Received: 12 March 2025 | Accepted: 6 August 2025

DOI: 10.1111/bjh.70101

BJHaem
BRITISH JOURNAL OF HAEMATOLOGY

ORIGINAL PAPER

Transplantation & Cellular Therapy

Graft-versus-host disease is not associated with reduced incidence of relapse following haploidentical stem cell transplantation with post-transplant cyclophosphamide for acute lymphoblastic leukaemia: A study on behalf of the Acute Leukaemia Working Party of European Society for Blood and Marrow Transplantation

Avichai Shimoni[1] | **Christophe Peczynski**[2] | **Myriam Labopin**[2] | **Alida Dominietto**[3] | **Mariya Koc**[4] | **Mutlu Arat**[5] | **Johanna Tischer**[6] | **Simona Sica**[7] | **Zafer Gülbas**[8] | **Gerard Socié**[9] | **Didier Blaise**[10] | **Pietro Pioltelli**[11] | **Hakan Ozdogu**[12] | **Jan Vydra**[13] | **Fabio Ciceri**[14] | **Arnon Nagler**[1] | **Mohamad Mohty**[2,15]

[1]Division of Hematology, Chaim Sheba Medical Center, Tel-Hashomer and Gray Faculty of Medical & Health Sciences, Tel-Aviv University, Tel-Aviv, Israel

[2]Sorbonne University, INSERM UMRs 938, Paris, France

[3]UO Ematologia e Terapie Cellulari, IRCCS Ospedale Policlinico San Martino, Genoa, Italy

[4]Bone Marrow Transplant Unit, Medicana International Hospital Istanbul, Istanbul, Turkey

[5]Hematology and Hematopoietic SCT Unit, Sisli Memorial Hospital, Istanbul, Turkey

[6]Department of Internal Medicine III, University Hospital of Munich-Campus Grosshadern, LMU, Munich, Germany

[7]Universita Cattolica S. Cuore, Istituto di Ematologia, Ematologia, Rome, Italy

[8]Bone Marrow Transplantation Department, Anadolu Medical Center Hospital, Kocaeli, Turkey

[9]Department of Hematology – BMT, Hopital St. Louis, Paris, France

[10]Programme de Transplantation and Therapie Cellulaire, Centre de Recherche en Cancérologie de Marseille, Institut Paoli Calmettes, Marseille, France

[11]Ospedale San Gerardo, Clinica Ematologica dell'Universita Milano-Biocca, Monza, Italy

[12]BMT Unit, Haematology Research Laboratory, Training and Medical, Haematology Division, Baskent University Hospital, Adana, Turkey

[13]Institute of Hematology and Blood Transfusion, Prague, Czech Republic

[14]Hematology and Bone Marrow Transplant Unit, San Raffaele Scientific Institute, Milan, Italy

[15]Hématologie Clinique et Thérapie Cellulaire, Hôpital Saint-Antoine, Paris, France

Correspondence
Avichai Shimoni, Department of Bone Marrow Transplantation, Chaim Sheba Medical Center, Tel-Hashomer 5265601, Israel.
Email: avichai.shimoni@sheba.health.gov.il

Summary

The graft-versus-leukaemia effect (GVL) is closely associated with graft-versus-host disease (GVHD) after human leucocyte antigen (HLA)-matched allogeneic stem-cell transplantation (SCT) in acute lymphoblastic leukaemia (ALL). However, there are no data on this association following haploidentical SCT (haploSCT) with post-transplant cyclophosphamide (PTCy). We assessed the impact of acute and chronic GVHD on haploSCT outcomes in 516 adult ALL patients. The cumulative incidence of acute GVHD grade II–IV and III–IV, chronic GVHD and extensive chronic GVHD was 33.3%, 11.7%, 35.3% and 11.8% respectively. The 2-year relapse incidence (RI), non-relapse mortality (NRM) and overall survival (OS) were 27.1%, 17.3% and 64.4% respectively. The time-dependent hazard ratios (HRs) of acute GVHD grade II, grade III–IV, limited and extensive chronic GVHD associated with RI were 0.92

(95% confidence interval [CI] 0.58–1.48, $p = 0.74$), 0.57 (95% CI, 0.27–1.22, $p = 0.15$), 1.06 (95% CI, 0.62–1.82, $p = 0.83$) and 0.95 (95% CI, 0.42–2.17, $p = 0.91$) respectively. Acute GVHD grade III–IV and extensive chronic GVHD were associated with higher NRM (hazard ratio [HR] 1.95 [95% CI, 1.09–3.48, $p = 0.002$] and 3.3 [95% CI, 1.41–7.73, $p = 0.006$]) and reduced OS (HR 1.91 [95% CI, 1.07–3.39, $p = 0.03$] and 3.27 [95% CI, 1.4–7.66, $p = 0.006$]) respectively. In conclusion, acute and chronic GVHD are not statistically associated with reduced RI after haploSCT with PTCy in ALL. Higher GVHD grades are associated with higher NRM and lower OS.

