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ORIGINAL ARTICLE

Comparable outcome after haploidentical and HLA-matched allogeneic stem cell transplantation for high-risk acute myeloid leukemia following sequential conditioning—a matched pair analysis

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Abstract

In acute myeloid leukemia (AML), primary refractory or relapsed disease, secondary AML, and leukemia with unfavorable genetics are considered high-risk AML (hrAML), with allogeneic stem cell transplantation (SCT) representing the standard treatment. Sequential conditioning has been successfully used for SCT in hrAML in HLA-matched transplants, and found its way into HLA-haploidentical SCT (haplo-SCT) later on. Hence, sequential conditioning had become standard for all patients with hrAML in our two centers, regardless of donor type. Thereby, HLA-matched family or unrelated transplants were first/second choice, post-transplant cyclophosphamide (PTCY)-based haplo-SCT was chosen in patients missing matched donors or requiring urgent transplantation. To compare the outcome after HLA-matched and haplo-SCT for hrAML following sequential conditioning, we performed a retrospective, matched-pair comparison, using disease stage, genetic subgroups and age as matching criteria. Thirty-four well-matched pairs were identified. At SCT, patients (median age 54 years) were untreated (9%), had remission (13%), or active disease (78%). Three-year overall and leukemia-free survival (OS/LFS) of the entire cohort was 56 ± 7%/49 ± 7%, without significant differences between donor types (OS after HLA-matched/haplo-SCT 62 ± 10%/52 ± 9% ($p = 0.21$), LFS 53 ± 10%/46 ± 9% ($p = 0.26$)). Similarly, the cumulative incidence of relapse, non-relapse-mortality and chronic GvHD, as well as GvHD-free, relapse-free survival (GRFS), and chronic GvHD-free, relapse-free survival (cGRFS), were comparable. However, a higher incidence of acute GvHD ≥ II° was observed after HLA-matched SCT (15 ± 1% versus 50 ± 2%, $p = 0.001$). In conclusion, sequential conditioning SCT achieved remarkable results in hrAML, independently from donor type. PTCY-based haplo-SCT produced results that were comparable to HLA-matched SCT and can be used as an alternative option.

Keywords AML · High-risk AML · Haploidentical stem cell transplantation · Sequential conditioning · FLAMSA-RIC

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Introduction

Acute myeloid leukemia (AML) is a life-threatening condition with poor prognosis. Several subgroups, such as primary refractory or relapsed disease, secondary AML, and leukemia harboring unfavorable genetics, are associated with a particularly poor outcome and are therefore referred to as high-risk AML (hrAML) [1, 2]. Allogeneic stem cell transplantation (SCT) is the most effective treatment for these patients. Whereas both myeloablative and reduced intensity conditioning (MAC/RIC) regimens frequently led to unsatisfying results [3], sequential conditioning protocols, comprising cytoreductive chemotherapy, followed by RIC after few days of rest, have been established as an effective approach [4, 5].

In recent years, the introduction of post-transplant cyclophosphamide (PTCY) for in vivo elimination of alloreactive T cells [6] has enabled a substantial increase of SCT from haploidentical related donors [7]. Initially, haploidentical SCT (haplo-SCT) was performed following non-myeloablative conditioning [6]. Subsequently, more intensive and even myeloablative protocols have shown to be feasible [8, 9]. The use of sequential conditioning prior to haploidentical HSCT (haplo-SCT) has been reported by our group for patients with active acute leukemia, undergoing either first or second SCT [10].

Based on these results, sequential conditioning has become the standard approach in our two centers prior to both matched-donor and haplo-SCT in high-risk AML. Regarding donor selection, an HLA-matched related donor (MRD) was first choice, followed by HLA-matched unrelated donors (MUD), allowing 10/10 or 9/10 antigen matching. In patients missing an HLA-matched donor, or in patients with aggressive disease requiring an urgent transplant, haploidentical donors (haplo-D) were chosen. To further elucidate the role of haplo-SCT following sequential conditioning in hrAML, we performed a retrospective matched-pair comparison among the different types of SCT.

