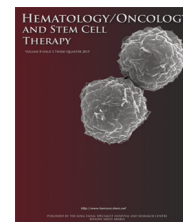




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# Reduced intensity is preferred over myeloablative conditioning allogeneic HCT in chronic lymphocytic leukemia whenever indicated: A systematic review/meta-analysis

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## KEYWORDS

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## Abstract

Despite availability of new and more effective therapies for chronic lymphocytic leukemia, presently this disease remains incurable unless eligible patients are offered an allogeneic hematopoietic cell transplant. Recent published clinical practice recommendations on behalf of the American Society for Blood and Marrow Transplantation relegated the role of for allogeneic hematopoietic cell transplantation to later stages of the disease. To our knowledge, no randomized controlled trial has been performed to date comparing myeloablative versus reduced intensity conditioning regimens in chronic lymphocytic leukemia patients eligible for the procedure. We performed a systematic review/meta-analysis to assess the efficacy of allogeneic hematopoietic cell transplantation when using myeloablative or reduced intensity conditioning regimens. We report the results in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines. Based on lower non-relapse mortality and slightly better overall survival rates, reduced intensity conditioning regimens appear to be

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the most desirable choice whenever the procedure is indicated for this disease. It appears highly unlikely that a RCT will be ever performed comparing reduced intensity vs. myeloablative allogeneic hematopoietic cell transplantation in chronic lymphocytic leukemia. In the absence of such a study, results of this systematic review/meta-analysis represent the best available evidence supporting this recommendation whenever indicated in patients with chronic lymphocytic leukemia.

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## Introduction

Increased availability of novel and more effective therapies for chronic lymphocytic leukemia (CLL) have disrupted traditional treatment algorithms even when high-risk disease features are present [1–5]. A decade ago, the European Society for Blood and Marrow Transplantation (EBMT) published a consensus paper with guidelines indicating optimal timing for allogeneic hematopoietic cell transplantation (allo-HCT) for CLL, recommending the procedure for patients who showed evidence of relapse within 12 months of receiving purine analogue-containing therapy or after failing an autologous hematopoietic cell transplant (HCT) [6]. Moreover, presence of *TP53* mutation and/or Del17p was considered then an indication to offer allo-HCT in the front-line setting [6]. While acknowledging that failure of purine analogue-based regimens remains to this date a prognostic predictor of aggressive clinical behavior, emergence of therapies such as ibrutinib, idelalisib, venetoclax, or others, have proven to be effective in these cases and/or in the presence of other adverse prognostic features [1–5]. For instance, treatment using ibrutinib in heavily pre-treated CLL patients (median of 4 prior lines of therapy), including post-nucleoside analogue failures (95%) showed overall response rates (ORR) of 90% and 30-month

progression-free survival (PFS) of 70% [1,2]. Moreover, venetoclax, an oral, small-molecule BCL2 inhibitor, showed impressive ORR of 79%, mostly partial responses (PR) in a multicenter phase 2 study in Del17p CLL with relapsed or refractory disease [4].

Recent published clinical practice recommendations for allo-HCT for CLL on behalf of the American Society for Blood and Marrow Transplantation (ASBMT) have relegated the role of allo-HCT to later stages of the disease [7]. To our knowledge, no randomized controlled trial (RCT) has been performed to date (and perhaps will never be) comparing myeloablative (MAC) versus reduced intensity (RIC) conditioning allo-HCT regimens in CLL. In fact, RIC regimens are already more commonly used by virtue of necessity considering that CLL patients are generally of advanced age and they have existing comorbidities which would preclude them from receiving MAC regimens. Non-randomized comparisons using registry data from the Center for International Blood and Marrow Transplant Research (CIBMTR) showed a better 3-year probability of survival with RIC allo-HCT regimens (58% vs. 50%,  $p < 0.001$ ) [8]. Here, we describe results of a systematic review and meta-analysis which aimed at assessing the totality of evidence pertaining to efficacy of RIC or MAC allo-HCT in patients with CLL. For the purposes of this analysis, we included non-