KEYWORDS
acute lymphoblastic leukaemia, graft-versus-host disease, graft-versus-leukaemia effect, haploidentical transplantation, post-transplant cyclophosphamide

INTRODUCTION

Allogeneic stem cell transplantation (SCT) is a curative therapy for acute lymphoblastic leukaemia (ALL).[1–3] It provides both dose-intensive chemo-radiotherapy and enhancement of the graft-versus-leukaemia (GVL) effect.

The association of graft-versus-host disease (GVHD) and GVL in ALL is well established.[4–7] Horowitz et al. have shown that both acute and chronic GVHD are associated with a lower risk of relapse after SCT for leukaemia.[5] However, only the mild forms were associated with better survival as the more severe GVHD forms also resulted in increased non-relapse mortality (NRM). Acute GVHD was more important in controlling relapse in patients with ALL. A more recent analysis of the correlation between relapse and GVHD in a megafile of >48 000 transplants reported to the European Society for Blood and Marrow Transplantation (EBMT) confirmed the well-known association of GVHD and GVL.[6] However, the strength of the association was different between diseases. A strong association was seen in chronic myeloid leukaemia and ALL.

Marked changes have been introduced in modern SCT over the past two decades. These include SCT for older patients, the use of reduced intensity conditioning (RIC), more common use of peripheral blood stem cells (PBSC) as the stem cell source and increased use of alternative donors such as haploidentical donors (haploSCT). These changes as well as the marked improvement in supportive care and treatment of GVHD[8] improved NRM, but did not markedly change the rate of disease relapse.[9] The association of GVHD and GVL with the current use of modern SCT techniques in the human leucocyte antigen (HLA)-matched setting was confirmed both in ALL and acute myeloid leukaemia (AML).[7,10]

The use of haploSCT has markedly increased over the last decade with outcomes that have constantly improved with time, approaching those of unrelated donor transplants.[11] This is mostly related to the shift towards non-T-cell-depleted transplants with the use of post-transplant cyclophosphamide (PTCy). The use of haploidentical donors in ALL has also constantly increased with improving results. The outcome of patients with ALL after haploSCT is now similar to that after HLA-matched related or unrelated donors.[12–15] There are limited data regarding the association of GVHD and GVL in the haploidentical setting with PTCy. In the current study, we explored this association in a relatively large cohort of adult patients with ALL who had received haploSCT with PTCy.

PATIENTS AND METHODS

Study design and data collection

This is a retrospective multicentre analysis. Patient data were obtained from the EBMT registry. The EBMT is an international research collaborative group comprising over 650 transplant centres required to report annually on all transplants performed. Quality control measures of this multicentre registry include confirmation of the validity of the entered data by the reporting team, cross-checking with national registries and regular in-house and external data audits. The study was approved by the Acute Leukaemia Working Party (ALWP) of the EBMT and was performed in compliance with the Declaration of Helsinki and under the guidance of the EBMT. All patients provided written informed consent authorizing the use of information for research purposes.

Patients were eligible for the study if they were aged 18 years or more, had B-cell or T-cell ALL and received a haploSCT with PTCy, cell source bone marrow (BM) or PBSC, in first complete remission (CR1) or second CR (CR2), between the years 2010–2019. Minimal residual disease status at the time of transplant was not available for a large proportion of patients and was therefore not analysed.

Haploidentical donors were defined as two or more HLA mismatches from a family-related donor. Patients were excluded if they received ex vivo T-cell depletion, had an autologous transplantation before, received anti-thymocyte globulin (ATG) or alemtuzumab for GVHD prophylaxis, did not engraft after haploSCT or had missing information on acute or chronic GVHD.

Data collected included recipient and donor characteristics, disease features, transplant-related factors including the conditioning regimen, type of GVHD prophylaxis and

outcome variables including the occurrence and timing of acute and chronic GVHD, relapse and survival data.