Patients and methods

Data was retrospectively obtained from patient records at two the University Hospital of Munich-Grosshadern and Klinikum Augsburg, both associated to the Ludwig-Maximilians University of Munich. All consecutive patients ≥ 18 years, who fulfilled the following criteria, were included: (a) diagnose of hrAML, as defined by either primary refractory or relapsed AML, secondary AML, or AML harboring genetic aberrations classified as intermediate-high or adverse according to the European Leukemia Network (ELN) risk classification [11]; (b) undergoing first allogeneic SCT between January 1st 2009 and July 31, 2016; and (c) use of a sequential conditioning regimen for SCT from either HLA-matched or haploidentical donor.

A matched pair analysis was performed to compare outcome of SCT following sequential conditioning in the haploidentical and the matched donor setting. The matched donor cohort comprised matched family donors and MUD with 9/10 and 10/10 HLA match, since outcome has shown to be comparable in sequential SCT in hrAML [12]. The following pre-defined matching variables were used in descending hierarchy: (a) disease stage at SCT, (b) genetic risk category according to ELN-criteria, and (c) patient age at HSCT (± 5 years).

Definitions and statistics

The refined disease risk index (DRI) [13] and HCT Comorbidity Index (HCT-CI) [14] were calculated as published. Complete hematologic remission (CHR) was defined as ≤ 5% blasts in a representative bone marrow (BM) smear plus a simultaneously obtained peripheral blood (PB) sample, showing no evidence of blasts, neutrophils > 1000/μl, platelets > 100,000/μl, and transfusion independence. Complete remission with incomplete recovery (CRi) was defined as persistent neutropenia (< 1000/μl) and/or thrombocytopenia (< 100,000/μl) without evidence of leukemia. As recommended [15], primary induction failure was defined by persisting leukemia following either ≥ two courses of standard chemotherapy or ≥ 1 course containing high-dose cytarabine. Relapse was defined by BM blast counts of > 5%, extramedullary manifestation, or the recurrence of leukemic blasts in PB. Acute and chronic Graft-versus-Host disease (aGvHD/cGvHD) and invasive aspergillosis (IA) were classified as described [16–18]. Engraftment was defined by neutrophils > 500/μl, overall survival (OS) as the period between transplantation and date of death or last follow-up, leukemia-free survival (LFS) as the period between transplantation and date of relapse, date of death in remission, or last follow-up. As described [19], GvHD-free, relapse-free survival (GRFS) was defined as the time after transplantation without grades III–IV aGvHD, cGvHD requiring systemic treatment, relapse, or death. Chronic GvHD-free, relapse-free survival (cGRFS) was defined as the time after transplantation without moderate or severe cGvHD, relapse, or death. Non-relapse mortality (NRM) indicates death without evidence of leukemia. Deaths of any cause occurring with refractory leukemia or after post-transplant relapse were considered as leukemia-associated.

Summary statistics were reported using standard measures for categorical and continuous data. Time-to-event outcomes were computed using the Kaplan-Meier method [20]. Univariate analysis for variables influencing outcome was performed using log rank test. Cumulative incidences (CI) for relapse and NRM were calculated, considering both events

as competing risks. Similarly, death was considered as competing event for acute and chronic GvHD. Differences between groups were calculated using Gray's test [21]. SPSS version 18 and 22 (SPPS Inc., Chicago, IL, USA) and R software version 3.2.3 (R Core Team 2017, R: A language and environment for statistical computing, R Foundation for Statistical Computing, Vienna, Austria, URL: https://www.R-project.org/) were used.

Ethics

The study was approved by the ethical committee of the medical faculty, Ludwig-Maximilian-University of Munich. Before treatment, all patients had given written informed consent for transplantation and data analysis. All procedures were in accordance with the ethical standards of the responsible committees on human experimentation (institutional and national) and with the Helsinki Declaration (2008 revision).

Results

Patients

Among all consecutive patients from the two centers, 41 recipients of haploidentical and 166 recipients of HLA-matched SCT fulfilled the inclusion criteria. Using the matching strategy described above, 34 recipients of haplo-SCT could be pair-matched with recipients of HLA-matched SCT, who had been transplanted from MRD ($n = 9$), 10/10 MUD ($n = 21$), or 9/10 MUD ($n = 4$). Haploidentical donors were children ($n = 16$), siblings ($n = 9$), parents ($n = 5$), or other relatives ($n = 4$).

