Med Oncol (2013) 30:762
DOI 10.1007/s12032-013-0762-x

ORIGINAL PAPER

High incidence of chronic graft-versus-host disease after myeloablative allogeneic stem cell transplantation for chronic lymphocytic leukemia in Sweden: graft-versus-leukemia effect protects against relapse

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Received: 17 October 2013 / Accepted: 29 October 2013 / Published online: 9 November 2013

Abstract Allogeneic hematopoietic stem cell transplantation (allo-SCT) is a potentially curative treatment option for eligible patients with chronic lymphocytic leukemia (CLL). However, it is known that cure of CLL is only possible if a graft-versus-leukemia effect is present. Between 1994 and 2007, 48 adults underwent allo-SCT for poor-risk CLL in Sweden. Of these, ten (21 %) patients aged 24–53 years (median: 46 years) received myeloablative conditioning (MAC), based on TBI and cyclophosphamide. All MAC patients had refractory, poorly controlled CLL before allo-SCT (partial remission in 9/10 patients and progressive disease in one). The cumulative incidence of acute graft-versus-host disease (GVHD) grades II–IV was 30 %. Nine patients developed chronic GVHD; extensive in four. Rates of nonrelapse mortality at 1, 3 and 10 years were 0, 10 and 20 %, respectively. Two patients relapsed 36 and 53 months after transplantation. Six patients were still alive after a median follow-up time of 11.5 years (range 5.9–13.7). The probabilities of relapse-free and overall survival from 1, 3 and 5 years after transplantation were 100, 90 and 70 %, and 100, 90 and 80 %, respectively. Nevertheless, our analysis of long-term outcome after MAC allo-SCT for CLL suggests that younger patients with poorly controlled CLL may benefit from MAC allo-SCT.

Keywords Allogeneic stem cell transplantation · Chronic lymphocytic leukemia · Myeloablative conditioning · Graft-versus-host disease · Graft-versus-leukemia · Survival

Introduction

B cell chronic lymphocytic leukemia (CLL) is the most common form of leukemia and one of the most frequent lymphoproliferative malignancies in Europe and North America (incidence of 3–6 cases per 100,000 individuals

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per year) [1]. CLL is a heterogeneous disease with a highly variable outcome, and it remains incurable with conventional therapy [2]. Some patients in the early stage of CLL have a life expectancy of more than 10 years and never require treatment, or can be treated effectively with palliative chemotherapy. However, for patients with relapsed or refractory CLL, the median survival time remains less than 3 years [3].

Autologous hematopoietic stem cell transplantation (SCT) may extend survival in CLL, but it is unlikely to be curative [1, 4–6]. The major advantage of allogeneic SCT (allo-SCT) in CLL is the potential for a graft-versus-leukemia (GVL) effect [2]. Since 1998, reduced-intensity conditioning (RIC) has been introduced in an attempt to diminish the nonrelapse mortality (NRM) associated with myeloablative conditioning (MAC) and to improve overall survival (OS) after allo-SCT [7, 8]. Nevertheless, MAC allo-SCT might be preferable in younger patients with poorly controlled CLL [1, 2].

In the present study, we report the long-term outcome of patients who underwent myeloablative allo-SCT for CLL in Sweden, and compare these results with our previously reported results of RIC allo-SCT for CLL [9].

Patients and methods

Between February 1994 and September 2007, 48 consecutive adult patients underwent allo-SCT for poor-risk CLL in Sweden. Of these, ten patients underwent myeloablative allo-SCT at three Swedish centers for hematopoietic stem cell transplantation (Stockholm $n = 7$, Lund $n = 2$, Uppsala $n = 1$) and were included in the study. The patients and their donors were identified by the respective centers and relevant data were collected locally at each participating center from patient files, local registries and the EBMT database. General characteristics of the patients, donors and stem cell sources are presented in Table 1.

Six patients (60 %) had previously been exposed to purine analog therapy (2-CdA in 2 cases and fludarabine in 4 cases). None of the patients had previously undergone autologous SCT. The median time from diagnosis to allo-SCT was 4.4 years. All patients underwent transplantation outside complete remission. Splenomegaly and lymphadenopathy prior to allo-SCT were documented in seven patients. None of them showed bulky lymphadenopathy (≥5 cm). Metaphase analyses were performed on bone marrow (BM) aspirates or peripheral blood (PB) at CLL diagnosis and on BM aspirates before allo-SCT in four patients; none of them presented with an unfavorable cytogenetic profile, defined as the presence of del (17p) and/or del (11q) at any time prior to allo-SCT [10]. Individual patient characteristics are presented in Table 2.