Conditioning regimens and GVHD prophylaxis

The conditioning regimen was selected at the discretion of the participating centre.[16] Dose intensity was defined according to standard EBMT criteria.[17] All transplants were non T-cell depleted, and the GVHD prophylaxis regimen was based on PTCy with or without additional GVHD prophylactic agents (excluding ATG and alemtuzumab) according to the participating centre policy. GVHD prophylaxis included a calcineurin inhibitor (ciclosporin or tacrolimus) with mycophenolate mofetil in most cases. The duration of immune suppression therapy was at the attending physician's discretion.

Evaluation of outcomes

Overall survival (OS) was calculated from the day of SCT until death from any cause or the date of last follow-up. Leukaemia-free survival (LFS) was defined as survival with no relapse. Relapse was defined according to standard haematological criteria. NRM was defined as death without prior disease recurrence. Acute GVHD was graded and staged according to the consensus criteria.[18] Chronic GVHD was graded according to the Seattle criteria.[19]

Statistical analysis

The primary objective of the study was to evaluate the impact of acute and chronic GVHD on relapse incidence after haploSCT. Secondary end-points were NRM, LFS, OS and the incidence of acute and chronic GVHD. The probabilities of OS and LFS were calculated using the Kaplan–Meier method.[20] Relapse incidence, NRM and the incidence of acute and chronic GVHD were estimated using cumulative incidence analysis, considering competing risks.[21] In the estimation of acute and chronic GVHD, relapse and death were considered as competing events. Baseline characteristics of patients, disease and transplantation procedures were expressed as frequency and percentage for qualitative data and as median and interquartile range for quantitative data. Continuous variables were categorized and the median used as a cut-off point. To study the effect of GVHD on SCT outcomes, we used a Cox proportional hazards model including acute and chronic GVHD as time-dependent variables. The following covariates were also included in the multivariable models: year of transplantation (continuous), cell source (BM vs. PBSC), ALL type (B or T cell), status at transplant (CR1 vs. CR2), patient age (continuous), donor to recipient gender combination (female to male vs. other) and intensity of conditioning (RIC vs. myeloablative conditioning [MAC]). These variables were selected because of known clinical relevance and/or significance in the univariate analysis. Hazard ratios (HRs) and 95% confidence intervals (95% CIs) are reported. The interpretation of the results is based on the multivariable analyses where p-values are given versus reference groups which are the absence of acute GVHD or grade I acute GVHD, and absence of chronic GVHD. The time-dependent effect of acute GVHD was divided into two modalities: grade II and grade III–IV. Chronic GVHD was also divided into two modalities: limited and extensive chronic GVHD. Differences were considered statistically significant when $p < 0.05$. Statistical analyses were performed with R 4.1.2.[22]

RESULTS

Patient characteristics

The study included 516 adult patients with B-cell (75%) or T-cell (25%) ALL in CR1 (68%) or CR2 (32%) and who were given a first T-cell replete haploSCT with PTCy during the years 2010–2019. Patient characteristics are shown in Table 1. The median patient age was 36 years (range, 18–75). The median donor age was 39 years (range, 8–72). Thirty-six per cent were Philadelphia chromosome positive (missing data for 118 patients). The conditioning regimen was MAC (with no total body irradiation [TBI]) in 44%, MAC with TBI in 37% and RIC in 19% of patients. GVHD prophylaxis included a calcineurin inhibitor and mycophenolate mofetil in addition to PTCy in most patients. The planned time for discontinuation of GVHD prophylaxis is not available. The stem cell source was BM in 47% and PBSC in 53% of patients.

SCT outcomes

Transplantation outcomes are presented in Table 2. The 2-year OS after haploSCT was 64.4% (95% CI, 59.9–69.3). The 2-year LFS and GVHD-free relapse-free survival were 55.7% (95% CI, 51.1–60.7) and 43.7% (95% CI, 39.2–48.8) respectively. The incidence of relapse and NRM at 2 years after haploSCT was 27.1% (95% CI, 22.8–31.5) and 17.3% (95% CI, 13.9–20.9) respectively.

Acute GVHD and the impact on SCT outcomes

The incidence of acute GVHD grade II–IV and III–IV at day +180 after haploSCT was 33.3% (95% CI, 29.3–37.5) and 11.7% (95% CI, 9.1–14.6) respectively. The Cox multivariable model showed that acute GVHD grade II had no statistically significant impact on the incidence of relapse, HR 0.92 (95% CI, 0.58–1.48, $p = 0.74$). NRM and OS were also not different

TABLE 1 Patient characteristics.

