Biol Blood Marrow Transplant 25 (2019) 1695–1700

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Efficacy of Allogeneic Hematopoietic Cell Transplantation in Human T Cell Lymphotropic Virus Type 1–Associated Adult T Cell Leukemia/Lymphoma: Results of a Systematic Review/Meta-Analysis

Madiha Iqbal[1], Tea Reljic[2], Farina Klocksieben[2], Taimur Sher[1], Ernesto Ayala[1], Hemant Murthy[3], Ali Bazarbachi[4], Ambuj Kumar[2], Mohamed A. Kharfan-Dabaja[1,*]

[1] *Division of Hematology-Oncology and Blood and Marrow Transplantation Program, Mayo Clinic, Jacksonville, Florida*
[2] *Program for Comparative Effectiveness Research, Morsani College of Medicine, University of South Florida, Tampa, Florida*
[3] *Blood and Marrow Transplantation and Malignant Hematology Program, University of Florida Health Cancer Center, Gainesville, Florida*
[4] *Department of Internal Medicine, Division of Hematology-Oncology, American University of Beirut, Beirut, Lebanon*

Article history:
Received 8 March 2019
Accepted 23 May 2019

Key Words:
Human T cell lymphotropic virus type 1 (HTLV-1)
HTLV-1–associated adult T cell leukemia/lymphoma (ATLL)
Allogeneic hematopoietic cell transplantation

A B S T R A C T

Human T cell lymphotropic virus type 1 (HTLV1)-associated adult T cell leukemia/lymphoma (ATLL) is an aggressive malignant disorder. Intensive conventional chemotherapy regimens and autologous hematopoietic cell transplantation (HCT) have failed to improve outcomes in ATLL. Allogeneic HCT (allo-HCT) is commonly offered as front-line consolidation despite lack of randomized controlled trials. We performed a comprehensive search of the medical literature using PubMed/Medline, EMBASE, and Cochrane reviews on September 10, 2018. We extracted data on clinical outcomes related to benefits (complete response [CR], overall survival [OS], and progression-free survival [PFS]) and harms (relapse and nonrelapse mortality [NRM]), independently by 2 authors. Our search strategy identified a total of 801 references. Nineteen studies (n = 2446 patients) were included in the systematic review; however, only 18 studies (n = 1767 patients) were included in the meta-analysis. Reduced intensity conditioning regimens were more commonly prescribed (52%). Bone marrow (50%) and peripheral blood (40%) were more frequently used as stem cell source. The pooled post-allografting CR, OS, and PFS rates were 73% (95% confidence interval [CI], 57% to 87%), 40% (95% CI, 33% to 46%), and 37% (95% CI, 27% to 48%), respectively. Pooled relapse and NRM rates were 36% (95% CI, 28% to 43%) and 29% (95% CI, 21% to 37%), respectively. The heterogeneity among the included studies was generally high. These results support the use of allo-HCT as an effective treatment for patients with ATLL, yielding pooled OS rates of 40%, but relapse still occurs in over one-third of cases. Future studies should evaluate strategies to help reduce relapse in patients with ATLL undergoing allo-HCT.

INTRODUCTION

Adult T cell leukemia/lymphoma (ATLL) is a rare aggressive subtype of mature T cell neoplasms [1]. The pathogenic role of human T cell lymphotropic virus type 1 (HTLV-1) in ATLL was later elucidated, corresponding with the endemic distribution of ATLL in Japan, Central Caribbean, tropical Africa, and South America [2–4]. Four clinical subtypes have been proposed based on laboratory values and extent of clinical involvement: acute, lymphoma, chronic, and smoldering [5]. Acute and lymphoma types represent the more aggressive variants, with median survival times of 5 and 10 months, respectively [5].