Table 1 Patient, donor and graft characteristics

Characteristic	MAC group ($n = 10$)	RIC group ($n = 38$) [9]
Age	46 (24–53)	53 (42–64)
Sex (M/F)	6/4	27/11
Donor		
Matched related	8 (80 %)	18 (47 %)
Mismatched (1 allele) related	0	1 (3 %)
Matched unrelated[a]	2 (20 %)	11 (29 %)
Mismatched (1 allele) unrelated	0	8 (21 %)
F donor to M recipient	1 (10 %)	11 (29 %)
Number of previous treatment lines	3 (3-4)	3 (1-6)
Previous purine analog exposure	6 (60 %)	35 (92 %)
Status at allo-SCT		
CR	0	4 (11 %)
PR	9 (90 %)	23 (61 %)
PD	1 (10 %)	11 (29 %)
Splenomegaly	3/7 (43 %)	18/38 (47 %)
Lymphadenopathy	2/7 (29 %)	27/38 (71 %)
Bulky ≥ 5 cm	0	3/38 (8 %)
CLL engagement of bone marrow		
≥50 %	1 (10 %)	20 (53 %)
49–10 %	4 (40 %)	4 (10 %)
<10 %	1 (10 %)	9 (24 %)
Not determined	4 (40 %)	5 (13 %)
Cytogenetics		
Del (17p) or del (11q)	0	8 (21 %)
Other than del (17p) or del (11q)	4 (40 %)	5 (13 %)
Not determined	6 (60 %)	22 (58 %)
Time from diagnosis to allo-SCT (years)	4.4 (0.7–10.5)	5 (0.5–12)
Conditioning		
Chemotherapy + TBI	10 (100 %)	11 (29 %)
Chemotherapy	0	27 (71 %)
Stem cell source		
PBSC	5 (50 %)	37 (97 %)
BM	5 (50 %)	1 (3 %)
CD34 dose ($\times 10^6$/kg)	4.1 (0.7–13)	6.85 (2.67–18.5)
GVHD prophylaxis CsA + MTX	10 (100 %)	21 (55 %)

Data are number of individuals (%) or median (range)

M male, *F* female, *allo-SCT* allogeneic stem cell transplantation, *PR* partial remission, *PD* progressive disease, *CLL* chronic lymphocytic leukemia, *TBI* total body irradiation, *PBSC* peripheral blood stem cell, *BM* bone marrow, *GVHD* graft-versus-host disease, *CsA* cyclosporine A and *MTX* methotrexate

[a] HLA-A, HLA-B and HLA-DRβ1 matched-unrelated donor

The study protocol was developed according to the ethical standards of the declaration of Helsinki and approved by the Regional Ethics Review Board in Gothenburg, Sweden.

Table 2 Myeloablative allo-SCT for CLL in Sweden

Pt	Year of Tx	Dx-Tx (years)	Number of previous treatment lines	CLL status at Tx	CLL in BM	Sm	Lgll	Cytogen	Donor	Graft source
F/48	1994	5.6	3	PR	–	–	–	ND	MRD	BM
M/42	1995	4.7	3	PR	–	–	–	ND	MRD	BM
M/49	1996	1.8	3	PR	19 %	Y	N	46,XY	MRD	BM
F/53	1996	3.1	4	PR	28 %	N	N	46,XX	MRD	PBSC
F/52	1997	5.0	3	PR	–	–	–	ND	MRD	BM
F/24	1997	0.7	3	PR	0.1 %	N	N	del19p	MRD	BM
M/49	1997	4.1	3	PR	90 %	N	N	ND	MRD	PBSC
M/45	1999	5.5	3	PR	25 %	Y	N	ND	MRD	PBSC
M/39	1999	10.5	4	PD	–	Y	Y	+11	MUD[a]	PBSC
M/40	2003	2.0	4	PR	29 %	N	Y	ND	MUD	PBSC