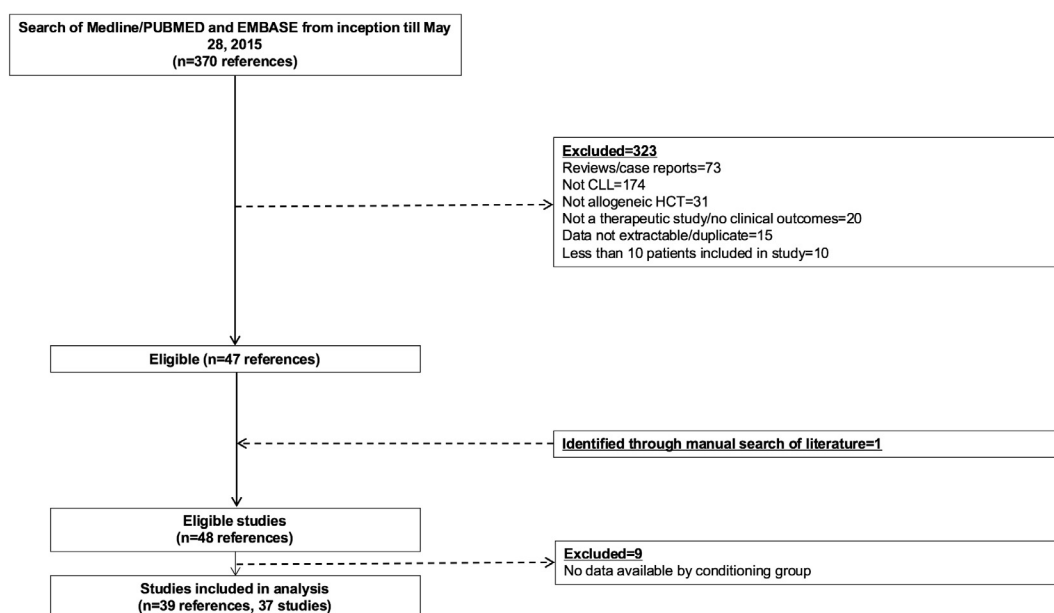


Fig. 1 Study selection process.

**Table 1** Studies of MAC allo-HCT in patients with CLL.

Author (year) [ref]	Study type	N	Median (range) age-years	Median (range) time from Dx to allo-HCT-months	Conditioning regimen	Donor type	Cell source	Median (range) F/U months	OS
Khouri et al. (1997) [28]	Retrospective	15	43 (25–55)	40 (13–119)	CY-TBI (10.2–12 Gy)	MRD = 11 (73%)	BM = 12 PBSC = 2 BM + PBSC = 1	35 (3–60)	56.5% (2-years)
Pavletic et al. (2000) [30]	Retrospective	23	46 (29–60)	19 (4–160)	Various	MRD = 20 URD = 3	BM = 16 PBSC = 7	26 (9–115)	62% (5-years)
Doney et al. (2002) [29]	Retrospective	25	46.6 (14.5–59.4)	Not reported	BUCY or CY-TBI	MRD = 21 Syngeneic = 3 MMRD = 1	BM = 22 PBSC = 3	39.2 (9.5–101.9)	32% (5-years)
Dreger et al. (2003) [22]	Retrospective	77	54 (30–66)	49 (8–146)	Intensive/moderate	Various	Not specified	18 (1–44)	72% (2-years)
Pavletic et al. (2005) [17]	Retrospective	38	45 (26–57)	51 (8–213)	CY-TBI+/- other = 92%	URD = 38	Not specified	72 (36–108)	33% (5-years) (95%CI = 19–48%)
Gribben et al. (2005) [23]	Retrospective	25	47 (28–55)	45 (11–145)	CY-TBI (T-cell depleted)	MRD = 25	BM = 25	Not reported	55% ± 10% (6-years)
Toze et al. (2005) [18]	Retrospective	30	48 (32–59)	57.6 (3.6–156)	CY-TBI = 15 BUCY = 15	MRD = 20 URD = 10	BM = 30	51.6 (28.8–153.6)	39% (20–58%) (4-year)
Pavletic et al. (2007) [19]	Retrospective	19	51 (37–68)	27 (5–171)	TBI-based = 95%	Identical twins = 19	BM = 11 PBSC = 8	89 (31–171)	61% (5-years)
Malhotra et al. (2008) [24]	Retrospective	12	44 (18–55)	60 (11–81)	TBI-based = 10/12	MRD = 10 MUD = 2	PBSC = 2 BM = 10	124 (83–134)	50% (10-years)
Sabloff et al. (2014) [25]	Retrospective	180	48 (24–64)	42 (2–223)	Various	MRD = 180	PBSC = 102 BM = 78	130 (3–175)	42% (5-years)
Machacza et al. (2013) [26]	Retrospective	10	46 (24–53)	53 (8–126)	TBI-based	MRD = 8 MUD = 2	PBSC = 5 BM = 5	138	80% (5-years)
Esteve et al. (1998) [20]	Retrospective	12	39 (29–53)	34 (6–62)	CY-TBI BEAC = 1	NA	BM = 5 PBSC = 7	NA	NA
Michallet et al. (1991) [21]	Retrospective	17	40 (32–49)	41 (5–96)	CY-TBI	MRD = 17	BM = 17	26 (4–48)	NA
Khouri et al. (1997/2002) [27,28]	Retrospective	28	43 (26–58)	Not extractable	CY-TBI = 27 BEAM = 1	MRD = 20 MMRD = 1 MUD = 7	BM = 23 PBSC = 5	66 (18–122)	45% (5-years)

**Abbreviations:** N: number of patients; Dx: diagnosis; F/U: follow up; OS: overall survival; CY: cyclophosphamide; TBI: total body irradiation; MRD: matched-related donor; BM: bone marrow hematopoietic cells; PBSC: G-CSF mobilized peripheral blood stem cells; URD: unrelated donor; BUCY: busulfan plus cyclophosphamide; MMRD: mismatched related donor; MUD: matched-unrelated donor.