The overall prognosis of ATLL is generally poor [6]. Use of intensified chemotherapy regimens has not yielded durable responses [7]. A phase III trial comparing the efficacy of a dose-intensified multiagent chemotherapy regimen versus a biweekly combination of cyclophosphamide, doxorubicin, vincristine, and prednisone reported 3-year overall survival (OS) of 24% versus 13%, respectively, but at the expense of higher toxicity [8]. Responses to chemotherapy are further limited by emergence of drug resistance [9]. The combination of zidovudine and IFN-α has also been explored with reportedly high response rates and prolonged survival in newly diagnosed patients with chronic and smoldering subtypes as well as a subset of patients with acute ATLL [10]. Mogamulizimab (anti-CCR4 monoclonal antibody) was

Financial disclosure: See Acknowledgments on page 1700.
* Correspondence and reprint requests: Mohamed A. Kharfan-Dabaja, MD, MBA, FACP, Division of Hematology-Oncology, Blood and Marrow Transplantation Program, Mayo Clinic, 4500 San Pablo Road, Mangurian Building 3rd Floor, Jacksonville, FL, 32224.
E-mail address: KharfanDabaja.Mohamed@Mayo.Edu (M.A. Kharfan-Dabaja).
https://doi.org/10.1016/j.bbmt.2019.05.027
1083-8791/

approved in Japan for treatment of ATLL, resulting in encouraging response rates [11]; however, durability of response remains controversial, with most patients still requiring allogeneic hematopoietic cell transplantation (allo-HCT) for long-term disease control.

Because of a lack of efficacy, autologous HCT is not recommended [12]. Conversely, allo-HCT has shown a beneficial role with near doubling of median disease-free survival compared with conventional chemotherapy [13,14]. A retrospective analysis of a relatively large cohort of patients has shown a 3-year OS of up to 45% [15]. Multiple studies have also shown a bona fide graft-versus-ATLL effect manifested by attainment of complete response (CR) in relapsing patients [15,16]. Because of the relatively advanced age (median age, 60 years) of ATLL patients at the time of diagnosis [4,17], reduced-intensity conditioning (RIC) regimens have been frequently used; nonrandomized comparisons have shown similar outcomes to those receiving myeloablative conditioning allo-HCT [18,19]. Recently, The American Society for Transplantation and Cellular Therapy, formerly known as the American Society for Blood and Marrow Transplantation, published clinical practice guidelines recommending allo-HCT as front-line consolidation in patients with the acute and lymphoma type ATLL [20]. Here, we summarize the results of a systematic review and meta-analysis that assessed the totality of evidence pertaining to the efficacy of allo-HCT in patients with HTLV-1–associated ATLL.

METHODS

Search and Study Selection

According to a predefined protocol, a comprehensive search of the published medical literature was undertaken using PubMed/Medline, EMBASE, and Cochrane databases on September 10, 2018 (Supplemental Table 1). We also performed a manual search of cited references listed on relevant nonsystematic or narrative review articles to identify additional pertinent studies that may have been missed by our search strategy. We did not apply any search limits based on language, country of origin, or type of study (prospective, retrospective from a single center or multiple centers, or registry data), but we excluded studies that were only reported in abstract form.

To be eligible for inclusion, studies must have enrolled ≥10 patients who underwent an allo-HCT for treatment of ATLL. Selection of studies was performed by 2 authors (M.I. and M.A.K.-D.). Disagreements were resolved by consensus with 2 other authors (T.R. and A.K.).

Data Collection

We extracted data on clinical outcomes related to benefits (CR, OS, and progression-free survival [PFS]) and harms (relapse and nonrelapse mortality [NRM]) independently by 4 authors (M.I., H.M., T.R., and M.A.K.-D.). Assessment of the methodologic quality of included studies was performed by 2 authors (T.R. and A.K.) using the Newcastle-Ottawa scale modified for single-arm cohort studies [21].

Statistical Analysis

We calculated proportions for each specific outcome of interest. For the purpose of the meta-analysis, proportions were transformed into quantities according to the Freeman-Tukey variant of the arcsine square root–transformed proportion. The pooled proportion was calculated as the back-transformation of the weighted mean of the transformed proportions using the random-effects model proposed by DerSimonian and Laird [22], which was used to pool data from studies with similar definitions pertaining to study design, study subjects, and aforementioned allo-HCT outcomes [23].

Assessment of Heterogeneity

Heterogeneity among included studies included was assessed by the I^2 test as described by Higgins et al. [24]. Low, moderate, and high heterogeneity were defined as $I^2 < 30\%$, $I^2 > 30\%$, and $I^2 > 60\%$, respectively. All analyses reported in this systematic review were performed using the Stata 14 software (SataCorp LLC, College Station, TX, USA) and the MetapropOne software package [25]. The review is reported in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines [26].

