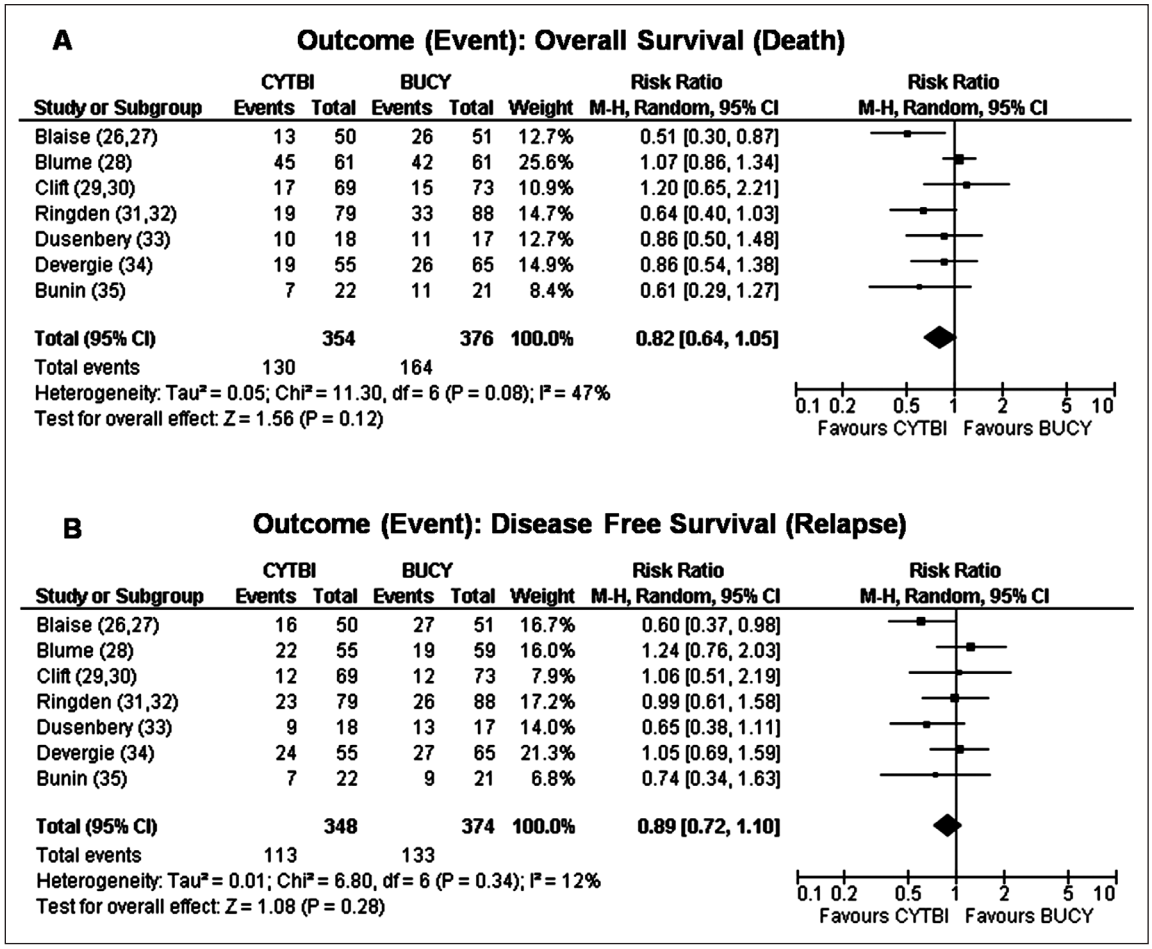

Figure 2. Forest plot of overall survival (A) and disease-free survival (B). Each study is represented by the point estimate of the risk ratio (square proportional to weight of the study) with 95%CI. Summary pooled estimates with 95%CI are shown as diamonds at the bottom of each figure.