Besides accordance in the matching criteria, the two cohorts were well balanced with respect to the majority of patient and transplant characteristics. However, whereas in HLA-matched SCT, the FLAMSA regimen (Fludarabine, AraC, and Amascrine [4]) was uniformly used for cytoreductive chemotherapy prior to the actual conditioning, recipients of haplo-SCT received either clofarabine-based ($n = 17$), or a FLAMSA-based ($n = 17$) combinations prior to RIC ($p < 0.001$). Further, 12/34 recipients of haplo-SCT received a BM transplant, whereas PBSC grafts were consistently used in HLA-matched SCT ($p < 0.001$). As published, prophylactic immunosuppression consisted of ATG, cyclosporine A, and MMF in HLA-matched [4] and of PTCy, tacrolimus, and MMF in haplo-SCT [6]. Patient characteristics are summarized in Table 1.

Engraftment, response, and chimerism

Median time to engraftment was 18 days (range 12–40) for the entire cohort and was equal between donor types (17.5 days after HLA-matched SCT, 18 days after haplo-HSCT, $p = 0.742$). Neutrophil recovery was achieved in all but two patients, who both died in aplasia after haplo-HSCT. One recipient of HLA-matched SCT died from sepsis shortly after engraftment. No graft failure was observed. By day + 30 after transplantation, unselected BM donor chimerism ≥ 95% was achieved in 91% after HLA-matched SCT and 94% after haplo-SCT ($p = 0.99$). CHR or CRi was achieved in 65 patients (95%) (HLA-matched 97%, haploidentical 94%, $p = 0.99$). By day + 90, CR/CRi rate was 91% after HLA-matched and 82% after haplo-SCT ($p = 0.48$).

Infections

In a landmark analysis by day + 100, no differences with respect to infectious complications (occurring in 20 patients after matched donor and 21 after haploidentical donor SCT) or CMV reactivation (occurring in 12 patients after matched donor and 14 after haploidentical donor SCT) were observed. Further details are provided in Table 2.

Outcome

Median follow-up among survivors was 35 (range 4–95) months. OS after 3 years was 56 ± 7% for the entire cohort, and it was not statistically different between donor types (52 ± 9% after haplo-SCT versus 66 ± 9% after HLA-matched SCT, $p = 0.21$). The corresponding 3-year LFS was 49 ± 7% for all patients and did not show either a significant difference between haploidentical (46 ± 9%) and HLA-matched SCT (53 ± 10%, $p = 0.26$). Similarly, 3-year GRFS (34 ± 8% vs. 28 ± 8%, $p = 0.78$) and cGRFS (40 ± 9 vs 37 ± 9%, $p = 0.98$) were comparable between donor types (Fig. 1).

GvHD, relapse, and non-relapse mortality

Twenty-seven recipients of HLA-matched SCT developed aGvHD, reaching grades I ($n = 10$), II ($n = 12$), III ($n = 4$), and IV ($n = 1$). No difference was observed among patients transplanted from MRD, 10/10 or 9/10 MUD. After haploidentical SCT, aGvHD occurred in 23 patients and achieved grade I in 18, grade II in 2, and grades III–IV in one patient each. Hence, CI of aGvHD ≥ grade II by day + 100 was 50 ± 8% and 13 ± 4% after HLA-matched and haploidentical SCT ($p < 0.001$, Fig. 2a). In contrast, CI and severity of cGvHD were comparable: Overall CI of cGvHD was 35 ± 2% and 27 ± 2% ($p = 0.32$) after HLA-matched and haploidentical SCT, while CI of moderate/severe cGVHD was 24 ± 2% and 15 + 2% ($p = 0.35$; Fig. 2b).