Pt	Year of Tx	CD34 dose (10^6/kg)	CMV R/D	EBV R/D	Conditioning	aGVHD (grade)	cGVHD (grade)	Overall survival (months)	Outcome
F/48	1994	2.2	ND	ND	CY/TBI	I	Lim	193	Secondary cancer
M/42	1995	1.5	ND	ND	CY/TBI	I	Ext	23	MOF
M/49	1996	0.7	+/+	+/+	CY/TBI	I	Lim	168+	Alive
F/53	1996	6.0	+/+	ND	CY/fTBI	II	Ext	144+	Alive
F/52	1997	2.0	ND	ND	Flu/CY/TBI	I	Lim	99	PTLD
F/24	1997	1.6	−/+	+/+	CY/TBI	I	Lim	150+	Alive
M/49	1997	7.0	−/−	+/+	CY/TBI	None	Ext	39	Relapse
M/45	1999	13.0	+/+	+/ND	CY/fTBI	II	Lim	133+	Alive
M/39	1999	7.6	−/+	ND	CY/TBI	III	Ext	128+	Alive
M/40	2003	6.2	+/−	+/+	CY/TBI	I	None	70+	Alive

Individual patient characteristics

allo-SCT allogeneic stem cell transplantation, *CLL* chronic lymphocytic leukemia, *Pt* patient (sex/age in years), *F* female, *M* male, *Tx* transplantation (i.e., allo-SCT), *Dx* diagnosis, *Dx-Tx* time period between diagnosis and allo-SCT, *PR* partial remission, *PD* progressive disease, *BM* bone marrow, *Sm* splenomegaly, *Y* yes, *N* no, *Lgll* lymphadenopathy, *Cytogen* cytogenetics, *ND* not determined, *MRD* matched-related (sibling) donor, *MUD* matched-unrelated donor, *PBSC* peripheral blood stem cell, *CMV* cytomegalovirus serology, *R/D* recipient/donor, *EBV* Epstein–Barr virus serology, *CY* cyclophosphamide, *TBI* total body irradiation, *fTBI* fractionated TBI, *Flu* fludarabine, *aGVHD* acute graft-versus-host disease, *cGVHD* chronic graft-versus-host disease, *Lim* limited, *Ext* extensive, *MOF* multiorgan failure and *PTLD* post-transplant lymphoproliferative disease

[a] Female donor to male recipient

Conditioning regimens and GVHD prophylaxis

The conditioning regimens were based on total body irradiation (TBI) and cyclophosphamide (CY; 60 mg/kg i.v. for 2 days) in all patients. In eight patients, TBI was given as a single dose of 10 Gy (with lung shielding), and in two patients, it was fractionated (fTBI; 3 Gy × 4). One patient received fludarabine at 180 mg/m^2 in addition to CY/TBI (Table 2). Two patients who underwent allo-SCT from an unrelated donor were treated with anti-thymocyte globulin (ATG) before transplantation, for in vivo T-cell depletion.

All patients were treated with a combination of cyclosporine A (CsA) and a short course of methotrexate (MTX) for graft-versus-host disease (GVHD) prophylaxis, as previously described [11, 12].

Engraftment and GVHD

The time of neutrophil engraftment was defined as the first of three consecutive days with an absolute neutrophil count (ANC) of >0.5 × 10^9/L, and the time of platelet engraftment as the first of seven consecutive days with an unsupported platelet count of >20 × 10^9/L.

Acute GVHD (aGVHD) and chronic GVHD (cGVHD) were diagnosed on the basis of clinical symptoms and/or findings in tissue biopsy samples from affected sites, according to consensus criteria [13, 14].

Analysis of data

The probabilities of progression-free survival (PFS) and OS were estimated by the method developed by Kaplan and Meier [15] and compared with the log-rank test. The incidences of GVHD, nonrelapse mortality (NRM) and relapse were estimated using a nonparametric estimator of cumulative incidence curves [16]. Patients were censored at the time of death, relapse or last follow-up. Analyses were performed using the cmprsk package (developed by Gray, June 2001), Splus 6.2 software (Insightful, Seattle, WA, USA) and Statistica software (StatSoft, Tulsa, OK, USA).

Comparison of MAC versus RIC allo-SCT for poor-risk CLL in Sweden

The key clinical analyses such as the cumulative incidences of aGVHD and cGVHD, incidence of relapse, rate of NRM, and probabilities of relapse-free and overall survival obtained for the patients who underwent MAC allo-SCT for CLL in Sweden were compared with our published results of RIC allo-SCT for poor-risk CLL [9]. Shortly, the RIC allo-SCT group consisted of 38 adult patients with CLL (Table 1), who between March 1999 and September 2007 underwent allo-SCT after RIC at six Swedish centers for hematopoietic stem cell transplantation, as previously reported.