**Table 2** Studies of RIC allo-HCT in patients with CLL.

Author (year)	Study type	N	Median (range) age-years	Median (range) time from Dx to allo-HCT-months	Conditioning regimen	Donor type	Cell source	Median (range) F/U months	OS
Schetelig et al. (2003) [47]	Retrospective	30	50 (12–63)	48 (12–204)	FLU-BU-ATG	MRD = 13 MUD = 15 Others = 2	PBSC = 27 BM = 3	24 (7–43)	72% (2 year)
Ritgen et al. (2004) [53]	Retrospective	9	53 (40–63)	44 (8–129)	FLU-CY+/- ATG for URD	Various	PBSC = 9	29 (14–41)	8/9 (med f/u 29 months) 68%
Soligo et al. (2004) [48]	Retrospective	12	55 (45–59)	93.5 (18–161)	FLU-CY-TBI	MRD = 12	PBSC = 12	22 (9–45)	(3-year)
Caballero et al. (2005) [44]	Retrospective	30	53 (35–67)	44 (6–201)	FLU-MEL = 63% others = 37%	MRD = 30	PBSC = 30	47.3 (12–74.6)	72% (5-years)
Khouri et al. (2007) [54]	Retrospective	39	57 (34–70)	54 (24–306)	FLU-CY-Rituximab = 100%	MRD = 32 Others = 7	PBSC = 32 BM = 7	27 (4–80)	48% (4-years)
Ritgen et al. (2008) [45]	Retrospective	37	Prospective 54 (27–65) Retrospective 51 (40–57)	53 (6–270)	FLU-CY+/- ATG for URD	MUD = 18/37	NE	42 (7–70)	71% (3-years)
Sorrer et al. (2008) [31]	Retrospective	82	56 (42–72)	54 (6–296)	TBI (2Gy) +/- FLU	MRD = 52 MUD = 30	NE	NR	50% (5-years)
Delgado-a et al. (2008) [32]	Retrospective	41	52 (37–64)	56 (5–105)	FLU-MEL	MRD = 32 MUD = 5 MMUD = 4	PBSC = 41	46 (6–103)	65% (3-years)
Delgado-b et al. (2008) [32]	Retrospective	21	54 (34–64)	47 (11–132)	FLU-MEL	MRD = 18 MUD = 1 MMUD = 2	PBSC = 21	47 (6–103)	57% (3-years)
Delgado et al. (2009) [55]	Retrospective	37	55 (37–64)	56 (11–129)	FLU-MEL	MRD = 30 MUD = 3 MMUD = 4	PBSC = 37	17 (0–112)	40% (4-years)
Dreger et al. (2010) [40]	Prospective	90	53 (27–65)	57 (2–270)	FLU-CY	MRD = 40% MUD = 13 Others = 32% NA = 15%	PBSC = 87 BM = 3	46 (7–102)	65% (4-years)
Delioukina et al. (2011) [33]	Retrospective	27	53 (38–68)	53.4 (12.8–123.3)	FLU-CY FLU-MEL FLU-TBI	MRD = 15 MUD = 12	PBSC = 24 BM = 3	25.1 (5.8–81.5)	64% (2-years)
Khouri et al. (2011) [52]	Retrospective	86	58 (36–70)	62 (6–307)	FLU-CY-RITUX FLU-MEL-RITUX	MRD = 43 URD = 43	NR	37.2 (11.4–131.1)	51% (5-years)
McClune et al. (2012) [34]	Retrospective	12	53 (43–67)	74 (28–145)	FL-CY-TBI (2Gy)	MRD = 12	NR	37.2 (5–59)	71% (3-years)