Three-year CI of relapse was 34 ± 4% for the entire cohort, occurring in 10 patients after HLA-matched and 11 after haploidentical SCT. Whereas relapse was observed earlier after haplo-SCT (median 4.7 months vs. 11.0 months after

Table 1 Patients characteristics

Variable	Total	HLA-matched donor	Haploidentical donor	*p*
Number of patients	68	34	34	
Age at transplant (years)[a]				0.87
Median age, years (range)	54 (28–71)	54.5 (31–71)	54 (28–71)	
Age < 40 years, *n* (%)	10 (15)	5 (15)	5 (15)	
Age = 40–59 years, *n* (%)	32 (47)	17 (50)	15 (44)	
Age ≥ 60 years, *n* (%)	26 (38)	12 (35)	14 (41)	
Gender				0.33
Male, *n* (%)	33 (49)	14 (41)	19 (56)	
Female (%)	35 (51)	20 (59)	16 (44)	
Female donor/male recipient, *n* (%)	11 (16)	3 (9)	8 (24)	0.1
Diagnosis, *n* (%)				0.3
De novo AML	46 (68)	26 (76)	20 (59)	
Secondary AML	19 (28)	7 (21)	12 (35)	
Therapy-associated AML	3 (4)	1 (3)	2 (6)	
Year of transplant				0.8
2009–2012	27 (40)	14 (41)	13 (38)	
2013–2016	41 (60)	20 (59)	21 (62)	
Median, year	2013	2013	2013	
Range, year	2009–2016	2009–2016	2010–2016	
Stem cell source, *n* (%)				< 0.001
Bone marrow	12 (18)	0 (0)	12 (35)	
Peripheral blood	56 (82)	34 (100)	22 (65)	
CMV recipient serostatus, *n* (%)				0.8
CMV positive	27 (40)	13 (38)	14 (41)	
CMV negative	41 (60)	21 (62)	20 (59)	
CMV donor/recipient serostatus, *n* (%)				0.78
Negative/negative	24 (35)	12 (35)	12 (35)	
Negative/positive	15 (22)	9 (26)	6 (18)	
Positive/negative	3 (4)	1 (3)	2 (6)	
Positive/positive	26 (38)	12 (35)	14 (41)	
Genetics according to ELN classification[a], *n* (%)				0.95
Favorable	10 (15)	5 (15)	5 (15)	
Intermediate-I	37 (54)	18 (53)	19 (56)	
Intermediate-II	5 (7)	3 (9)	2 (6)	
Adverse	16 (24)	8 (24)	8 (24)	
Adverse and complex karyotype	11 (16)	6 (18)	5 (15)	
Stage at start of sequential conditioning[a], *n* (%)				0.99
CR	9 (13)	5 (15)	4 (12)	
Primary Induction failure (PIF)	12 (18)	6 (18)	6 (18)	
Relapse	41 (60)	20 (59)	21 (62)	
Untreated	6 (9)	3 (9)	3 (9)	
Cytoreductive chemotherapy, *n* (%)				< 0.001
FLAMSA-based	51 (75)	34 (100)	17 (50)[b]	
Clofarabine	17 (25)	0 (0)	17 (50)	
Disease-Risk Index (DRI), *n* (%)				0.87
Intermediate	9 (13)	5 (15)	4 (12)	
High	48 (71)	23 (68)	25 (73)	
Very high	11 (16)	6 (18)	5 (15)	
HCT-CI score, *n* (%)				0.15

Table 1 (continued)

Variable	Total	HLA-matched donor	Haploidentical donor	*p*
Score 0–1	32 (47)	19 (56)	13 (38)	
Score ≥ 2	36 (53)	15 (44)	21 (62)	

[a] Served as matching criteria

[b] One patient received mitoxantron instead of amsacrin

HLA-identical transplantation, $p = 0.12$), CI at 3 years was comparable (33 ± 8% after HLA-matched and 36 ± 9% after haploidentical SCT ($p = 0.63$ Fig. 2c). Three-year CI of NRM was 16 ± 2%, affecting four and six patients after HLA-matched and haplo-SCT, respectively, with infections being the most relevant cause of death in both cohorts. The corresponding 3y-CI was 14 ± 5% for HLA-matched and 18 ± 5% for haploidentical SCT ($p = 0.45$, Fig. 2d). In total, 27 patients died within follow-up, with relapse being the most frequent cause of in both groups (8 after haploidentical, 9 after HLA-matched SCT each). Details on causes of death are reported in Table 3.