Results

Engraftment and GVHD

All ten patients engrafted and survived beyond day +100 of allo-SCT. The median times to neutrophil and platelet engraftment were 17 and 20 days, respectively. The cumulative incidence of grades II–IV aGVHD was 30 %, which did not differ from the result observed among Swedish CLL patients who underwent RIC allo-SCT, as previously reported (Fig. 1) [9]. Nine patients (90 %) developed cGVHD. One of them had no prior aGVHD (de novo cGVHD). The cumulative incidence of cGVHD in patients after MAC allo-SCT was significantly higher than in patients who underwent RIC allo-SCT ($P = 0.01$) (Fig. 2). Post-transplantation outcomes are summarized in Table 3.

Nonrelapse mortality and morbidity

Three patients (30 %) died of nonrelapse causes. One patient died of multiorgan failure due to *Staphylococcus* sepsis. One patient developed post-transplant lymphoproliferative disease (PTLD) 7 years after allo-SCT and died 8 months later. One patient developed low differentiated adenocarcinoma of the uterus 14 years after allo-SCT and died of metastatic malignancy almost 2 years later. Nonrelapse mortality rates in the myeloablative and RIC allo-SCT groups did not differ (Fig. 3). Six patients were at risk

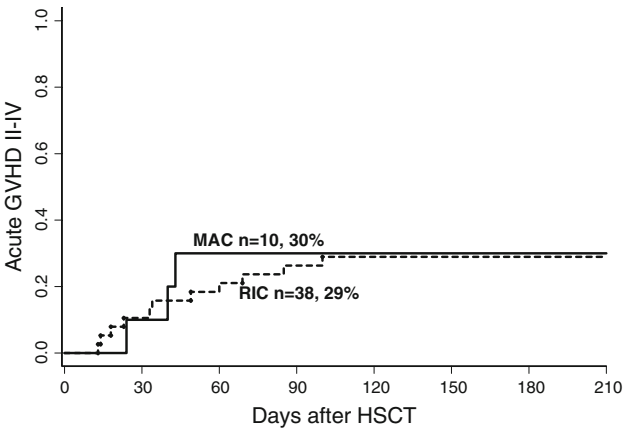

Fig. 1 Acute GVHD grades II–IV after myeloablative conditioning (MAC) *versus* reduced-intensity conditioning (RIC) allo-SCT for poor-risk CLL

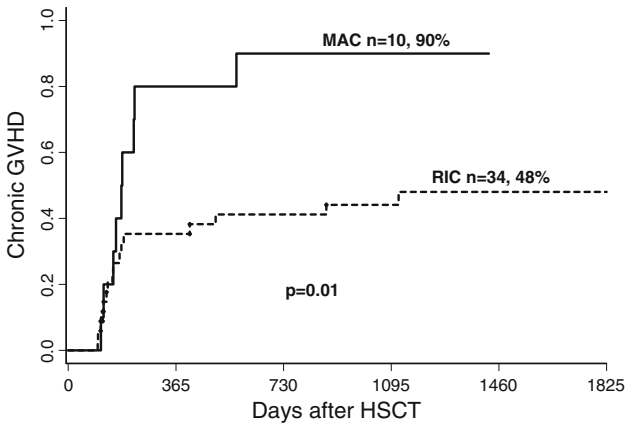

Fig. 2 Chronic GVHD after myeloablative conditioning (MAC) *versus* reduced-intensity conditioning (RIC) allo-SCT for poor-risk CLL

Table 3 Transplantation outcomes MAC group ($n = 10$)

Follow-up of all patients (years after MAC allo-SCT)	11.5 (1.9–16.1)
Follow-up of survivors (years after MAC allo-SCT)	11.5 (5.9–13.7)
Engraftment	
Neutrophils (days to $>0.5 \times 10^9$/L)	17 (12–26)
Platelets (days to $>20 \times 10^9$/L)	20 (13–26)
Acute GVHD	
Grade I	6 (60 %)
Grades II–IV	3 (30 %)
Day of onset	24 (19–49)
Chronic GVHD	
Limited	5 (50 %)
Extensive	4 (40 %)
Day of onset	180 (111–570)
Nonrelapse mortality	
1 year	0 %
3 years	10 %
5 years	10 %
10 years	20 %
Causes of death	
Infection	1 (10 %)
PTLD	1 (10 %)
Secondary cancer	1 (10 %)
Relapse	1 (10 %)

Data are number of individuals (%) or median (range)

MAC myeloablative conditioning, *allo-SCT* allogeneic stem cell transplantation, *GVHD* graft-versus-host disease, *PTLD* post-transplant lymphoproliferative disease

of CMV reactivation (CMV-seropositive donor and/or recipient); four patients developed CMV infection but none of them developed CMV disease.