RESULTS

Search Results and Characteristics of Eligible Studies

Our search strategy identified 801 studies (Figure 1). Nineteen studies met our inclusion criteria (allo-HCT, 2446 patients) and were included in this systematic review. Eighteen of 19 studies contributed to the meta-analysis (1767 patients). Detailed characteristics of the eligible studies are shown in Table 1.

Assessment of Methodologic Quality of Included Studies

Risk of bias for the included studies is summarized in Table 2. All but 2 included studies represented retrospective cohort studies [16,19]. These 2 studies represented prospective phase I trials that assessed the clinical impact of the addition of antithymocyte globulin to allo-HCT RIC regimens. Exposure was ascertained from secure records in each study, and adequate measures were taken to ensure that outcomes of interest were not present at the start of each study. All studies had an adequate follow-up time for outcomes of interest to occur (>1 year).

Outcomes

Benefits

The benefits were CR, OS, and PFS. CR after allo-HCT was reported in 8 studies (135 patients). The pooled CR rate was 73% (95% confidence interval [CI], 57% to 87%; I^2 = 68%). OS was reported in 17 studies (1757 patients), and the pooled postallograft OS rate was 40% (95%CI, 33% to 46%; I^2 = 84%). The follow-up of included studies ranged from 1 to 3 years (Table 1, Figure 2). PFS was reported in 7 studies (221 patients). The pooled postallograft PFS rate was 37% (95% CI, 27% to 48%; I^2 = 65%). Follow-up of included studies ranged from 1 to 3 years.

Harms

Harms were relapse and NRM. Relapse was reported in 14 studies (834 patients), and the pooled relapse rate was 36% (95% CI, 28% to 43%; I^2 = 75%) (Figure 3). NRM was reported in 15 studies (1570 patients). The pooled NRM rate was 29% (95% CI, 21% to 37%; I^2 = 90.3%).

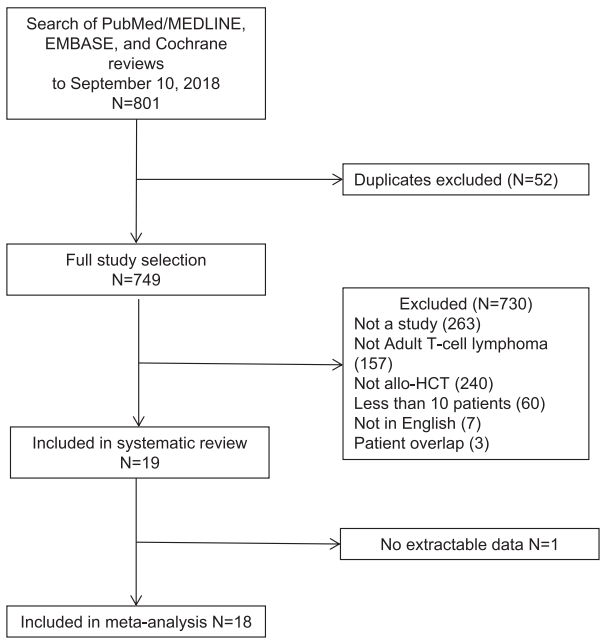

Figure 1. Study selection flow diagram.

