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ARTICLE

Outcomes of haploidentical stem cell transplantation for chronic lymphocytic leukemia: a retrospective study on behalf of the chronic malignancies working party of the EBMT

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Abstract

Allogeneic hematopoietic stem cell transplantation (HCT) may result in long-term disease control in high-risk chronic lymphocytic leukemia (CLL). Recently, haploidentical HCT is gaining interest because of better outcomes with post-transplantation cyclophosphamide (PTCY). We analyzed patients with CLL who received an allogeneic HCT with a haploidentical donor and whose data were available in the EBMT registry. In total 117 patients (74% males) were included; 38% received PTCY as GVHD prophylaxis. For the whole study cohort OS at 2 and 5 yrs was 48 and 38%, respectively. PFS at 2 and 5 yrs was 38 and 31%, respectively. Cumulative incidence (CI) of NRM in the whole group at 2 and 5 years were 40 and 44%, respectively. CI of relapse at 2 and 5 yrs were 22 and 26%, respectively. All outcomes were not statistically different in patients who received PTCY compared to other types of GVHD prophylaxis. In conclusion, results of haploidentical HCT in CLL seem almost identical to those with HLA-matched donors. Thereby, haploidentical HCT is an appropriate alternative in high risk CLL patients with a transplant indication but no available HLA-matched donor. Despite the use of PTCY, the CI of relapse seems not higher than observed after HLA-matched HCT.

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Introduction

High risk relapsed/refractory (R/R) CLL patients can nowadays be treated with novel agents targeting various kinases downstream of the B-cell receptor. The median progression-free survival (PFS) on the BTK-inhibitor ibrutinib for R/R CLL patients with del(17p) is 26 months (95% CI 18–37) with an estimated 1-year PFS of 80%, while for all other patients median PFS is at least twice as long [1, 2]. Two-third of these progressive patients have only CLL, the remainder have a Richter's transformation at the time of progression. These latter patients nowadays still have a very poor prognosis [3]. Patients failing ibrutinib with CLL can subsequently be treated with idelalisib which results in an overall response of approximately 35% and a median PFS of 9 to 12 months [4, 5], or the BCL2 inhibitor venetoclax which results in an overall response of approximately 70% and a median PFS that had not been reached yet in two studies although with a relatively short follow-up (<12–14 months) [5, 6]. Treatment options in case of refractoriness of ibrutinib, idelalisib, and venetoclax are scarce and the outcome is poor.

Allogeneic hematopoietic stem cell transplantation (alloHCT) may be a valuable option for fit high risk patients with CLL with del(17) or TP53 mutation or when refractory to one or more of the new agents. An alloHCT is currently the only treatment able to achieve longer-lasting PFS especially in the many patients that achieve MRD-negativity [7] and its effect is not influenced by the presence of del(17p), TP53 or other high risk molecular abnormalities [8, 9]. The fact that MRD-negativity typically occurs during or after tapering of post-transplantation immunosuppression and/or in the context of chronic graft vs. host disease (GVHD) suggests an actual graft vs. leukemia effect [10–12].

In several retrospective registry studies 5-year PFS and overall survival (OS) after alloHCT for CLL were 36 to 46% [13, 14]. In most patients in these studies HLA-identical donors were used. Approximately 15 to 20% of patients lack a HLA-identical sibling or fully HLA-matched unrelated donor, but very few publications addressed the issue of using alternative donor sources for alloHCT in CLL. The use of HLA-mismatched unrelated donors for CLL patients reduces 3 and 5-year overall survival when compared to HLA-matched related or unrelated donors as a result of increased non-relapse mortality [15], while umbilical cord blood transplantation resulted in almost comparable 3-year overall survival compared with HLA-matched transplantations [16]. These effects on outcome of a lower degree of HLA matching between donor and patient are seen in various other hematological malignancies too [17].