Number	516
Age, median (range)	36 years (18–75)
Donor age, median (range)	39 (8–72)
Missing data (number of patients)	28
Gender (% male)	61%
Donor gender (% male)	58%
Female donor to male recipient	25%
Immune phenotype	
B cell	75%
T cell	25%
Missing data (number of patients)	42
Cytogenetics	
Philadelphia chromosome positive	36%
Missing data (number of patients)	118
Status at SCT	
CR1	68%
CR2	32%
Conditioning	
MAC	81%
RIC	19%
TBI in conditioning	53%
Dose 2–6 Gy	74%
Dose 8–12 Gy	26%
Missing data (number of patients)	6
Stem cell source	
BM	47%
PBSC	53%
GVHD prophylaxis (in addition to PTCy)	
CSA/MMF	63%
Tacrolimus/MMF	25%
Other	12%
KPS <90	25%
Missing data (number of patients)	14
Time between diagnosis SCT, median (range)	8 months (1–224)
Year of SCT, median (range)	2017 (2010–2019)

Abbreviations: BM, bone marrow; CMV, cytomegalovirus; CR, complete remission; CSA, ciclosporin; D, donor; GVHD, graft-versus-host disease; KPS, Karnofsky performance score; MAC, myeloablative conditioning; MMF, mycophenolate mofetil; PBSC, peripheral blood stem cells; PTCy, post-transplant cyclophosphamide; R, recipient; RIC, reduced intensity conditioning; SCT, stem cell transplantation; TBI, total body irradiation.

from patients who did not have acute GVHD or had acute GVHD grade I, with HR 1.39 (95% CI, 0.8–2.4, $p = 0.24$) and HR 1.35 (95% CI, 0.78–2.34, $p = 0.28$) respectively. Acute GVHD grade III–IV was not significantly associated with reduced incidence of relapse, HR 0.57 (95% CI, 0.27–1.22, $p = 0.15$). However, the risk of NRM was increased and OS was reduced in comparison with patients who did not have acute GVHD, with HR 1.95 (95% CI, 1.09–3.48, $p = 0.024$) and HR 1.91 (95% CI, 1.07–3.39, $p = 0.028$) respectively (Table 3).

TABLE 2 Transplantation outcomes.

Total number	***N* = 516**
2-Year overall survival	64.4% [59.9–69.3]
2-Year leukaemia-free survival	55.7% [51.1–60.7]
2-Year incidence of relapse	27.1% [22.8–31.5]
2-Year non-relapse mortality	17.3% [13.9–20.9]
Acute GVHD (day 180)	
Grade II–IV	33.3% [29.3–37.5]
Grade III–IV	11.7% [9.1–14.6]
Chronic GVHD (2 years)	
All grades	35.3% [30.8–39.9]
Extensive	11.8% [8.9–15.1]
2-year GVHD-free, relapse-free survival	43.7% [39.2–48.8]

Abbreviation: GVHD, graft-versus-host disease.

Chronic GVHD and the impact on SCT outcomes

The incidence of chronic GVHD of all grades and extensive chronic GVHD, at 2 years after SCT, was 35.3% (95% CI, 30.8–39.9) and 11.8% (95% CI, 8.9–15.1) respectively. The Cox multivariable model showed that limited chronic GVHD was associated with a similar risk of relapse, HR 1.06 (95% CI, 0.62–1.82, $p = 0.83$) in comparison with patients with no chronic GVHD. There was a non-statistically significant increase in NRM and a significant reduction of OS in comparison with patients with no chronic GVHD with HR 2.09 (95% CI, 0.95–4.63, $p = 0.068$) and HR 2.29 (95% CI, 1.07–4.94, $p = 0.034$) respectively. Extensive chronic GVHD was also not associated with reduced incidence of relapse, HR 0.95 (95% CI, 0.42–2.17, $p = 0.91$). However, NRM was increased and OS was reduced in comparison with patients who did not have chronic GVHD, with HR 3.3 (95% CI, 1.41–7.73, $p = 0.006$) and HR 3.27 (95% CI, 1.4–7.66, $p = 0.006$) respectively (Table 3).

DISCUSSION

In this study, we confirm the feasibility and favourable outcome of haploSCT with PTCy in adult patients with ALL in a relatively large registry-based study. A 2-year OS rate of 64% with a low incidence of NRM (17%) and relapse (27%) compares with other donor types.

Historically, ALL patients with GVHD had a lower incidence of relapse than patients with no GVHD suggesting a strong correlation between GVL and GVHD in this disease.[4,5] An analysis of a megafile of >48 000 transplants reported to the EBMT confirmed the well-known association of GVHD and GVL.[6] The strength of the association was different between diseases. A strong association was seen in chronic myeloid leukaemia and in ALL that was more

TABLE 3 Multivariable analysis of factors associated with relapse incidence, non-relapse mortality and overall survival after SCT.