Prognostic factors

Univariate testing was performed for relevant prognostic factors known from the literature or imbalanced between cohorts. In this high-risk cohort, the HCT-CI confirmed its prognostic meaning, showing statistically significant differences in OS ($p = 0.05$ between risk-groups). There were no further differences in terms of outcome according to other risk factors. The complete risk factor analysis is provided in the supplementary table.

Discussion

The concept of sequential therapy intends to reduce leukemic burden by an intensive course of chemotherapy few days prior to the actual conditioning regimen. Promising results have been published in matched donor transplants [4]. Subsequently, the concept has been successfully transferred to haplo-SCT [10]. Hence, sequential conditioning has been broadly used [22–25] and has become standard practice in our two centers for SCT in hrAML, regardless of donor type. The matched-pair analysis presented here was performed to further elucidate the role of sequential conditioning in haplo-SCT for hrAML.

Overall, sequential therapy produced encouraging outcomes with comparable results after haploidentical and HLA-matched SCT. Considering the patients' high-risk profile, including 87% transplanted not in remission and 87% with a DRI of high or very high, 3-year OS (56%) and LFS (49%) for the entire cohort are remarkable. Results were based on relatively low overall rates of both relapse (34 ± 4%) and NRM (16 ± 2%) at 3 years. Comparison among donor types revealed similar rates of NRM and relapse, although relapse occurred earlier after haplo-SCT. This might be explained by different schedules for immunosuppressive medication, being 90 days after HLA-matched, and 180 days after haplo-SCT. As reported by others [26, 27], less aGVHD grades II–IV was observed after haplo-SCT, which, however, may in part be due to the inclusion of 1 AG mismatched unrelated donors and the more frequent use of PBSCs rather than BM in the HLA-matched cohort [28, 29]. Thus, the combined endpoint of GFRS was again not different between donor groups.

Various comparisons between PTCY-based haplo-SCT and HLA-matched transplantation for AML in general have been performed: Di Stasi et al. reported similar outcomes for a population of 227 patients transplanted from MRD ($n = 87$), MUD ($n = 108$), and haplo-D ($n = 32$) following a Fludarabine/Melphalan-based conditioning, adding Thiotepa

Table 2 Infectious complications before day 100

	Total	HLA-matched donor	Haploidentical donor	*p*
CMV reactivation (%[a])	26 (59)	12 (55)	14 (64)	0.76
Invasive aspergillosis (%)				0.14
Probable	19 (28)	7 (21)	13 (38)	
Proven	8 (12%)	3 (9)	5 (15)	
Sepsis (%)	20 (29)	8 (24)	12 (35)	0.29
Pulmonary infections (%)	20 (29)	10 (29)	10 (29)	1
Intestinal infections (%)	16 (24)	9 (26)	7 (21)	0.57

[a] Percentages relate to the 44 donor/recipient pairs (22 in each donor group) with either donor or recipient or both being CMV seropositive