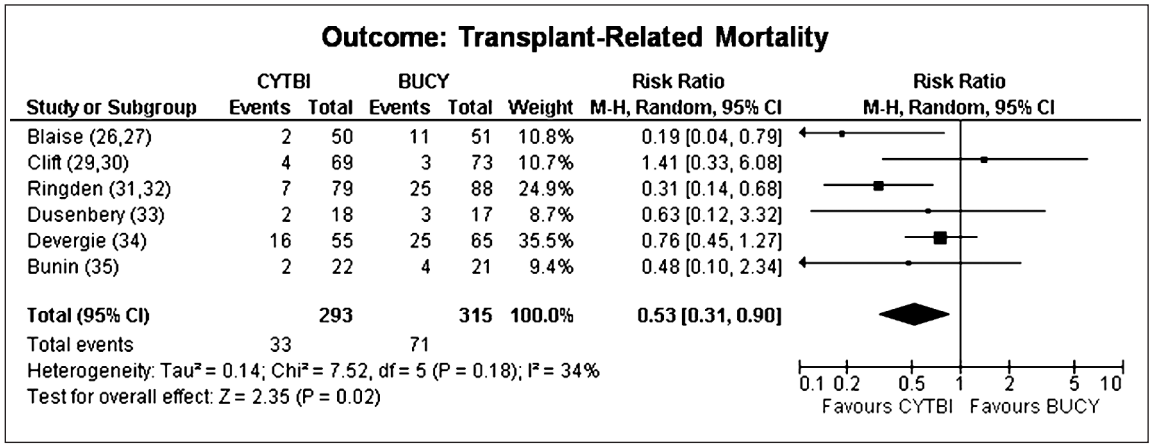

Figure 3. Significant relative reduction in the risk of transplant-related mortality with CYTBI as compared to BUCY regimen.

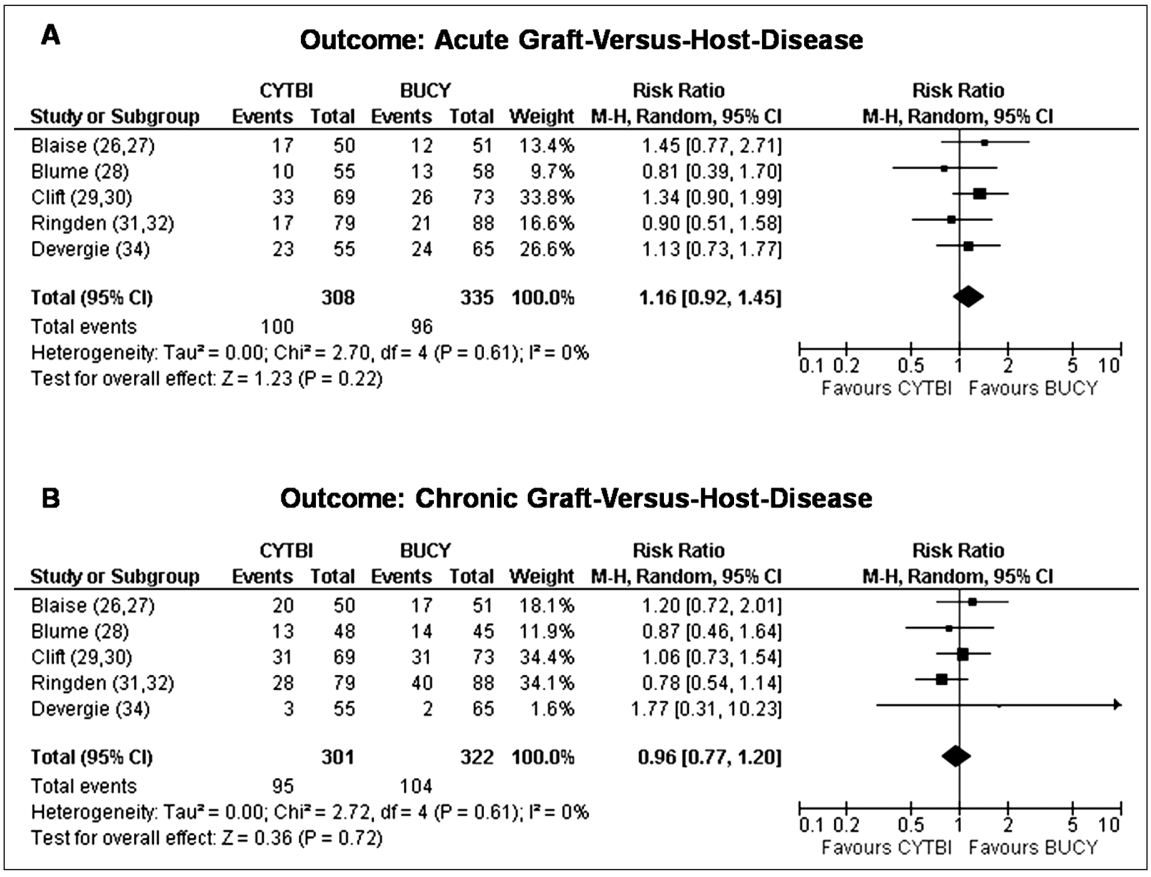

Figure 4. Forest plot of acute GVHD (A) and chronic GVHD (B) showing no significant differences between CYTBI and BUCY