	Relapse incidence		Non-relapse mortality		Overall survival	
	HR [95% CI]	*p*-Value	HR [95% CI]	*p*-Value	HR [95% CI]	*p*-Value
Acute GVHD grade II	0.92 [0.58-1.48]	0.74	1.39 [0.8–2.4]	0.24	1.35 [0.78–2.34]	0.28
Acute GVHD grade III–IV	0.57 [0.27–1.22]	0.15	1.95 [1.09–3.48]	0.024	1.91 [1.07–3.39]	0.028
Chronic GVHD limited	1.06 [0.62–1.82]	0.83	2.09 [0.95–4.63]	0.068	2.29 [1.07–4.94]	0.034
Chronic GVHD extensive	0.95 [0.42–2.17]	0.91	3.3 [1.41–7.73]	0.006	3.27 [1.4–7.66]	0.006
Age[a]	1 [0.98–1.01]	0.75	1.02 [1–1.03]	0.01	1.02 [1–1.03]	0.01
CR2 vs. CR1	3.18 [2.15–4.7]	<0.001	1.55 [0.98–2.46]	0.064	1.52 [0.96–2.42]	0.073
Immune type						
T cell vs. B cell	1.93 [1.29–2.89]	0.001	1.05 [0.62–1.76]	0.87	1.03 [0.61–1.74]	0.9
PBSC vs. BM	1.31 [0.88–1.96]	0.18	1.57 [0.98–2.5]	0.059	1.6 [1.01–2.55]	0.047
MAC vs. RIC	0.97 [0.57–1.63]	0.9	1.67 [0.91–3.07]	0.099	1.71 [0.93–3.13]	0.084
No. of female to male gender combination	1.13 [0.73–1.76]	0.59	1.37 [0.79–2.39]	0.26	1.39 [0.8–2.42]	0.24
Year of SCT[a]	0.88 [0.81–0.95]	0.001	0.98 [0.89–1.09]	0.73	0.99 [0.9–1.1]	0.87

Abbreviations: BM, bone marrow; CI, confidence interval; CR, complete remission; GVHD, graft-versus-host disease; HR, hazard ratio; MAC, myeloablative conditioning; PBSC, peripheral blood stem cells; RIC, reduced intensity conditioning; SCT, stem cell transplantation.

[a]Continuous variable.

prominent than that seen in AML. ALL was sensitive to all types and grades of GVHD while GVL in AML was apparent only in extensive chronic GVHD.

The most recent analysis performed by the Center for International Blood and Marrow transplantation (CIBMTR) consisted of 5215 patients divided into three cohorts: adults in CR1/CR2 ($n = 2593$), children in CR1/CR2 ($n = 1619$) and patients with advanced ALL ($n = 1003$).[7] Acute and chronic GVHD were associated with reduced incidence of relapse in ALL in CR1/CR2, but only acute GVHD grade III–IV and chronic GVHD resulted in reduced incidence of relapse in advanced ALL. Acute GVHD grade III–IV was associated with higher NRM that abrogated any survival advantage in reducing relapse. The best OS was observed in patients in CR1/CR2 with acute GVHD grade I–II and no chronic GVHD. Among patients with advanced ALL, the best outcome was seen in patients with chronic GVHD and no severe acute GVHD.

Natural killer (NK) cell activity is one of the mechanisms for GVL in the absence of GVHD. HaploSCT with extensive T-cell depletion is associated with low rates of GVHD, and allo-reactivity is mostly related to NK-cell activity. This NK alloreactivity effect was prominent in AML but was not seen in adult ALL, most probably due to the lack of expression of the essential adhesion molecules required for effector-target conjugate formation and/or effector cell activation.[23] The role of NK allo-reactivity in non-T-cell-depleted HaploSCT is much more controversial. An EBMT study showed that killer-cell immunoglobulin-like (KIR) mismatching was not associated with reduced relapse risk in AML or ALL in the PTCy setting.[24]

PTCy limits the rate of severe acute GVHD and of chronic GVHD following haploSCT.[25] However, there are limited data regarding the association of GVHD and GVL in this setting. We have previously shown there was a lack of association between GVHD and GVL in patients with AML following haploSCT with PTCy.[26,27] Patients with acute or chronic GVHD of any grade were not associated with a reduced incidence of relapse. Acute GVHD of any grade and extensive chronic GVHD were associated with increased NRM and reduced LFS. This study was followed by a large study of >12 000 patients with AML following HLA-matched SCT (sibling or 10/10 matched unrelated in CR1/CR2).[10] In the cohort of patients given standard GVHD prophylaxis (the majority of patients), GVHD and GVL were closely associated. However, in the smaller group of patients given PTCy, GVHD and GVL were separated and there was no reduction of relapse in patients with GVHD. Thus, it seems that this observation of separation of GVHD and GVL in AML in the haploidentical setting was related to the effect of PTCy rather than to the haploSCT setting.