Disease relapse and progression

Two patients (20 %) suffered relapse, at three and at 4.4 years after transplantation. One of them died of progressive CLL and bacterial sepsis shortly after relapse diagnosis. The other patient was treated with three doses of donor lymphocyte infusion (DLI) and achieved complete remission (CR), but died of PTLD 4 years later. The cumulative incidences of relapse after allo-SCT for CLL stratified by MAC versus RIC did not differ statistically (Fig. 4).

Survival

Six patients (60 %) were still alive after a median follow-up time of 11.5 years. The probabilities of relapse-free and

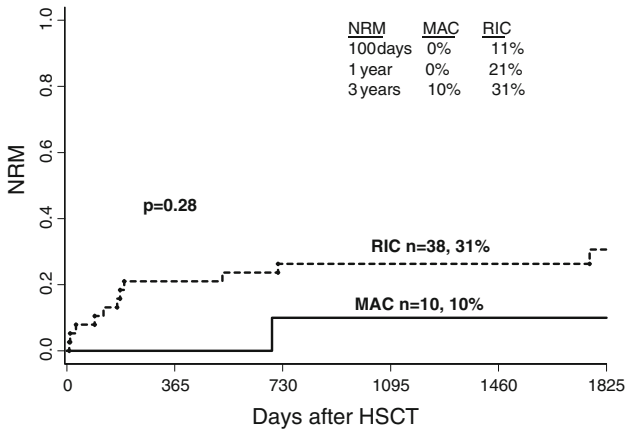

Fig. 3 Cumulative incidence of nonrelapse mortality (NRM) after allo-SCT for poor-risk CLL stratified by myeloablative conditioning (MAC) *versus* reduced-intensity conditioning (RIC)

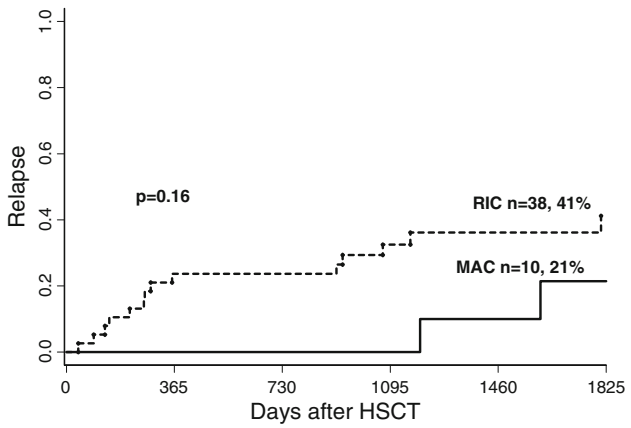

Fig. 4 Cumulative incidence of relapse after allo-SCT for poor-risk CLL stratified by myeloablative conditioning (MAC) *versus* reduced-intensity conditioning (RIC)

overall survival from 1, 3 and 5 years after transplantation were 100, 90 and 70 %, and 100, 90 and 80 %, respectively. The patients who underwent MAC showed better relapse-free ($P = 0.040$) and overall ($P = 0.035$) survival than the patients who underwent RIC (Figs. 5, 6).

Discussion

The results of autologous SCT in CLL have shown that myeloablative therapy alone cannot cure CLL [1, 4, 17, 18]. There is evidence that allo-SCT can cure CLL only if a