Table 1
Characteristics of eligible studies

Author, year of publication [ref]	Number of patients enrolled and no. included in analysis (Gender)	Median age (Range)	Donor status	Cell source	Conditioning regimen	Disease status at time of HCT	Overall survival
Kato et al. 2007 [30]	33 (M = 18, F = 15)	49 (24-59)	MURD = 13, MMURD = 14 ND = 6	BM = 33	MAC = 27, RIC = 6	CR = 13 (CR1 = 11, CR2 = 2), PR = 2, NR = 14, ND = 4	OS = 49.5% (1 year)
Kami et al. 2003 [14]	11 (M = 7, F = 4)	47 (15-59)	MRD = 9, MMRD = 1 MURD = 1	BM = 7, PB = 3 PB and BM = 1	MAC = 9, RIC = 2	CR = 6, PR = 1, NR = 4	OS = 54.5+/-30% (1 year)
Ishida et al. 2012 [18]	586 (M = 315, F = 271)	53 (15-72)	MRD =213, MMRD = 63 MURD = 308 Related with HLA typing unknown = 2	BM+PB = 2, PB = 186, CB = 398	MAC = 280, RIC = 306	CR = 208, Non-CR = 339, Unknown = 39	OS = 36% (3 year)
Fukushima et al. 2011 [31]	10 (M = 4, F = 6)	48 (48-57)	MRD-BM = 3, MRD-PB = 3 MMRD-PB = 1 CB = 3	BM = 3, PB = 4 CB = 3	MAC = 6, RIC = 4	CR = 1, PR = 2, NC = 2, Relapse = 1 PIF = 4	OS = 40% (3 year)
Fukushima et al. 2005 [15]	40 (M = 22, F = 18)	44 (28-53)	MRD = 27, MMRD = 5 MURD = 8	BM = 21, PB = 19	MAC = 39, RIC = 1	CR = 15 (CR1 = 14, CR2 = 1), PR = 13, NC = 3, PD = 9	OS = 45.3% (3 year)
Tanosaki et al. 2008 [19]	14 (M = 9, F = 5)	56 (50-64)	MRD = 14	PB = 14	RIC = 14	CR = 4, PR = 10	OS = 36% (3 year)
Okamura et al. 2005 [16]	16 (M = 9, F = 7)	57 (51-61)	MRD = 16	PB = 16	RIC = 16	Either CR or PR, number not specified	OS = 33.3+/-12.2% (2 year)
Fujiwara et al. 2017 [32]	131*	54	MRD = 38, MMRD = 8 MUD = 55	BM = 55, PB/BM = 38 CB = 30, Not classifed = 8	MAC = 61, RIC = 61 Missing = 9	R1 = 107, R2 = 24	OS = 22% (1 year) OS = 12.5% (3 year)
Fuji et al. 2016 [1]	500*	52	MRD = 374, MMRD = 93 Missing = 33	BM = 164, PB = 336	MAC = 185, RIC = 257, Missing =58	CR = 161, NR = 323, Missing = 16	OS = 32.5% (4 year)
Yonekura et al. 2008 [33]	21 (M = 13, F = 8)	49 (37-62)	Matched = 14, Mismatched = 7	BM = 5, PB = 14, CB = 2	MAC = 10, RIC = 11	CR = 7, PR = 1, SD = 5, PD = 8	OS = 33.2+/-10.9% (3 year)
Shigmatsu et al. 2014 [34]	56 (M = 28, F = 28)	57 (37-69)	MRD = 20, MMD = 14 MURD = 22	BM = 39, PB = 11, CB = 6	MAC = 17, RIC = 39	CR = 23, Non-CR = 33	OS = 55.4% (1 year) OS =46.1% (5 year)
Utsunomiya et al. 2001 [13]	10 (M = 7, F = 3)	43 (33-51)	MRD = 9, MURD =1	BM = 8, PB = 1, BM+PB = 1	MAC = 10	CR = 4, PR = 5, NC = 1	ND
Tokunaga et al. 2017 [35]	70 (M = 40, F = 30)	52 (32-65)	ND	BM = 50, PB = 20	MAC = 50, RIC = 20	CR = 29, PR = 10, SD = 5, PD = 26	OS = 35.2% (3 year)
Bazarbachi et al. 2014 [36]	17 (M = 9, F = 8)	47 (21-67)	MRD = 6, Haploidentical = 3 MURD = 7, Unknown = 1	ND	MAC = 4, RIC = 13	CR1 = 9, PR = 4, Refrac- tory disease = 4	OS = 34.3% (3 year)
Fuji et al. 2018 [37]	132*	61 (25-70)	MRD = 28, MMRD = 14 Unrelated = 55 CB = 43	ND	MAC = 50, RIC = 82	CR = 18, PR = 29, SD = 16, PD = 68	OS = 37.9% (1 year)
Inoue et al. 2018 [38]	76 (M = 35,F = 41)	56 (28-69)	Matched = 49, Mismatched = 27	BM = 44, PB = 31 CB = 1	MAC = 14, RIC = 62	CR = 17, PR = 29, SD = 18, PD = 12	OS = 56.9% (2 year)
Shiratori et al. 2008 [39]	15 (M = 3,F = 12)	57 (41-66)	MRD = 10, MUD = 5	BM = 8, PB = 4, PB+BM = 3	MAC = 5, RIC = 10	CR = 9, PR = 5, PD = 1	OS = 73.3% (3 year)
Kawada et al. 2015 [40]	29 (M = 15, F =14)	55 (32-62)	MRD = 5, MMD = 15 MUD = 9	BM = 14, PB = 14, CB = 1	MAC = 2, RIC = 27	CR = 10, PR = 5, SD = 1, PD = 13	OS = 44.9% (3 year)
Hishizawa et al. 2010 [41]	417, 386 included (M = 209, F = 177)	51 (18-79)	MRD = 154, MMRD = 43 Unrelated = 99, CB = 90	BM = 157, PB = 137, BM+PB = 2, CB = 90	MAC = 114, RIC = 196	CR = 118, Not CR = 246, Unknown = 22	OS = 33% (3 year)