In recent years the use of haploidentical donors has substantially increased because the use of post-transplantation cyclophosphamide (PTCY) after T-cell replete stem cell transplantation effectively prevents severe acute GVHD in the majority of patients while retaining T-cell mediated anti-infectious immunity resulting in an acceptably low NRM (11–14% after 1–4 years) and PFS in various hematological malignancies [18, 19]. These results seem comparable or only slightly inferior to outcome after matched unrelated donor transplantations [20] and matched sibling donor transplantations [17], even though prospective randomized trials are lacking. Up to now no study specifically focused on the outcome of haploidentical HCT in CLL patients, while some larger series reporting on haploidentical HCT with PTCY contained only a few patients with CLL [17, 21–23].

We now report for the first time on the results of alloHCT with haploidentical donors in CLL with special emphasis on the effect of PTCY on relapse given the requirement of active donor immune cells for an operative graft-vs.-leukemia effect.

Methods

Study design: patients and definitions

All patients aged 18 years or older with CLL who received a first alloHCT with a related haploidentical donor and whose data were available in the European Society for Blood and Marrow Transplantation database between November 1984 and February 2016 were included in this study. All patients provided informed consent for the registration and the alloHCT, according to the Declaration of Helsinki.

The primary endpoint was to describe PFS after haploidentical HCT, defined as time from alloHCT to relapse, disease progression, or death. The 2 and 5 years after alloHCT landmarks were selected for reporting point-estimates. Secondary endpoints were the probability of OS, defined as the probability of survival regardless of disease state in any point of time; acute GVHD at day 100; relapse or progression; and non-relapse mortality (NRM), defined as death without previous relapse or progression.

The intensity of the conditioning was based on the reported dosage of drugs and TBI and categorized according to published guidelines [24].

Statistical analysis

Median values and ranges are reported for continuous variables and percentages for categorical variables. The probabilities of OS and PFS were calculated using the

Table 1 Patient characteristics

Parameter	Classification	All patients ($n = 117$) N (%)	PTCY ($n = 40$) N (%)
Patient gender ($n = 117/n = 40$)	Male	86 (74)	27 (68)
	Female	31 (26)	13 (32)
Median Age at alloHCT [years] ($n = 117/n = 40$)	Median (range)	53.5 (27–71)	56.5 (27–68)
Karnofsky Index ($n = 98/n = 36$)	≥70	94 (96)	35 (97)
	<70	4 (4)	1 (3)
Interval CLL diagnosis—alloHCT [months] ($n = 117/n = 40$)	Median (range)	67 (4–207)	59 (5–156)
Previous autologous HCT ($n = 116/n = 40$)	Yes	18 (16)	6 (15)
	No	98 (84)	34 (85)
Remission Status at alloHCT ($n = 110/n = 38$)	Complete Remission	17 (16)	10 (26)
	Partial Remission	43 (39)	15 (40)
	Stable disease	15 (13)	5 (13)
	Progressive disease	35 (32)	8 (21)

Table 2 Transplantation characteristics

Parameter	Classification	All patients N (%)	PTCY N (%)
Year of alloHCT ($n = 117/n = 40$)	1984–1999	10 (9)	0
	2000–2004	18 (15)	0
	2005–2009	23 (20)	0
	2010–2016	66 (56)	40 (100)
Stem cell source ($n = 117/n = 40$)	PB	79 (68)	17 (42)
	BM	38 (32)	23 (58)
Conditioning regimen ($n = 112/n = 39$)	MAC	47 (42)	17 (44)
	RIC	65 (58)	22 (56)
Recipient-Donor sex-match ($n = 116/n = 39$)	Patient male – Donor male	54 (46)	15 (38)
	Patient male – Donor female	31 (27)	11 (28)
	Patient female – Donor male	16 (14)	8 (21)
	Patient female – Donor female	15 (13)	5 (13)
Recipient CMV-status ($n = 93/n = 37$)	Patient negative	19 (20)	4 (11)
	Patient positive	74 (80)	33 (89)
Donor CMV-status ($n = 92/n = 37$)	Donor negative	37 (40)	15 (41)
	Donor positive	55 (60)	22 (59)

Kaplan–Meier method and 95% confidence intervals are given. A log-rank test was used for univariate comparisons. *P*-values <0.05 were considered statistically significant.

Relapse/progression, NRM and acute GVHD were analyzed in a competing risk framework [25]. The outcomes of the patients with and without PTCY were compared using a Gray's test. Statistical analyses were performed using SPSS 23 and R 3.1.0, packages "survival" and "cmprsk".