In the current study, we extend these observations to patients with ALL. We show that, in patients given haploSCT with PTCy, acute and chronic GVHD of any grade are not associated with a reduction in the incidence of relapse post-transplant. The more severe forms are associated with increased NRM and reduced survival. This suggests that PTCy allows the separation of GVL from GVHD in haploSCT with PTCy also in patients with ALL. Similar results were reported by the Japanese registry in 938 patients with haematological malignancies given haploSCT with PTCy.[28] GVHD of any type or grade was not associated with a reduced relapse rate while the more severe forms were associated with higher NRM. The same observations were seen in the subgroup of 146 patients with ALL.

These observations contrast with the known strong association of GVHD and GVL in ALL in the HLA-matched setting.[4–7] They also contrast with the data reported by the

John Hopkins group from 340 patients with various haematological malignancies (including 24 patients with ALL) following haploSCT with non-myeloablative conditioning and PTCy.[29] They showed that acute GVHD grade II was associated with reduced relapse rates, similar NRM and improved OS compared to no GVHD. Acute GVHD grade III–IV did not reduce relapse, probably due to the high immune suppression burden, markedly increased NRM and reduced OS. Chronic GVHD showed a trend towards reduction of relapse but no effect on survival. Different transplantation platforms including conditioning regimen, stem cell source (PBSC vs. BM), as well as different patient characteristics and the low ALL patient number in the Baltimore study may explain some of these differences.

Both GVHD and GVL are mediated by donor T cells and NK cells and therefore occur in parallel. They require the presence of mismatched allo-antigens between donor and recipient and activation of the immune response. It remains debatable as to whether these effects can be separated. Some researchers have shown that there are differences between the two effects that can allow targeting of GVL without GVHD.[30,31] The mechanisms of GVHD prevention after PTCy are different from those after standard GVHD prophylaxis. There are different immune signatures and T-cell subset reconstitution is different, which may allow the separation between these effects. Earlier experiments suggested that allo-reactive T-cell elimination and thymic clonal deletion are the major mechanisms for GVHD prevention.[25] However, it was shown that PTCy impairs the proliferation and cytokine production of alloreactive T cells but does not completely eradicate them.[25,32] Thus, it may reduce the progression to a severe form of GVHD and persistence of the GVL effect. Theoretically, rapidly proliferating T cells directed against HLA antigens will easily be eliminated following PTCy in the haploidentical setting, while T cells that target the underlying leukaemia and infectious agents without causing GVHD will be spared. Therefore, there will not be any additional advantage in disease control for those having GVHD. The threshold level of T cells necessary to trigger GVL is lower than that required to trigger GVHD, and a lower level of GVHD may be sufficient to reduce the risk of relapse.[33]

PTCy promotes the recovery of regulatory T cells (T-regs).[32] T-regs, similar to haematopoietic stem cells, are protected from PTCy by a relatively high expression of aldehyde dehydrogenase.[34] They contribute to long-term post-transplant tolerance and prevention of progression to severe acute GVHD and to chronic GVHD by limiting T-cell proliferation and downregulation of pro-inflammatory cytokines, while maintaining CD8+ T-cell anti-leukaemia activity.

This study has several limitations. As a retrospective registry-based study, several disease and treatment characteristics are not completely reported. It is unknown why patients were referred for haploSCT and whether this may have had an impact on GVHD or GVL. Minimal residual status data at SCT are missing in a significant fraction of patients and could not be analysed and this may have had an impact on relapse analysis. The additional GVHD prophylaxis, in addition to the PTCy, and the planned duration of calcineurin inhibitor and mycophenolate are not uniform and may have had an impact on GVHD. The dataset does not allow significant subset analysis. For example, in Philadelphia-positive ALL, Tyrosine kinase inhibitor maintenance treatment may have reduced relapse and suppressed GVHD, altering the expected GVHD/GVL association.