M, Male; F, Female; MURD, Matched unrelated donor; MMURD, Mismatched unrelated donor; ND, Not described; MRD, Matched related donor; MMRD, Mismatched related donor; MMD, Mismatched; BM, Bone marrow; PB, Peripheral blood; CB, Cord blood; MAC, Myeloablative; RIC, Reduced intensity; CR, Complete remission; PR, Partial remission; NR, Non remission; NC, No change; PIF, Primary induction failure; PD, Progressive disease; R1, 1ST Relapse; R2, 2nd Relapse; SD, Stable disease; JSHCT, Japan Society of HCT; JMDP, Japan Marrow Donor Program.

* Gender not specified

Table 2
Risk of bias in included studies

Author, year of publication [ref]	Representativeness of the cohort	Ascertainment of exposure	Outcome not present beginning	Assessment of outcome	Appropriate length of follow-up	Adequacy of follow-up
Kato et al. 2007 [30]	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk
Kami et al. 2003 [14]	Low risk	Low risk	Low risk	Unclear	Low risk	Low risk
Ishida et al. *2012 [18]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Fukushima et al. 2011 [31]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Fukushima et al. 2005 [15]	Unclear	Low risk	Low risk	High risk	Low risk	Low risk
Tanosaki et al. 2008 [19]	Low risk	Low risk	Low risk	Unclear	Low risk	Low risk
Okamura et al. 2005 [16]	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk
Fujiwara et al. 2017 [32]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Fuji et al. 2016 [1]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Yonekura et al. 2008 [33]	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk
Shigmatsu et al. 2014 [34]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Ishida et al.* 2013 [42]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Kanda et al* 2012 [43]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Utsunomiya et al. 2001 [13]	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk
Tokunaga et al. 2017 [35]	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk
Bazarbachi et al. 2014 [36]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Fuji et al. ¥ 2018 [37]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Fuji et al. ¥ 2016 [44]	High risk	Low risk	Low risk	Low risk	Low risk	Low risk
Inoue et al. 2018 [38]	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk
Shiratori et al. 2008 [39]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Kawada et al. 2015 [40]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Hishizawa et al. * 2010 [41]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

Footnote: data were obtained from 22 manuscripts (19 studies).
*, ¥ Manuscripts reporting overlapping cases. In some cases more than 1 manuscript could have been included because they reported on different outcomes of interest.