Results

Baseline patient and disease characteristics

Patient and disease characteristics are summarized in Table 1. One-hundred-seventeen patients with CLL (74%

males) underwent a mismatched related donor transplantation between 1984 and 2015 (1984–1999: 10, 2000–2004: 18, 2005–2009: 23, 2010–2016: 66). Median follow up of patients alive after HCT in the whole cohort was 37.6 months (range 2–187 months); the median follow up of the patients alive after HCT with PTCY was 30.5 months (range 2–67 months). Median age at transplantation was 54 years (yrs) (range 27–71 yrs). Median time from diagnosis to HCT was 67 months (range 4–207 months). Eighteen patients (15%) had previously undergone autologous HCT (ASCT). Disease status at HCT was complete remission (CR) in 16%, partial remission (PR) in 39%, stable disease (SD) in 13% and progressive disease (PD) in 32%. Karnofsky score was known for 98 patients (84%), of these 96% had a score of 70 or more at the time of HCT.

Baseline transplantation characteristics

Transplantation characteristics are summarized in Table 2. Fifty-eight percent of patients received reduced-intensity conditioning, 42% myeloablative conditioning. Peripheral blood stem cells were used in 68% of patients, bone marrow in 32%. HCT was sex-matched in 59% of recipient-donor pairs. Forty patients (38%) received PTCY as GVHD prophylaxis. The characteristics of those patients are specified in Tables 1 and 2. Confounders were equally spread amongst patients with and without PTCY, except all the patients with PTCY were transplanted in the latest time period. In the other 77 patients various other methods of GVHD prevention were used, for example in vitro T cell depletion, ATG and alemtuzumab.

Transplantation Outcomes

Graft vs. host disease (GVHD)

The cumulative incidence (CI) of acute GVHD at 100 days was 32% for grade II-IV and 16% for grade III-IV with a median time of onset of 23 days (range 4–57 days). The CI of acute GVHD at 100 days with or without PTCY were similar for grade II-IV (28 vs. 31%, $p = 0.59$). The CI of severe acute GVHD (grade III/IV) were also not significantly different with or without the use of PTCY (11 vs. 17%, $p = 0.37$).

Non-relapse mortality (NRM)

Forty-seven patients experienced non-relapse mortality, causes of death were mostly transplantation-related (26 died of infection, 11 of GVHD, 2 of organ failure, 2 of toxicity, 2 of myocardial infarction, 1 of a secondary malignancy, 1 of a cerebral lesion of unknown origin, 1 of bleeding, 1 unknown HCT related). The cumulative incidence of NRM at 2 yrs was 40% (95% CI 30–50%) and at 5 yrs 44% (95% CI 34–54%). The CI of NRM and at 2 and 5 yrs were not statistically different in patients who received PTCY compared to other types of GHVD prevention (NRM: 39% (95% CI 23–55%) vs. 42% (95% CI 29–55%) at 2 yrs, 43% (95% CI 26–60%) vs. 47% (95% CI 33–60%) at 5 yrs, $p = 0.72$).