In conclusion, GVHD of any type or grade is not associated with an improved relapse incidence after T-cell replete haploSCT with PTCy in ALL and offers no survival advantage. Severe forms are associated with higher NRM and lower survival. Future novel strategies for the reduction of relapse and prevention of significant GVHD are warranted.

AUTHOR CONTRIBUTIONS

AS, CP, ML, AN and MM designed the research, analysed and interpreted data and wrote the manuscript; CP and ML performed the statistical analysis. AS, AD, MK, MA, JT, SS, ZG, GS, DB, PP, HO, JV, FC, AN and MM provided patients, collected and analysed data and critically reviewed the manuscript before submission. All authors read and approved the final manuscript.

ACKNOWLEDGEMENTS

The authors acknowledge the contribution of all the EBMT centres providing patients for this study.

FUNDING INFORMATION

None.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

Data can be provided upon a reasonable request.

ETHICS STATEMENT

The study was approved by the Acute Leukaemia Working Party under the guidance of the EBMT. All patients provided written informed consent authorizing the use of information for research purposes.

ORCID

Avichai Shimoni https://orcid.org/0000-0001-8782-6160
Mutlu Arat https://orcid.org/0000-0003-2039-8557
Johanna Tischer https://orcid.org/0000-0003-1821-1976
Gerard Socié https://orcid.org/0000-0002-2114-7533
Fabio Ciceri https://orcid.org/0000-0003-0873-0123
Arnon Nagler https://orcid.org/0000-0002-0763-1265
Mohamad Mohty https://orcid.org/0000-0001-8536-7781