McClune et al. (2012) [34]	Retrospective	14	54 (43–67)	75 (28–145)	FL-CY-TBI (2Gy)	Cord blood = 14	Cord blood	37.2 (5–59)	33% (3-years)
Arai et al. (2012) [46]	Retrospective	22	54.4 (31–65)	49.5 (9–195)	TLI + ATG	MRD = 12 URD = 8 MMUD = 2	PBSC = 22	48	73% (4-years)
Machaczka et al. (2012) [51]	Retrospective	38	53 (42–64)	60 (6–144)	Various	MRD = 18 MUD = 11 MMUD = 8 MMRD = 1	PBSC = 37 BM = 1	63 (25–132)	45% (5-years)
Mortensen et al. (2012) [50]	Retrospective	45	58 (34–70)	72.3 (14–208)	NR	MRD = 22 Others = 2 3	PBSC = 44 BM = 1	36 (5–130)	53% (5-years)
Wongergem et al. (2014) [49]	Retrospective	13	55 (46–68)	Not extractable	FLU-CY	MRD = 12 URD = 1	PBSC = 13	67 (19–130)	46% (4-years)
Shaffer et al. (2013) [36]	Retrospective	27	56 (37–71)	58 (17–205)	FLU-CY	MRD = 17 MUD = 8 MMUD = 2	PBSC = 27	32 (13–99)	57% (3-years)
Richardson et al. (2013) [37]	Retrospective	50	53 (32–64)	47 (7.6–156)	FLU-MEL- ALEMTUZUMAB	MRD = 36 MUD = 10 MMUD = 2 MMRD = 2	PBSC = 47 BM = 2 PBSC/BM = 1	40.8 (10.8–98.4)	75% (4-years)
Dreger et al. (2013) [40,41]	Prospective	90	53 (27–65)	NR	FLU-CY	MRD = 36 MUD = 54	PBSC = 90	NR	58% (6-years)
Jagowski et al. (2012) [38]	Retrospective	51	58 (37–73)	Not extractable	FLU-BU+/- ATG = 43 FLU-CY = 8	MRD = 19 MUD = 29 Cord = 2	PBSC = 48 BM = 1 Cord = 2	26 (4–59)	66% (18 months) (Complex = 35% Not Complex = 83%)
Laurenti et al. (2011) [39]	Retrospective	11	57 (49–70)	48 (11–99)	FLU-TBI = 8 Others = 3	MRD = 8 URD = 3	NE	30 (9–65)	73% (2.5 years)
Michallet et al. (2013) [33]	Prospective	40	54 (35–65)	58 (6–177)	FLU-TBI (2Gy)- Rituximab	MRD = 40%, MUD = 13%, Others = 32%	PBSC = 40 Cord blood = 3	28 (3–71)	55% (5-years)
Khouri et al. (2004) [34]	Prospective	17	54 (44–73)	67 (22–168)	FLU-CY+/- Rituximab	MRD = 17 MUD = 8 MMUD = 2	PBSC = 16 BM = 1	21 (11–84)	80% (2-years)
Brown et al. (2006) [39]	Retrospective	46	53 (35–67)	78 (2–176)	FLU-BU = 46	MRD = 15 MUD = 31	PBSC = 45 BM = 1	20 (6–48)	54% (2-years)

*Abbreviations:* N: number of patients; Dx: diagnosis; F/U: follow up; OS: overall survival; FLU: fludarabine; BU: busulfan; ATG: antithymocyte globulin; MRD: matched-related donor; MUD: matched-unrelated donor; PBSC: G-CSF mobilized peripheral blood stem cells; BM: bone marrow hematopoietic cells; CY: cyclophosphamide; URD: unrelated donor; MEL: melphalan; NE: not extractable; NR: not reported; MMRD: mismatched related donor; MMUD: mismatched unrelated donor.