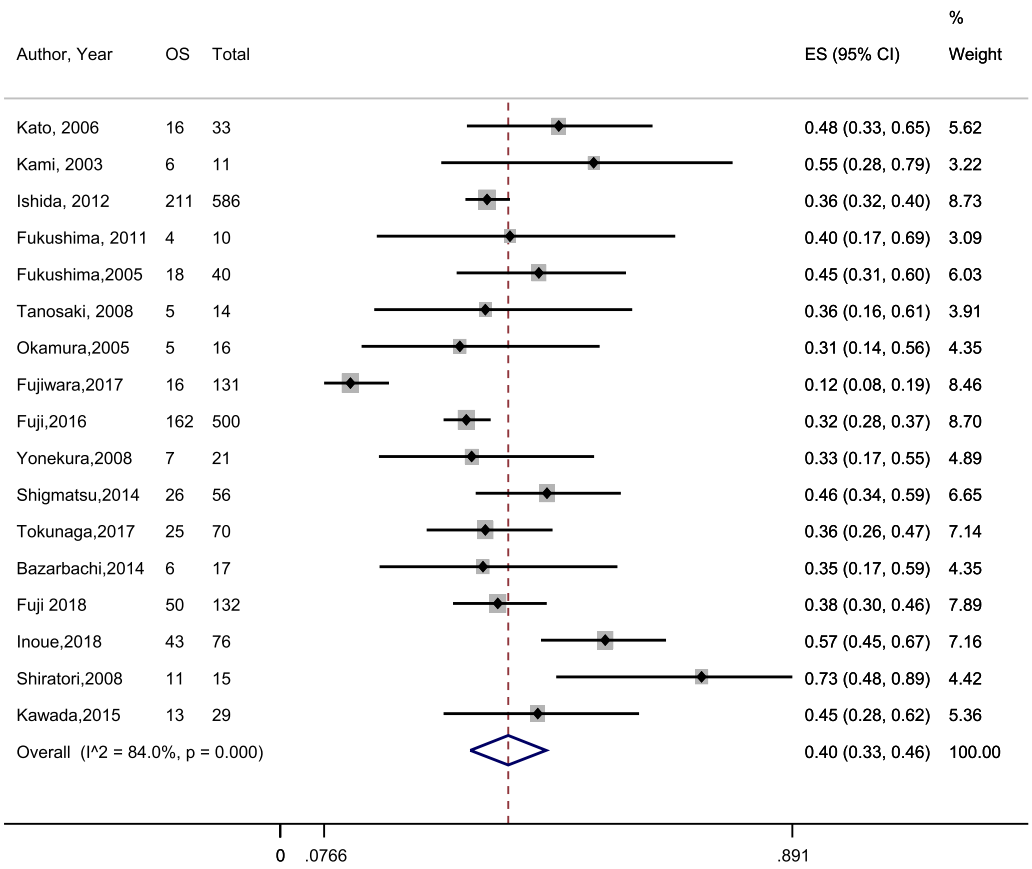

Figure 2. Pooled analysis for overall survival.

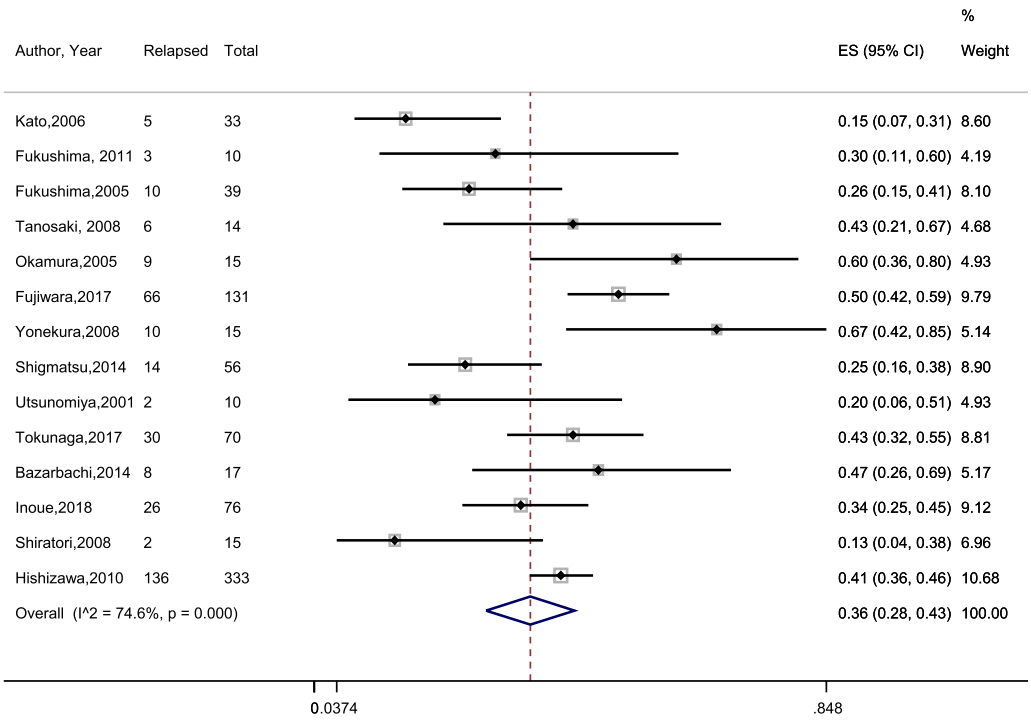

Figure 3. Pooled analysis for relapse.