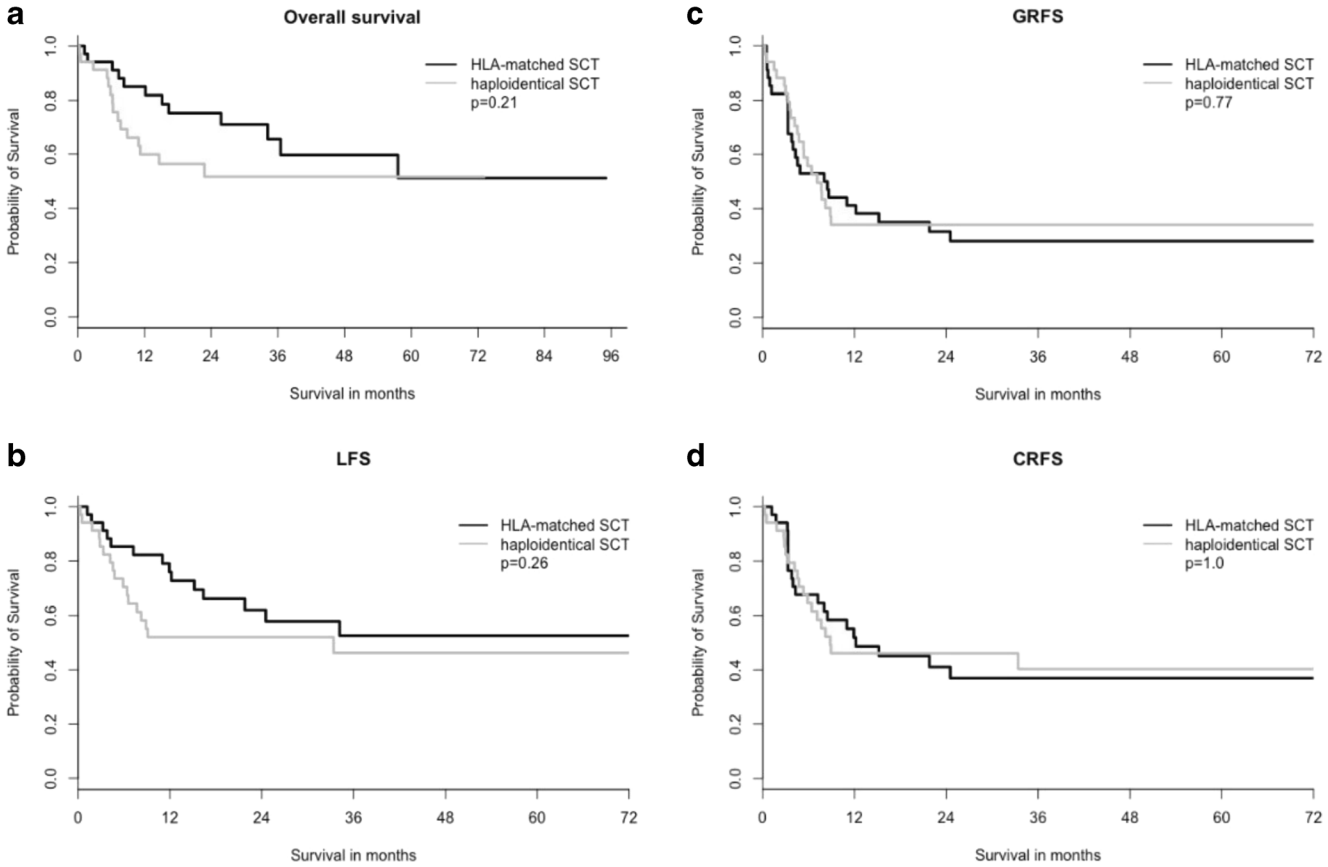

Fig. 1 Outcome after HLA-matched and haploidentical stem cell transplantation for high-risk AML using sequential conditioning. **a** Overall survival (OS). **b** Leukemia-free survival (LFS). **c** GvHD and relapse free survival (GRFS). **d** Chronic GvHD and relapse-free survival (CRFS)

in haplo-SCT. However, regardless of donor, outcome was poor in patients transplanted beyond CR [30]. The Center for International Blood and Marrow Transplant Research (CIBMTR) performed a large comparison between unrelated ($n = 1882$) and PTCY-based haploidentical ($n = 192$) transplants for AML. No significant differences in OS rates were reported, neither after MAC, nor after RIC. While the DRI was a significant factor for outcome, no subset analysis based on genetics or stage at SCT was presented. As in the study by di Stasi, certain imbalances concerning, age, stage, and conditioning between the groups had to be accounted for [27].