CYTBI regardless of type of leukemia (OR-0.68, 95%CI: 0.49-0.98; *P*=.02). The cumulative incidence of specific toxicities was somewhat dependent on the regimen. CYTBI was associated with higher rates of cataract (OR-12.69, 95%CI: 1.72-93.32; *P*=.01) interstitial pneumonitis (OR-1.70, 95%CI: 1.24-2.32; *P*=.0009) and later growth/development problems (OR-5.85, 95%CI: 1.55-22.13; *P*=.009), whereas BUCY resulted in higher rates of VOD (OR-0.42, 95%CI: 0.30-0.59; *P*<.00001) and hemorrhagic cystitis (OR-0.32, 95%CI: 0.19-0.54; *P*<.0001). Engraftment and GVHD (both acute and chronic) were similar between the two regimens. The authors concluded that conditioning regimens and type of leukemia may affect outcomes in terms of DFS, relapse rates, TRM, and complications. However, there are several limitations to this report. The authors pooled data from retrospective non-randomized studies and quasi-randomized studies (prone to bias), with randomized controlled trials. There was significant heterogeneity between comparisons in terms of diagnoses, setting, prior treatment, age, source of stem cells, dose and fractionation of TBI, which could potentially affect outcomes.

Strengths and limitations of the present study

Our analysis represents the largest systematic body of evidence comparing the efficacy and safety of CYTBI with BUCY as a conditioning regimen prior to HSCT in patients with leukemia. Pooling of data for meta-analysis was restricted only to randomized trials thereby reducing the potential for bias. However, several caveats and limitations remain that can potentially influence the results and interpretations. Transplant registries would have included patients from RCTs as well as individual comparative studies, resulting in them being counted more than once. Despite restricting the meta-analysis to RCTs, significant heterogeneity was present in most comparisons. The total number of patients in the pooled analysis was also limited (730 patients) and not enough to draw robust conclusions. Several changes in the practice of transplantation have occurred over the last two decades, ushering in newer paradigms. Non-myeloablative conditioning regimens are being increas-