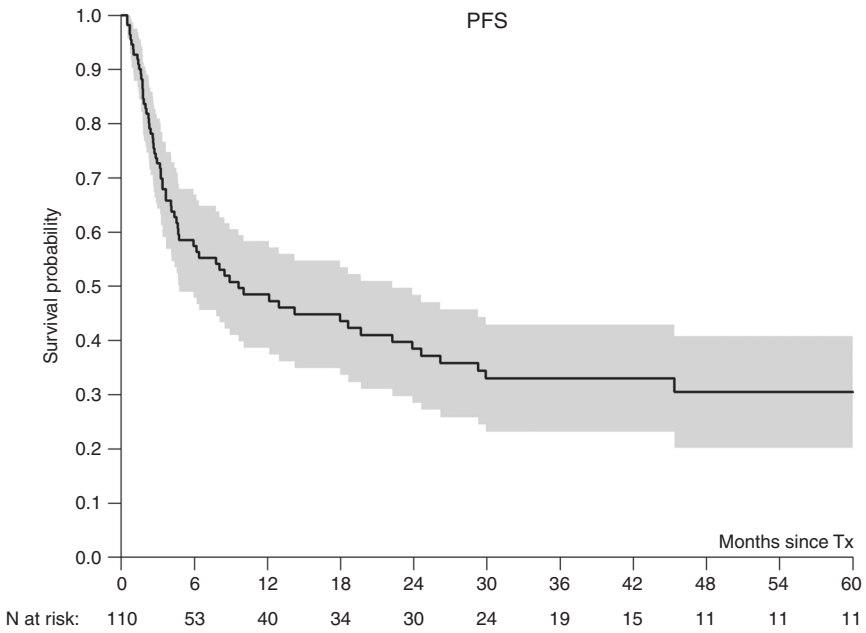

Fig. 1 PFS after mismatched related HCT for CLL

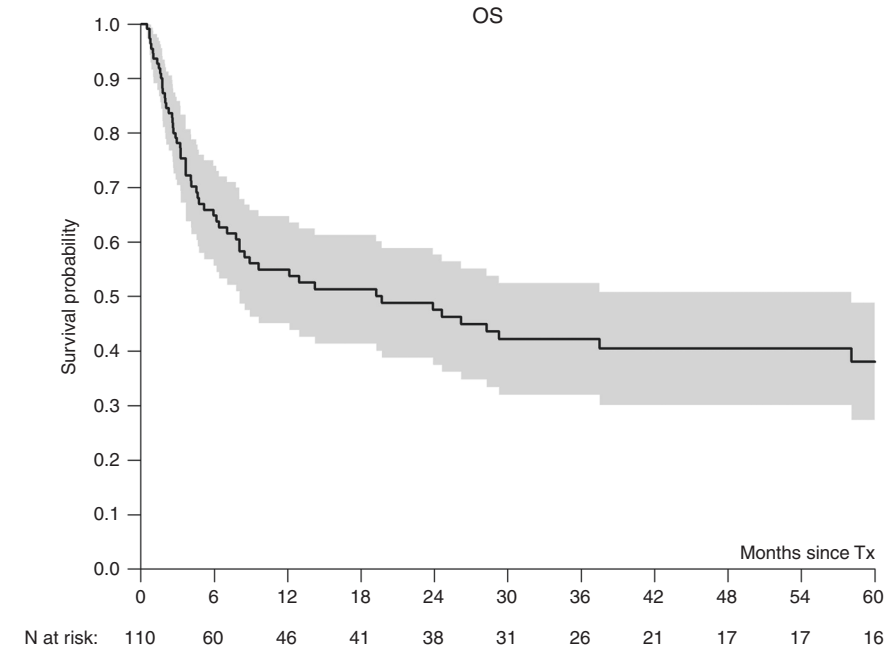

Fig. 2 OS after mismatched related HCT for CLL

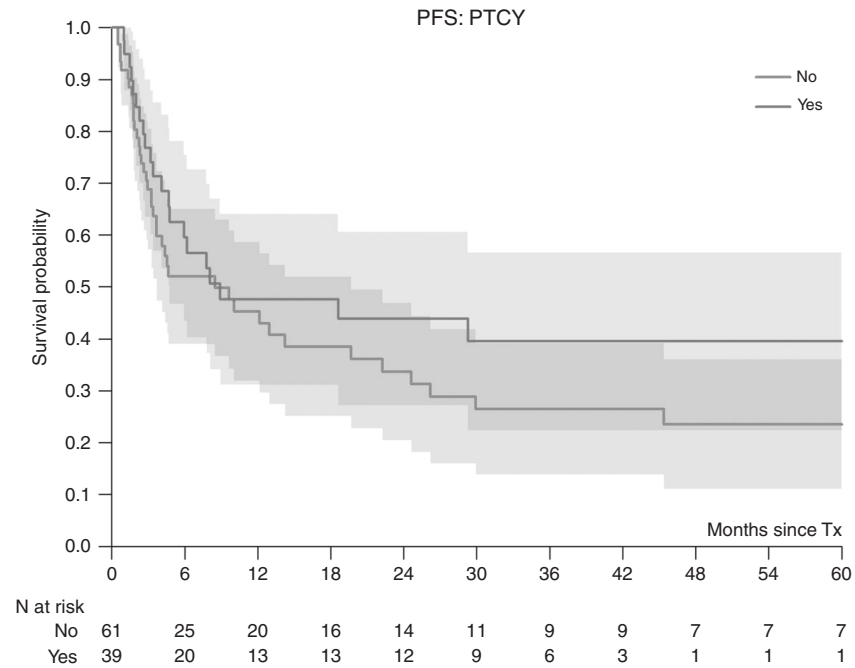

Fig. 3 PFS according to use of PTCY. (Color figure online)