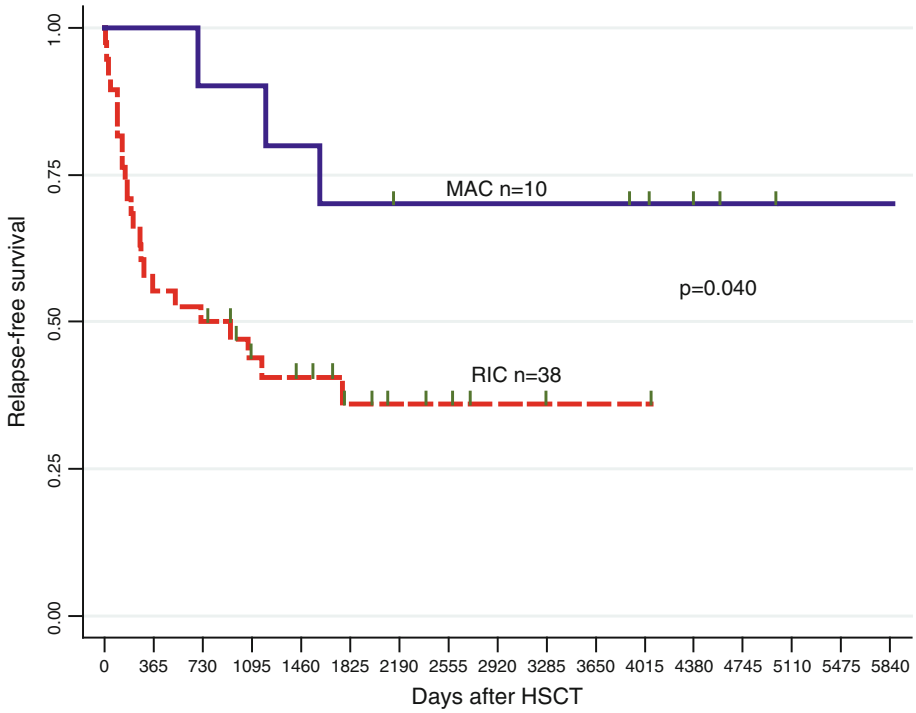

Fig. 5 Probabilities of relapse-free survival in Swedish CLL patients after allo-SCT stratified by myeloablative conditioning (MAC) *versus* reduced-intensity conditioning (RIC)

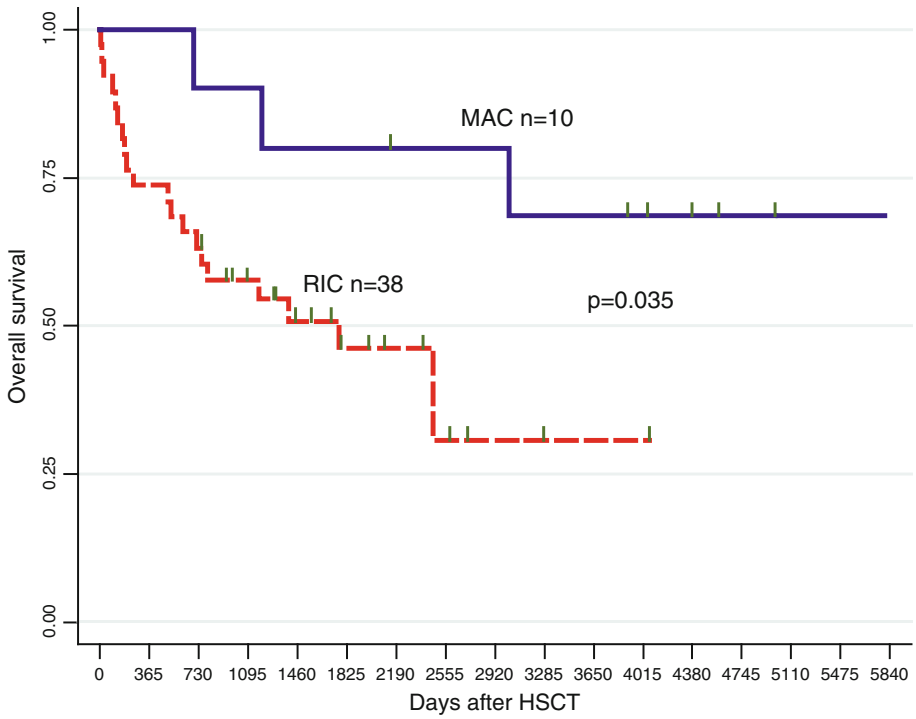

Fig. 6 Probabilities of overall survival in Swedish CLL patients after allo-SCT, stratified by myeloablative conditioning (MAC) *versus* reduced-intensity conditioning (RIC)

GVL effect is present [1, 2]. The presence of a GVL effect in CLL has been confirmed by (1) decreased risk of relapse in patients with cGVHD, (2) increased risk of relapse with T cell depletion and (3) clinical responses to cessation of immunotherapy and to DLI [2].