DISCUSSION

Results of this systematic review and meta-analysis show that in spite of a high pooled CR rate of 73%, the OS after allo-HCT remained below 50%. This is in part explained by the high relapse and NRM pooled rates of 36% and 29%, respectively.

This systematic review also highlights the higher frequency of use of RIC regimens (52%), which is likely explained by the relatively advanced age and frailty of patients undergoing allo-HCT for ATLL [27]. The impact of dose intensity of the conditioning regimen has been studied in nonrandomized controlled trials by Ishida et al. [18], which reported comparable 3-year OS in recipients of myeloablative conditioning (39%) or RIC (34%) regimens. Furthermore, early allo-HCT has been described as a favorable prognostic factor for OS in patients undergoing HLA-matched related allografting [1]. Unfortunately, the aggregate nature of the data used to conduct this systematic review and meta-analysis did not permit assessing the impact (or lack thereof) of time to allo-HCT (early versus late) on OS. Recognizing the limited efficacy of allo-HCT, or other therapies, in the relapsed/refractory setting, the American Society for Transplantation and Cellular Therapy issued clinical practice recommendations strongly favoring the use of allo-HCT in the front-line consolidation setting in patients with acute and lymphoma type ATLL [20].

NRM after allo-HCT for ATLL is high (29%) despite the transplant community favoring the use of less intense preparative regimens. Undergoing a late allo-HCT has also been shown to adversely affect 1-year NRM [1]. In our systematic review and meta-analysis we could not assess the effect of time of allo-HCT (early versus late) on NRM, mostly because these data were not extractable from the identified studies and/or were reported in aggregates. We speculate that several factors such as the need for additional therapies to control disease and the increased risk of infections because of the immune suppressive nature of the disease and/or its treatment play a role in increasing the risk of NRM when allo-HCT is prescribed later in the disease course.

There are several limitations pertinent to our systematic review and meta-analysis. For instance, most patients who underwent an allo-HCT were from Japan, with only 1 registry study from the European Society for Blood and Marrow Transplantation reporting outcomes outside Japan. This could potentially limit the generalizability of these results to developing countries that are known to be endemic with HTLV-1 such as the Caribbean, South America, West Africa, and the Middle East. Additionally, it is unclear whether the disease biology varies in different parts of the world. For example, patients with Afro-Caribbean and South American background have been described to have an earlier age of diagnosis and a more aggressive clinical presentation when compared with their Japanese counterparts [28,29]. A recent study reporting outcomes of patients with ATLL in a single center in the United States identified most patients as immigrants, with only 5 of 195 cases% undergoing allo-HCT [29]. Other limitations include the lack of individual patient data and absence of data regarding pretransplant prescribed therapies. Moreover, this systematic review and meta-analysis includes mostly registry studies or retrospective case series.

Because of the relative rarity of ATLL, the worldwide community should join efforts to develop and conduct international, multicenter, prospective studies evaluating novel therapies, whether as part of the allo-HCT conditioning regimens or as postallograft maintenance strategy, to continue to improve outcomes of this hitherto dreadful disease. It is unlikely that a randomized trial comparing chemotherapy with or without antiviral therapy versus allo-HCT as a consolidative strategy will ever be conducted, in our opinion. Accordingly, the results of this systematic review and meta-analysis represent the best evidence to support the use of allo-HCT in patients with ATLL.

ACKNOWLEDGMENTS

Conflict of interest statement: M.A.K.-D.: consultancy for Pharmacyclics and Daiichi Sankyo; T.S.: Research funding from Janssen

and Incyte corp. All other authors declare no relevant financial conflicts of interest.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at doi:10.1016/j.bbmt.2019.05.027.

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