Relapse or progression

The cumulative incidence of relapse or progression at 2 and 5 yrs were 22% (95% CI 13–30%) and 26% (95% CI 16–35%), respectively. Median time to relapse or progression was 3.4 months (range 0.5–118.2 months).

The cumulative incidence of relapse at 2 and 5 yrs were not statistically different in patients who received PTCY compared to other types of GVHD prevention (17% (95% CI 4–30%) vs. 25% (95% CI 13–36%) at 2 yrs, 17% (95% CI 4–30%) vs. 30% (95% CI 17–43%) at 5 yrs, $p = 0.34$).

Overall, 25 patients relapsed or progressed after mismatched related HCT. Of these patients, 8 were alive at last follow-up and 17 died.

Overall survival (OS) and progression-free survival (PFS)

The probabilities of OS at 2 and 5 yrs were 48% (95% CI 37–58%) and 38% (95% CI 27–49%), respectively (Fig. 1).

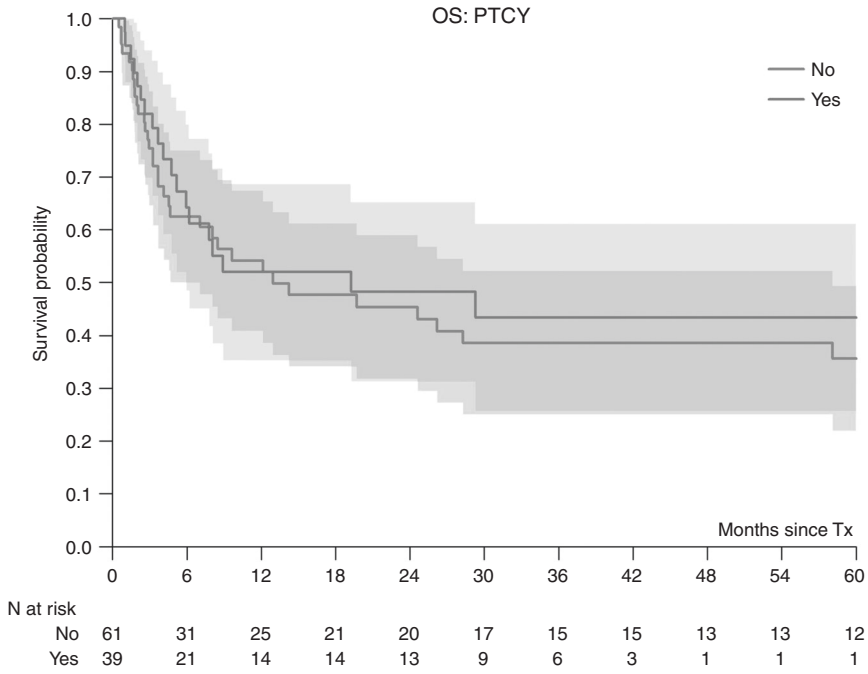

Fig. 4 OS according to use of PTCY. (Color figure online)