Studies on myeloablative allo-SCT in CLL have confirmed high CR rates [19–21], but there is also significant NRM of up to 40 % in relatively young patients [4, 20, 22–24]. However, a study of 25 patients with CLL who underwent myeloablative allo-SCT at the Fred Hutchinson Cancer Research Center showed that the NRM rate strongly depended on the type of myeloablative regimen, reaching 57 % at day +100 in patients who underwent conditioning by means of busulfan plus CY, compared with 17 % for patients conditioned with TBI-based regimens [25]. It is noteworthy that in our study all patients received TBI-containing conditioning, and there were no early deaths (i.e., before day +100 after SCT). The first death in our study occurred 23 months after allo-SCT and the median time for death was 5.8 years (range 1.9–16.1 years).

The major prospective goals of RIC for CLL have been reduction in short-term morbidity and mortality together with preservation of a GVL effect [2, 26, 27]. However, the major concern regarding RIC allo-SCT in CLL is whether or not nonmyeloablative conditioning regimens have the ability to overcome advanced disease and keep relapse rates at acceptably low levels [1]. Thus, the stronger direct cytotoxic activity of MAC compared with RIC may be beneficial in CLL patients without satisfactory disease control.

The present study is the first Swedish retrospective analysis of the long-term results of MAC allo-SCT in CLL. The patients were treated outside clinical trials in the everyday clinical practices of the national health-care system. In this study, all patients had poorly controlled CLL before they underwent MAC allo-SCT, despite 3–4 therapy lines used before transplantation. Of note, they underwent transplantation in a relatively good performance status (e.g., none of them had bulky lymphadenopathy). Interestingly, a significant proportion of our patients (90 %) developed cGVHD, this being extensive in four of them (40 %). The treatment resulted in significantly better disease control, with increased relapse-free and overall survival due to a GVL effect, compared with RIC allo-SCT. One can speculate why our MAC patients developed more cGVHD (and GVL effects) but not NRM. A possible explanation could be the lack of anti-CD52 antibodies and fludarabine (with the exception of one patient) in the conditioning regimens we used. However, another explanation may be the size of the study.

The present results must be interpreted with caution, for several reasons. The number of analyzed patients was small, although the long follow-up time of our MAC patients strengthens the value of the obtained results. The median age of the RIC patients was 7 years higher than that of the MAC patients (53 vs. 46 years) [9]. Although the cytogenetic profile of the MAC group was incomplete, no patients were detected with del (17p), indicating that the RIC patients had a more unfavorable CLL cytogenetic profile than the MAC patients. The patient groups differed with respect to prior exposure to purine analogs: 60 % (6/10) in the MAC patients and 92 % (35/38) in the RIC patients.

According to the European Group for Blood and Marrow Transplantation (EBMT) consensus published in 2007, allo-SCT is a reasonable treatment option for eligible patients with previously treated, poor-risk CLL [28]. Poor-risk CLL is defined by EBMT as a disease refractory to purine analogs, or relapse at <12 months after purine analog-based therapy, or relapse at <24 months after purine analog combinations or autologous SCT, or the presence of del (17p)/p53 deletion. The great majority of MAC patients in our study (90 %) had undergone transplantation before 2000, which was before the purine analog era as regards CLL. On the other hand, this also meant relatively poor availability of cytogenetic data (40 % of patients), because of different CLL work-up routines at that time.

Currently, myeloablative allo-SCT for CLL is recognized as being associated with unacceptable toxicity and mortality, and it is therefore generally not recommended [1, 2, 29]. Today's patients with CLL who proceed with allo-SCT have more unfavorable cytogenetic profiles and/or they are more heavily pre-treated with purine analog-based therapy and monoclonal antibodies (e.g., anti-CD20 antibodies, anti-CD52 antibodies) than in the present study [9]. They are more vulnerable to myeloablative conditioning prior to allo-SCT and could have difficulty to tolerate this treatment option. However, the long-term follow-up results of our study suggest that younger patients with poorly controlled CLL, but with good performance status may benefit from MAC allo-SCT. Thus, we suggest that besides the common acceptance of the preferable use of RIC allo-SCT in poor-risk CLL, the optimal choice of conditioning regimen should be individualized with the option of MAC in selected cases.

Acknowledgments We acknowledge Nick Bolton, PhD for linguistic expertise.

Conflict of interest The authors report no conflict of interest in this study.

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