More recent studies have compared haplo-SCT and HLA-matched transplants in defined stages of AML. Using a weighted Cox model, the Acute Leukemia Working Party of EBMT showed inferior results after non-T cell depleted haplo-SCT, as compared to 10/10 matched unrelated donor transplants for AML transplanted in CR. Differences were based on a lower NRM after 10/10 MUD transplantation. In contrast, results were comparable between haplo-SCT and 9/10 MUD transplants [31]. Focusing on patients with hrAML, Versluis et al. compared the outcome of SCT in CR1 from different donor types. All haplo-SCTs were T cell replete. Results after haplo-SCT compared well to matched related and 10/10 antigen MUD transplants [32]. Finally, in a single-center study, How et al. compared outcome after MRD, MUD, and haploidentical SCT in active AML, using various conditioning regimen. No differences among donor types were observed with respect to OS, EFS, RI, and TRM. However, 2-year EFS was below 25% in all cohorts [33]. With the limitation of the retrospective nature of these studies, this data as well as our results suggest an equivalence of matched donor and T cell replete haploidentical SCT in advanced disease. This is remarkable in the light of results from earlier studies on haploidentical SCT, using T cell-depleted PBSC grafts. In a large cohort reported by the EBMT, median OS of patients transplanted with advanced disease was 3 months, and 2-year LFS was 1% [34]. Hence, haplo-SCT was not regarded as an appropriate option for patients with advanced leukemia at that time.

There is only one report on sequential conditioning in the haploidentical setting [35]. Investigators from France published a retrospective multicenter analysis of 72 extensively pretreated patients with various hematologic malignancies, introducing an intensive sequential regimen comprising Thiotepa, Etoposide, Cyclophosphamide (TEC), followed by Fludarabine/Busulfan (Flu/Bu) conditioning and either a PTCY-based haploidentical ($n = 27$, including 17 with AML) or an HLA-matched transplant (10/10 MUD, $n = 22$,