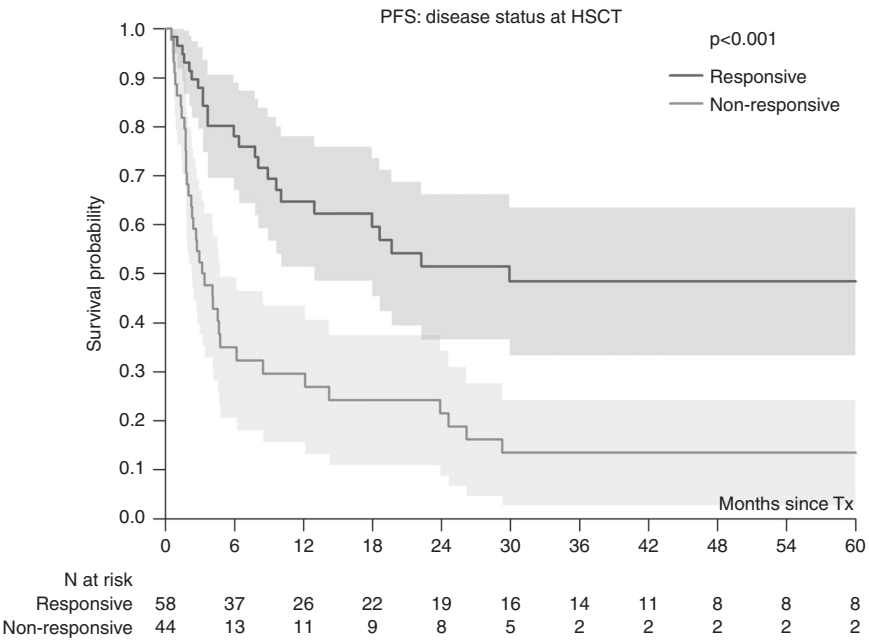

Fig. 5 PFS according to disease status at HCT. (Color figure online)

PFS at 2 and 5 yrs was 38% (95% CI 28–48%) and 30% (95% CI 20–41%), respectively (Fig. 2). Overall, 73 of the 117 patients died or relapsed.

In univariate analysis, the use of PTCY vs. other GVHD prophylactic methods did not have a significant impact on PFS (44% (95% CI 27–61%) vs. 34% (95% CI 20–47%) at 2 yrs, 40% (95% CI 22–57%) vs. 24% (95% CI 11–36%) at 5 yrs, $p = 0.27$) (Fig. 3) and OS (48% (95% CI 31–65%) vs. 45% (95% CI 32–59%) at 2 yrs, 43% (95% CI 26–61%) vs. 36% (95% CI 22-%) at 5 yrs, $p = 0.63$) (Fig. 4).

Univariate analysis did not show a statistically significant impact on 2-year PFS and OS of patient age (≤53 vs. >53 years old), type of conditioning (MAC or RIC), recipient donor gender match (female donor for male patients vs. all others), patient CMV status, stem cell source (PB or BM) and autologous transplantation before HCT.

Disease status (responsive disease (CR/PR) vs. non-responsive disease (SD/PD) at HCT had a very significant impact on PFS and OS. PFS at 2 yrs was 51% (95% CI 36–66%) for responsive disease and 22% (95% CI 9–34%) for

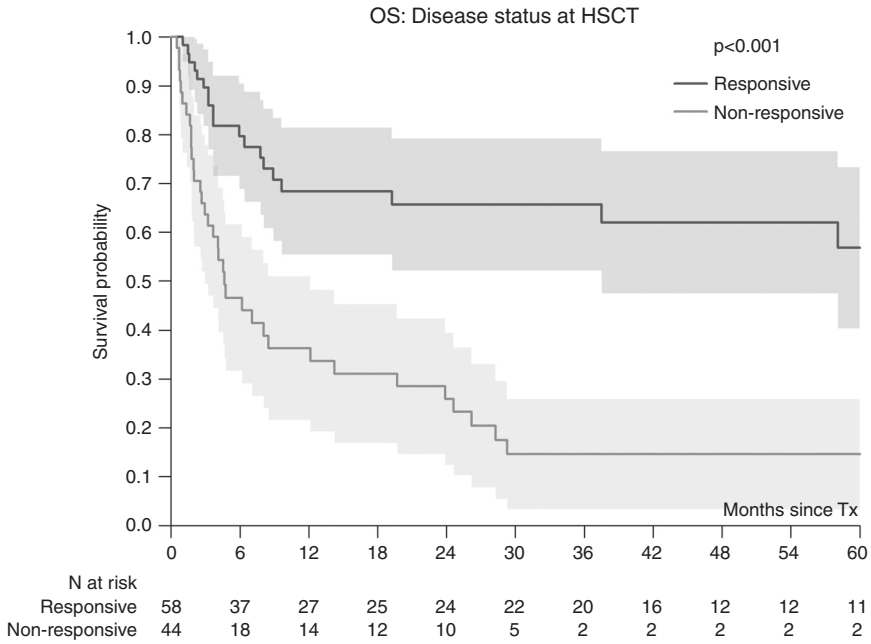

Fig. 6 OS according to disease status at HCT. (Color figure online)