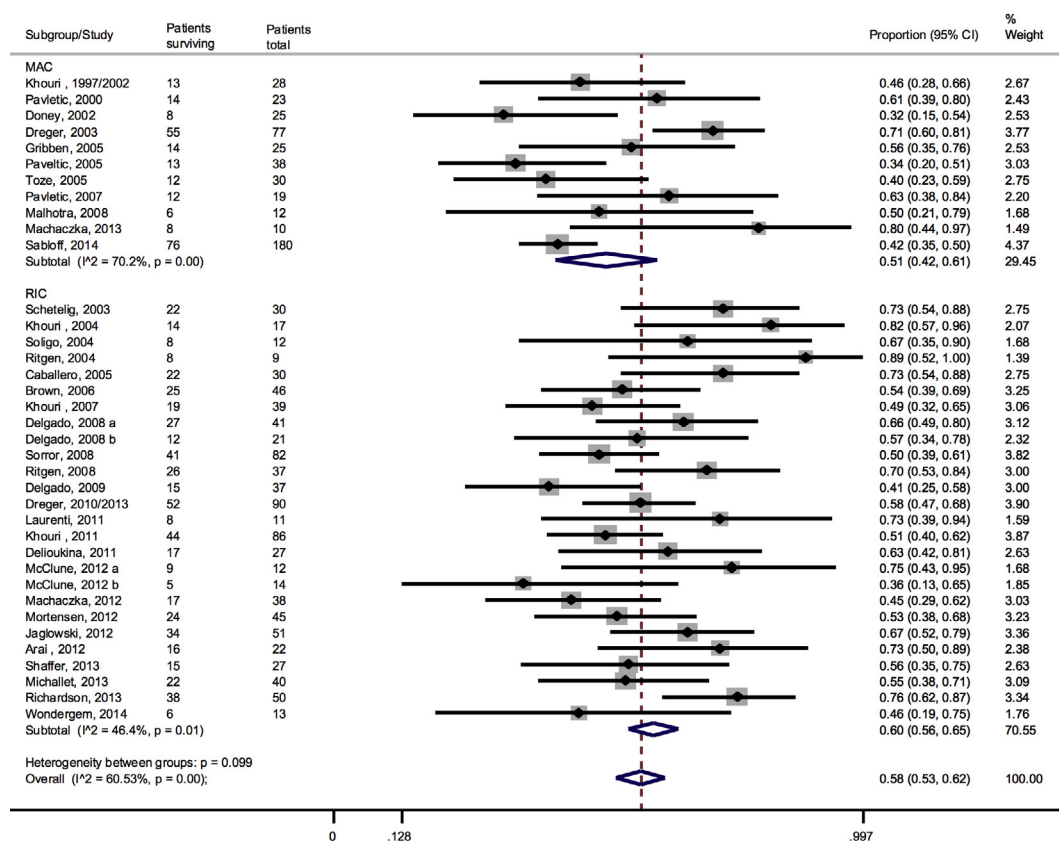


Fig. 2 Pooled results for the outcome of survival.

myeloablative regimens within the broader rubric of RIC regimens [9,10].

## Materials and methods

### Search and study selection

A comprehensive search of published medical literature was performed using PUBMED/MEDLINE and EMBASE databases from date of inception until May 28, 2015 using a MeSH (applicable to PUBMED/MEDLINE) and broadly general text terms (“Leukemia, Lymphocytic, Chronic, B-Cell” [Mesh]) AND “Transplantation, Homologous” [Mesh]). A manual search of references listed on relevant non-systematic/narrative review articles was also done to identify additional studies which may have been missed by our search strategy. No search limits were applied but we excluded studies that were only presented in abstract form.

To be included in the systematic review, studies must have enrolled at least 10 patients with CLL receiving an allo-HCT, regardless of being prospective or retrospective studies, from single or multiple institutions, or from data registries. Selection of studies was undertaken by two authors (M.A.K-D and J.E-A). Disagreements were resolved by consensus with two other authors (T.R and A.K).

### Data collection

Data on variables related to patient’s characteristics, post-transplant clinical outcomes (benefits and harms) and

methodological quality were extracted independently by three authors (M.A.K-D, J.E-A, and T.R). In the absence of individual patient data, we segregated MAC and RIC regimens using definitions from original publications. Assessed benefits included complete remission (CR) rates, event-free (EFS) and/or PFS and overall (OS) survival. Pertaining to harms, we extracted data whenever possible on non-relapse mortality (NRM), grade 2–4 acute graft-versus-host disease (GVHD) and chronic GVHD (all grades). We also assessed the methodological quality of included studies using the Newcastle-Ottawa scale modified for single-arm cohort [11].

### Statistical analysis

Consistent with standard methodology, proportion(s) were calculated for each particular outcome of interest. We used the random effects model [12,13] to pool data from studies with similar definitions pertaining to study design (prospective or retrospective), study subjects, treatment intervention (RIC or MAC allo-HCT) and post-transplant outcomes. We report all results as rates with corresponding 95% confidence intervals (95%CI). Moreover, we assessed heterogeneity using the  $I^2$  test [14]. Heterogeneity was considered moderate if  $I^2 > 30\%$  and high if  $I^2 > 60\%$ . All meta-analyses were performed using StatsDirect version 2.7.8 (Altrincham, UK) [15]. We report results of this systematic review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [16].

## Results

### Summary of search results and characteristics of eligible studies

The implemented search strategy identified a total of 370 references (PUBMED/MEDLINE = 248, EMBASE = 122). One additional study was identified by a secondary manual search of references cited within these articles bringing the total number of references to 371. Forty-eight references met inclusion criteria (N = 1903 patients). Fourteen studies evaluated the efficacy of allo-HCT in the setting of MAC regimens while in 26 studies outcomes following a RIC allo-HCT were reported. In 6 studies, aggregate outcomes were reported without discriminating between

regimens used (i.e. MAC or RIC); and in 2 studies aggregate outcomes were reported for patients with CLL and other hematologic malignancies. The study selection is shown in Fig. 1. Characteristics of treated patients, interventions, and outcomes of included studies are summarized in Tables 1 and 2 for MAC and RIC allo-HCT, respectively.