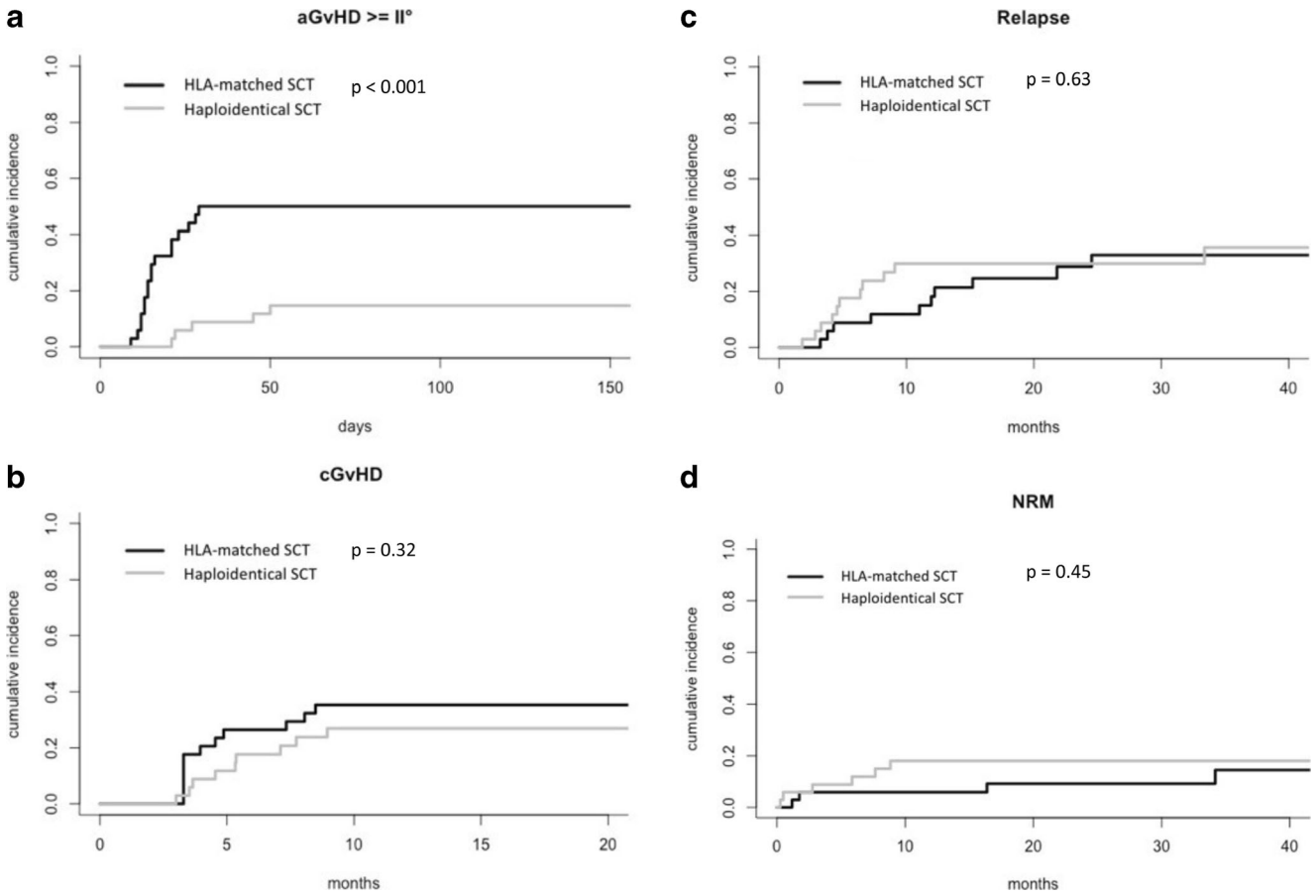

Fig. 2 Cumulative incidence of acute GvHD (**a**), chronic GvHD (**b**), relapse (**c**), and non-relapse mortality (NRM) (**d**) according to donor type; relapse and NRM were considered as competing events

9/10 MUD, $n = 7$, MRD, $n = 16$). All patients received antithymocyte globulin (ATG), and follow-up was 21 months. In accordance with our data, OS did not significantly differ among donor types. No disease-specific comparison among donor groups was reported, but the type of the malignancy did not influence outcome. Compared to the MUD setting, CI of aGvHD III–IV was significantly lower in the haploidentical group (3.7% vs. 31%, $p = 0.003$), as it was observed in our analysis. Although the inclusion of different diseases and differences in age and performance scores led to a somewhat heterogeneous population, this study, as ours, supports the use of sequential therapy in advanced hematologic malignancies.

Some limitations of our study should be considered. First, an unintended selection bias is an inherent risk of retrospective studies. However, sequential conditioning has been regarded as standard in hrAML in both centers for many years, and all consecutive patients meeting the inclusion criteria were considered for matching. Second, in spite of a high matching quality, some imbalances between the two cohorts remained. Nevertheless, neither cytoreduction (clofarabine- versus FLAMSA-based) nor graft source (PBSCs vs BM grafts)

Table 3 Causes of death

Cause of death	Total	HLA-matched donor	Haploidentical donor
Relapse	17	8	9
Infectious disease	4	1	3
Infectious disease and acute GvHD	2	1	1
Infectious disease and chronic GvHD	1	1	0
Chronic GvHD	1	1	0
Organ failure	2	0	2
Overall	27	12	15

showed influence on any outcome variable. The latter finding is consistent with recent data, comparing PBSCs with BM in PTCY-based haplo-SCT for acute leukemia, showing superimposable survival curves [28]. Third, the total patient number is relatively small. However, the precise definition of hrAML and a high matching quality ensured comparability between cohorts. Limitation to two closely related centers using similar supportive care and treatment strategies for GvHD minimized center effects. Nevertheless, confirmation in a larger cohort or a prospective trial would be desirable.

In summary, our study underscores the value of sequential conditioning regimen in high-risk AML. It shows similar survival, but less acute GvHD for PTCY-based haploidentical as compared to matched donor SCT. This is of direct practical relevance, since for patients in a non-remission stage, or with a genetically high-risk disease, immediate donor availability is substantial to avoid detrimental therapy delay. In contrast to earlier studies on T cell depleted haplo-SCT, as well as non-myeloablative conditioning for T cell replete haplo-SCT [36], the combination of sequential conditioning and post-grafting immunosuppression with PTCY might show a way to effective haplo-SCT in patients with AML not in remission. Nevertheless, with relapse being the most important cause of failure, development of post-transplantation maintenance strategies is warranted.

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Compliance with ethical standards

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

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