no-responsive disease, PFS at 5 yrs was 48% (95% CI 33–64%) for responsive disease and 13% (95% CI 3–24%) for non-responsive disease ($p < 0.001$) (Fig. 5). OS at 2 yrs was 66% (95% CI 52–79%) for responsive disease and 26% (95% CI 12–40%) for non-responsive disease, OS at 5 yrs was 57% (95% CI 40–73%) for responsive disease and 15% (95% CI 3–26%) for non-responsive disease ($p < 0.001$) (Fig. 6).

Discussion

This is the first study that focused on outcomes of haploidentical HCT for CLL patients.

Long-term outcome (5 yr PFS/OS) of haploidentical HCT in CLL was in the same range to other publications on alloHCT in CLL patients where mostly HLA-identical donors were used [13, 14] and this holds also true for the 40 patients that received PTCY as GVHD prophylaxis.

The use of PTCY seemed not to have a negative impact on the cumulative incidence of relapse as it seems identical to the reports on outcome after HLA-matched HCT where patients had similar baseline characteristics [13, 14].

NRM was higher in this study than in the publications on alloHCT in CLL where mostly HLA-identical donors were used [13, 14], but comparable to the results with UCBT and mismatched unrelated alloHCT [15]. The NRM in our study was also higher than described in other publications about haploidentical transplantations using PTCY [18, 19, 26], but in those studies patients were younger and were mostly in complete remission. NRM found in our study was comparable with studies on haploidentical HCT with in vivo T-cell depleted grafts [27–29].

The incidence of both grade II-IV and grade III-IV acute GVHD was comparable with other studies on HCT in CLL [13, 15, 30] and slightly lower than with UBCT in CLL [16]. The incidence of severe acute GVHD after PTCY was slightly higher than described in other publications on haploidentical HCT with use of PTCY [18, 19], but this could be just a coincidence due to the small amount of patients in this group.

In other studies, several risk factors have been identified for a poor outcome of alloHCT in CLL patients [13–15]. These include higher age, lower performance status, unrelated donor type, unfavorable sex-mismatch (female donor to male patient), prior autologous transplantation and remission status at transplantation [13]. In our study both PFS and OS were significantly better in patients with responsive disease compared to patients with non-responsive disease at transplantation. This was also the risk factor that had the highest HR for relapse and poor outcome in earlier studies [13]. Other risk factors (prior autologous HCT, lower performance status, unfavorable sex-mismatch and CMV status of patients) regarding the prognosis could not be identified in this small group of patients, but in earlier studies the impact of these factors was much lower than disease status at transplantation.

The availability of kinase and BCL2 inhibitors resulted in a decrease in the number of transplants because of their efficacy and relatively good tolerability. A subgroup of patients with del(17p)/TP53 mutation or being refractory to one or more of the new drugs may still benefit from alloHCT. The timing of alloHCT in these patients depends on the expected benefit from alloHCT, especially with respect to NRM, above that of continuing the (sequential)

use of the new drugs. The results of alloHCT appeared to be better for fit younger patients in remission and having a HLA- and, in case of males, sex-matched donor [13, 14]. A higher risk of NRM after alloHCT is however acceptable when patients become refractory or intolerable to two or more of the new drugs as the response rate and PFS seems lower when applied sequentially [5, 6]. In this case the use of alternative donors, including haploidentical, seems appropriate based on the results of this study. The best moment to perform the alloHCT is when the patients is in remission, since the results of patients with refractory or stable disease at HCT are dismal.

In conclusion, this retrospective multi-center analysis shows reasonable outcomes of CLL patients when transplanted with a haploidentical donor. Thereby, alloHCT with a haploidentical donor may be considered in patients with high-risk CLL and otherwise good risk transplantation characteristics that are refractory on kinase inhibitors and/or a BCL2 inhibitor. The use of PTCY as GVHD prevention seems not to compromise outcome in this setting.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interests.

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