### Methodologic quality of studies

Table 3 summarizes the methodologic quality of included studies. Briefly, majority of the included studies were classified as low/unclear risk for including a representative sample, ascertainment of treatment, baseline diagnosis, assessment methods, adequate follow-up time and dropouts.

**Table 3** Quality.

Author, year [Ref]	Selection bias			Outcome bias		
	Representative sample	Ascertainment of treatment	Baseline diagnosis	Assessment methods	Follow-up length (months)	Loss to follow-up
Arai, 2012 [46]	Unclear/High risk	Low risk	Low risk	Low risk	48	Low risk
Brown, 2006 [35]	Unclear/High risk	Low risk	Low risk	Low risk	20	Low risk
Caballero, 2005 [44]	Low risk	Low risk	Low risk	Low risk	47.3	Low risk
Delgado, 2008 a/b [32]	Low risk	Low risk	Low risk	Low risk	17	Low risk
Delgado, 2009 [55]	Low risk	Low risk	Low risk	Low risk	47	Low risk
Delioukina, 2011 [33]	Unclear/High risk	Low risk	Low risk	Low risk	25.1	Low risk
Doney, 2002 [29]	Unclear/High risk	Low risk	Low risk	Low risk	39.2	Low risk
Dreger, 2003 [22]	Unclear/High risk	Low risk	Low risk	Low risk	18	Low risk
Dreger, 2010/2013 [40,41]	Unclear/High risk	Low risk	Low risk	Low risk	46	Low risk
Esteve, 2001 [20]	Low risk	Low risk	Low risk	Low risk	NR	Low risk
Gribben, 2005 [23]	Low risk	Low risk	Low risk	Low risk	78	Low risk
Jagłowski, 2012 [38]	Low risk	Low risk	Low risk	Low risk	26	Low risk
Khouri, 1997/2002 [27,28]	Unclear/High risk	Low risk	Low risk	Low risk	66	Low risk
Khouri, 2004 [42]	Unclear/High risk	Low risk	Low risk	Low risk	NR	Low risk
Khouri, 2007 [54]	Unclear/High risk	Low risk	Low risk	Low risk	27	Low risk
Khouri, 2011 [52]	Unclear/High risk	Low risk	Low risk	Low risk	37.2	Low risk
Laurenti, 2011 [39]	Unclear/High risk	Low risk	Low risk	Low risk	30	Low risk
Machaczka, 2013 [26]	Low risk	Low risk	Low risk	Low risk	138	Low risk
Machaczka, 2012 [51]	Low risk	Low risk	Low risk	Low risk	63	Low risk
Malhotra, 2008 [24]	Low risk	Low risk	Low risk	Low risk	124	Low risk
McClune, 2012 a/b [34]	Low risk	Low risk	Low risk	Low risk	37.2	Low risk
Michallet, 1991 [21]	Unclear/High risk	Low risk	Low risk	Low risk	26	Low risk
Michallet, 2013 [43]	Unclear/High risk	Low risk	Low risk	Low risk	28	Low risk
Mortensen, 2012 [50]	Unclear/High risk	Low risk	Low risk	Low risk	36	Low risk
Pavletic, 2005 [17]	Unclear/High risk	Low risk	Low risk	Low risk	72	Low risk
Pavletic, 2000 [30]	Low risk	Low risk	Low risk	Low risk	26	Low risk
Pavletic, 2007 [19]	Low risk	Low risk	Low risk	Low risk	89	Low risk
Richardson, 2013 [37]	Low risk	Low risk	Low risk	Low risk	40.8	Low risk
Ritgen, 2004 [53]	Low risk	Low risk	Low risk	Low risk	29	Low risk
Ritgen, 2008 [45]	Unclear/High risk	Low risk	Low risk	Low risk	42	Low risk
Sabloff, 2014 [25]	Unclear/High risk	Low risk	Low risk	Low risk	130	Low risk
Schetelig, 2003 [47]	Unclear/High risk	Low risk	Low risk	Low risk	24	Low risk
Shaffer, 2013 [36]	Unclear/High risk	Low risk	Low risk	Low risk	32	Low risk
Soligo, 2004 [48]	Unclear/High risk	Unclear/high risk	Low risk	Low risk	22	Low risk
Sorró, 2008 [31]	Unclear/High risk	Low risk	Low risk	Low risk	12.6	Low risk
Toze, 2005 [18]	Unclear/High risk	Low risk	Low risk	Low risk	51.6	Low risk
Wondergem, 2014 [49]	Low risk	Low risk	Low risk	Low risk	67	Low risk