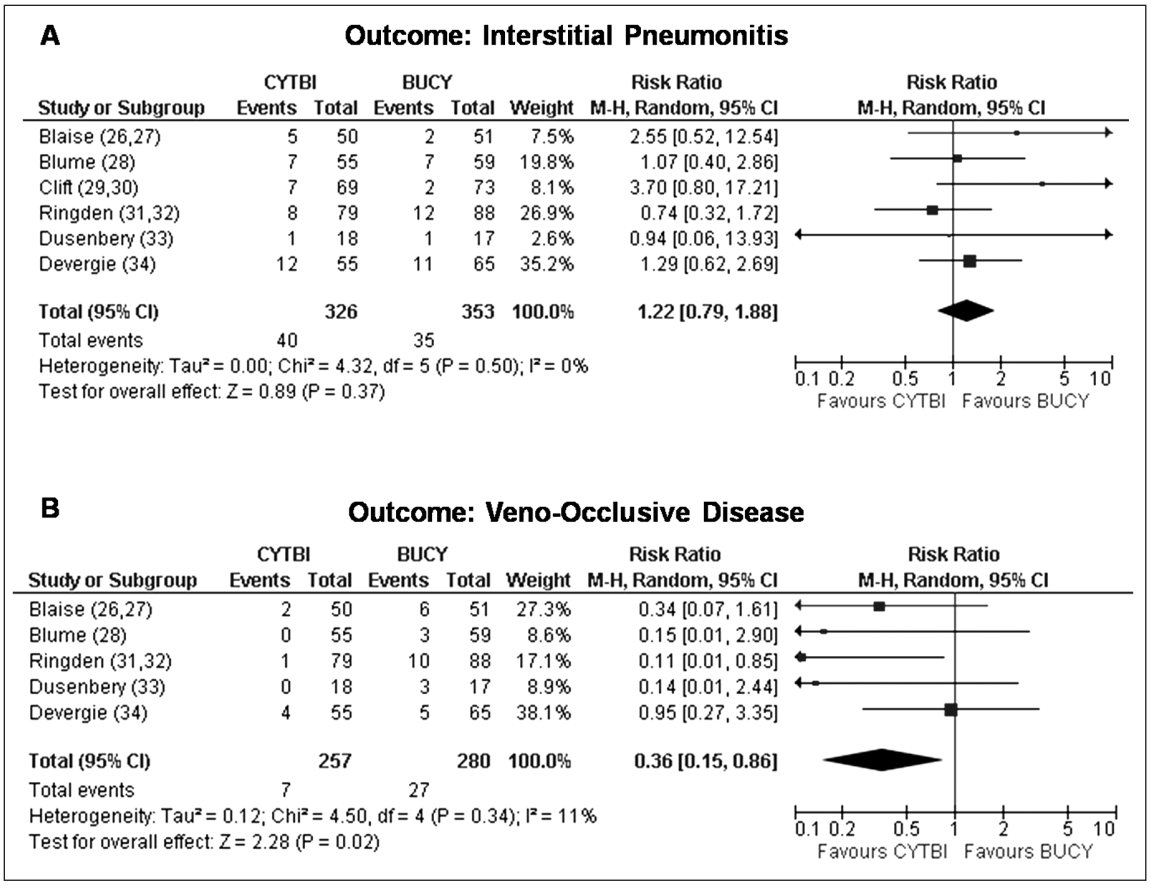

Figure 5. Meta-analysis of interstitial pneumonitis (A) and VOD (B). Note the increased relative risk of lung complications with CYTBI, but decreased risk of VOD as compared to BUCY

ingly used in allogeneic HSCT with impressive and encouraging results.[40] Peripheral blood stem cell transplantation has largely superseded bone marrow as the source of stem cells.[41] Intravenous busulfan with more predictable pharmacokinetics (with individualized dosing), which reduces the risk of VOD by avoiding first-pass metabolism in the liver has a better toxicity profile than oral busulfan and is being used more commonly in BUCY regimen.[42,43] Newer techniques of total marrow irradiation with significantly reduced toxicity[44] have been reported, that can be a suitable alternative to the standard TBI technique. Some of the recent improvements in outcomes can be partially attributed to better supportive care[45] with the use of newer antimicrobials, improved GVHD prophylaxis, and refinements in methodology to identify and modify immune response. None of studies included in this systematic review and meta-analysis involved any of these newer paradigms. Whether the superiority of one regimen over the other will still be relevant in contemporary oncologic practice remains uncertain.

The present analysis that includes all of these trials and their updates confirms the advantage of CYTBI over BUCY using modern meta-analytic methods, and can be considered the most robust evidence to date. Based on the above, it may be difficult to arrive at a definitive conclusion on the superiority of CYTBI over BUCY due to the lack of a large randomized controlled trial. However, given the expected magnitude of benefit, more than 1000 patients would need to be enrolled in such a trial to detect a clinically meaningful difference in survival, which is highly unlikely to happen.

Conclusion

This analysis represents the largest comparison of CYTBI with BUCY as a conditioning regimen prior to HSCT in patients with leukemia that includes retrospective non-randomized studies, matched-pair analyses, as well as randomized clinical trials. High-quality evidence from seven prospective RCTs was pooled together in a meta-analysis for evaluating their

relative efficacy and safety. TRM is significantly lesser with CYTBI compared to BUCY (oral busulfan), but this does not translate into a significant overall survival benefit. There remain valid concerns regarding the late sequelae of TBI, particularly in children. The cumulative incidence of major complications is not significantly different between the two groups; however, specific complications may vary according to the regimen. Although not outrightly superior, the weight of evidence favors CYTBI over BUCY as a first-choice conditioning regimen.

Author contributions

TG concieved the idea, did the literature search and data extraction, helped in analysis, and interpretation, and wrote the manuscript. SK did data extraction and statistical analysis. VD helped with the literature search, data extraction, and manuscript preparation. SL helped with preparation of manuscript and provided critical review. Partially presented and submitted as project work by Ms Vandana Dantkale for Masters of Science (MSc) in Clinical Research.

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