**Table 4** Post-allograft outcomes, pooled rates.

Outcomes	RIC pooled rates (95%CI)	MAC pooled rates (95%CI)
CR	66% (57–74%)	58% (48–67%)
EFS/PFS	46% (41–52%)	41% (32–50%)
OS	60% (56–65%)	51% (42–61%)
NRM	23% (19–27%)	32% (21–44%)
Grade 2–4 acute GVHD	46% (41–52%)	46% (40–52%)
Chronic GVHD (all grades)	55% (46–63%)	59% (46–71%)

*Abbreviations:* RIC: reduced intensity conditioning; MAC: myeloablative conditioning; CI: confidence interval; CR: complete remission; EFS/PFS: event-free survival/progression-free survival; OS: overall survival; NRM: non-relapse mortality; GVHD: graft-versus-host disease.

## Outcomes according to conditioning intensity

Table 4 summarizes results described below.

### MAC allo-HCT

#### CR rates

CR was reported in 5 studies (5 publications, 114 patients) [17–21]. The pooled CR rate was 58% (95% CI = 48–67%). There was no observed heterogeneity between eligible studies included ( $I^2 = 0\%$ ).

#### EFS/PFS

EFS/PFS was reported in 9 studies (10 publications, 419 patients) [17–19,22–28]. The pooled PFS rate was 41% (95% CI = 32–50%). There was high heterogeneity between eligible studies included ( $I^2 = 58\%$ ).

#### OS

OS was reported in 11 studies (12 publications, 507 patients) [17–19,22–30]. The pooled OS rate was 51% (95%CI = 42–61%). The heterogeneity among eligible studies was high ( $I^2 = 70\%$ ).

#### NRM

NRM was reported in 10 studies (11 publications, 356 patients) [18–21,24–30]. The pooled NRM rate was 32% (95%CI = 21–44%). The heterogeneity among eligible studies was high ( $I^2 = 75\%$ ).

#### Acute GVHD (grades 2–4)

Grade 2–4 acute GVHD was reported in 7 studies (8 publications, 390 patients) [17,18,22,24,25,27–29]. The pooled rate of grade 2–4 acute GVHD was 46% (95%CI = 40–52%). The observed heterogeneity among eligible studies was low ( $I^2 = 30\%$ ).

#### Chronic GVHD (all grades)

Chronic GVHD (all grades) was reported in 7 studies (8 publications, 278 patients) [17,21,22,25,27–30]. The pooled rate chronic GVHD (all grades) was 59% (95%CI = 46–71%). The observed heterogeneity among eligible studies was high ( $I^2 = 78\%$ ).

### RIC allo-HCT (prospective only)

#### CR rates

CR rates were reported in 3 studies (4 publications, 147 patients) [31–34]. The pooled CR rate was 74% (95% CI = 66–81%). There was no heterogeneity between studies included for this analysis ( $I^2 = 0\%$ ).

#### EFS/PFS

EFS/PFS was reported in 3 studies (4 publications, 147 patients) [31–34]. The pooled PFS rate was 43% (95% CI = 33–53%). Heterogeneity between studies was low ( $I^2 = 25\%$ ).

#### OS

OS was reported in 3 studies (4 publications, 147 patients) [31–34]. The pooled OS rate was 62% (95%CI = 49–75%; see Fig. 2). Heterogeneity among studies was moderate ( $I^2 = 54\%$ ).

#### NRM

NRM was reported in 3 studies (4 publications, 147 patients) [31–34]. The pooled NRM rate was 24% (95%CI = 17–32%). The heterogeneity among studies was negligible ( $I^2 = 0\%$ ).

#### Acute GVHD (grade 2–4)

Grade 2–4 acute GVHD was reported in 1 study (40 patients) [33]. The reported incidence of grade 2–4 acute GVHD was 45% (95%CI = 29–62%).

#### Chronic GVHD (all grades)

Chronic GVHD (all grades) was reported in 1 study (40 patients) [33]. The reported incidence of chronic GVHD (all grades) was 75% (95%CI = 59–87%).

### RIC allo-HCT (retrospective only)

#### CR rates

CR rates were reported in 9 studies (382 patients) [35–43]. The pooled CR rate was 63% (95% CI = 52–74%). There was high heterogeneity between eligible studies included for this analysis ( $I^2 = 76\%$ ).

#### EFS/PFS

EFS/PFS was reported in 20 studies (769 patients) [35–42,44–54]. The pooled PFS rate was 47% (95% CI = 4

0–53%). There was high heterogeneity between eligible studies included for this analysis ( $I^2 = 65\%$ ).

## OS

OS was reported in 21 studies (780 patients) [35–43,45–55]. The pooled OS rate was 60% (95%CI = 55–65%). Heterogeneity among studies was moderate ( $I^2 = 48\%$ ).

## NRM

NRM was reported in 17 studies (659 patients) [35–40,44–52,54,55]. The pooled NRM rate was 23% (95%CI = 18–28%). Heterogeneity among eligible studies was moderate ( $I^2 = 46\%$ ).

## Acute GVHD (grade 2–4)

Grade 2–4 acute GVHD was reported in 15 studies (596 patients) [35–39,41,43–45,47–50,52,54]. The pooled grade 2–4 acute GVHD rate was 46% (95%CI = 41–52%). The heterogeneity among studies was moderate ( $I^2 = 43\%$ ).

## Chronic GVHD (all grades)

Chronic GVHD (all grades) was reported in 12 studies (471 patients) [35,38,39,41,43–45,48–52]. The pooled chronic GVHD (all grades) rate was 53% (95%CI = 45–61%). The heterogeneity among studies was moderate ( $I^2 = 65\%$ ).

## Discussion

While acknowledging that the role of allo-HCT in CLL has been relegated to later stages of the disease as a result of emergence of more effective therapies, findings of this systematic review/meta-analysis suggest that higher dose intensity, as in MAC regimens, does not appear to confer an advantage in these patients. In fact, using MAC regimens appear to yield lower OS rates when compared to RIC regimens (Table 4). These findings are consistent with published data by CIBMTR which also suggest superior 3-year OS in favor of RIC allo-HCT (58% vs. 50%,  $p < 0.001$ ) [8]. The relatively inferior OS rates with MAC allo-HCT is likely explained by a higher NRM resulting from toxicities associated with high(er) regimen intensity. In our analysis the pooled NRM rates observed with MAC regimens exceeded 30%. Conversely, NRM rates with RIC allo-HCT regimens were lower (23–34%). This is not surprising when considering the high incidence of CLL in older patients who are likely to have age-related comorbidities, hence rendering them more susceptible to toxicities related to ablative doses of chemotherapy or chemoradiotherapy.

Use of myeloablative doses of chemotherapy or chemoradiotherapy is associated with higher incidence of acute GVHD [56,57]. However, in our analysis, we did not observe higher pooled rates of acute GVHD with MAC regimens. This could be explained by several reasons. First, all data from published MAC allo-HCT studies in CLL were from retrospective studies, raising concerns about inherent inaccuracies associated with retrospective attribution of GVHD grading. On the other hand, with advent of RIC regimens, allo-HCTs have become more widely available for patients of more advanced age. Recipient age has been shown to be a known risk factor for developing acute GVHD

[58]. Moreover, the apparent higher rate of chronic GVHD with RIC allo-HCT observed in our analysis is intriguing, but this data were extractable from only one study [33]. In that study, all 40 allo-HCT recipients received G-CSF mobilized PBSC which is a known risk factor for developing chronic GVHD [59–61]. A major limitation of our study is the fact that outcomes for acute and chronic GVHD were not extractable based on used cell source, as these outcomes were reported in aggregate in the majority of published manuscripts. Furthermore, the information provided in the included studies were limited and therefore we could not perform meaningful sensitivity analysis to assess reasons for heterogeneity. Additionally, we included all studies within the study time period (date of inception until May 28, 2015) and did not restrict the search to any particular time period. Accordingly, it is possible that this might have impacted the outcomes as the overall post-allo-HCT management has evolved over the years with improved antimicrobial therapy and better supportive care. Despite these limitations the findings provide the synthesis of all available evidence.

Use of RIC allo-HCT has been shown to yield superior survival in mantle cell lymphoma based on a systematic review/meta-analysis published by our group [62]. Similarly, non-randomized comparative studies appear to favor RIC allo-HCT in patients with diffuse large B cell (DLBC) non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma as well [63–67]. The benefit of RIC allo-HCT regimens (vs. MAC) in regards to lower NRM is countered by a higher incidence of relapse in patients with DLBC NHL [64,67]. This is also the case for patients with Hodgkin lymphoma who undergo RIC allo-HCT regimens [66,67]. Our analysis is limited by the fact that data for relapse was not reliably extractable in a large number of studies included in this systematic review/meta-analysis.

In our opinion, it appears highly unlikely that a RCT will be ever performed comparing RIC vs. MAC allo-HCT for patients with CLL. In the absence of such study, results of this systematic review/meta-analysis represent the best available evidence favoring a RIC allo-HCT whenever indicated in patients with CLL.

## Conflict of interest

None of the authors declare conflict of interest associated with this manuscript.

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