REFERENCES

1. DeFilipp Z, Advani AS, Bachanova V, Cassaday RD, Deangelo DJ, Kebriaei P, et al. Hematopoietic cell transplantation in the treatment of adult acute lymphoblastic leukemia: updated 2019 evidence-based review from the American Society for Transplantation and Cellular Therapy. Biol Blood Marrow Transplant. 2019;25(11):2113–23.
2. Giebel S, Marks DI, Boissel N, Baron F, Chiaretti S, Ciceri F, et al. Hematopoietic stem cell transplantation for adults with Philadelphia chromosome-negative acute lymphoblastic leukemia in first remission: a position statement of the European Working Group for Adult Acute Lymphoblastic Leukemia (EWALL) and the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation (EBMT). Bone Marrow Transplant. 2019;54(6):798–809.
3. Goldstone AH, Richards SM, Lazarus HM, Tallman MS, Buck G, Fielding AK, et al. In adults with standard-risk acute lymphoblastic leukemia, the greatest benefit is achieved from a matched sibling allogeneic transplantation in first complete remission, and an autologous transplantation is less effective than conventional consolidation/maintenance chemotherapy in all patients: final results of the International ALL Trial (MRC UKALL XII/ECOG E2993). Blood. 2008;111(4):1827–33.
4. Weiden PL, Flournoy N, Thomas ED, Prentice R, Fefer A, Buckner CD, et al. Antileukemic effect of graft-versus-host disease in human recipients of allogeneic-marrow grafts. N Engl J Med. 1979;300(19):1068–73.
5. Horowitz MM, Gale RP, Sondel PM, Goldman JM, Kersey J, Kolb HJ, et al. Graft-versus-leukemia reactions after bone marrow transplantation. Blood. 1990;75(3):555–62.
6. Stern M, de Wreede LC, Brand R, van Biezen A, Dreger P, Mohty M, et al. Sensitivity of hematological malignancies to graft-versus-host effects: an EBMT megafile analysis. Leukemia. 2014;28(11):2235–40.
7. Yeshurun M, Weisdorf D, Rowe JM, Tallman MS, Zhang MJ, Wang HL, et al. The impact of the graft-versus-leukemia effect on survival in acute lymphoblastic leukemia. Blood Adv. 2019;3(4):670–80.
8. Shah R, Murphy D, Logue M, Jerkins J, Jallouk A, Adetola K, et al. Multidisciplinary management of morbidities associated with chronic graft-versus-host disease. Clin Hematol Int. 2024;6(4):74–88.
9. McDonald GB, Sandmaier BM, Mielcarek M, Sorror M, Pergam SA, Cheng GS, et al. Survival, nonrelapse mortality, and relapse-related mortality after allogeneic hematopoietic cell transplantation: comparing 2003–2007 versus 2013–2017 cohort. Ann Intern Med. 2020;172(4):229–39.
10. Shimoni A, Peczynski C, Labopin M, Kulagin A, Meijer E, Cornelissen J, et al. Post-transplant cyclophosphamide separates graft-versus host disease and graft versus leukemia effects after HLA-matched stem-cell transplantation for acute myeloid leukemia. Leukemia. 2025;39(1):222–8.
11. Gagelmann N, Bacigalupo A, Rambaldi A, Hoelzer D, Halter J, Sanz J, et al. Haploidentical stem cell transplantation with posttransplant cyclophosphamide therapy vs other donor transplantations in adults with hematologic cancers: a systematic review and meta-analysis. JAMA Oncol. 2019;5(12):1739–48.
12. Shem-Tov N, Peczynski C, Labopin M, Itälä-Remes M, Blaise D, Labussière-Wallet H, et al. Haploidentical vs. unrelated allogeneic stem cell transplantation for acute lymphoblastic leukemia in first complete remission: on behalf of the ALWP of the EBMT. Leukemia. 2020;34(1):283–92.
13. Sanz J, Galimard JE, Labopin M, Afanasyev B, Sergeevich MI, Angelucci E, et al. Post-transplant cyclophosphamide containing regimens after matched sibling, matched unrelated and haploidentical donor transplants in patients with acute lymphoblastic leukemia in first complete remission, a comparative study of the ALWP of the EBMT. J Hematol Oncol. 2021;14(1):84.
14. Nagler A, Labopin M, Houhou M, Aljurf M, Mousavi A, Hamladji RM, et al. Outcome of haploidentical versus matched sibling donors in hematopoietic stem cell transplantation for adult patients with acute lymphoblastic leukemia: a study from the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation. J Hematol Oncol. 2021;14(1):53.
15. Nagler A, Labopin M, Swoboda R, Pioltelli P, Arat M, Yakoub-Agha I, et al. Haploidentical versus matched sibling donor hematopoietic stem cell transplantation for adult patients with relapsed/refractory acute lymphoblastic leukemia: a study from the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation. HemaSphere. 2022;6(11):e790.
16. Ben Abdeljelil N, Ouerghi R, Ben Yaiche I, Mekni S, Torjemane L, Belloumi D, et al. Total body irradiation-based conditioning versus chemotherapy before allogeneic stem cell transplantation for adults with acute lymphoblastic leukemia. Clinical Hematology International. 2024;6(3):4–8.
17. Spyridonidis A, Labopin M, Savani BN, Niittyvuopio R, Blaise D, Craddock C, et al. Redefining and measuring transplant conditioning intensity in current era: a study in acute myeloid leukemia patients. Bone Marrow Transplant. 2020;55(6):1114–25.
18. Przepiorka D, Weisdorf D, Martin P, Klingemann HG, Beatty P, Hows J, et al. 1994 Consensus conference on acute GVHD grading. Bone Marrow Transplant. 1995;15(6):825–8.
19. Shulman HM, Sullivan KM, Weiden PL, McDonald GB, Striker GE, Sale GE, et al. Chronic graft-versus-host syndrome in man. A long-term clinicopathologic study of 20 Seattle patients. Am J Med. 1980;69(2):204–17.
20. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc. 1958;53(282):457–81.
21. Gooley TA, Leisenring W, Crowley J, Storer BE. Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. Stat Med. 1999;18(6):695–706.
22. R Core Team. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2017. Available from: https://www.R-project.org/
23. Ruggeri L, Capanni M, Casucci M, Volpi I, Tosti A, Perruccio K, et al. Role of natural killer cell alloreactivity in HLA-mismatched hematopoietic stem cell transplantation. Blood. 1999;94(1):333–9.
24. Shimoni A, Labopin M, Lorentino F, Van Lint MT, Koc Y, Gülbas Z, et al. Killer cell immunoglobulin-like receptor ligand mismatching and outcome after haploidentical transplantation with post-transplant cyclophosphamide. Leukemia. 2019;33(1):230–9.
25. Kanakry CG, Fuchs EJ, Luznik L. Modern approaches to HLA-haploidentical blood or marrow transplantation. Nat Rev Clin Oncol. 2016;13(1):132.
26. Shimoni A, Labopin M, Angelucci E, Blaise D, Ciceri F, Koc Y, et al. The association of graft-versus-leukemia effect and graft-versus host disease in haploidentical transplantation with post-transplant cyclophosphamide for AML. Bone Marrow Transplant. 2022;57(3):384–90.
27. Baron F, Labopin M, Tischer J, Raiola AM, Vydra J, Blaise D, et al. GVHD occurrence does not reduce AML relapse following PTCy-based haploidentical transplantation: a study from the ALWP of the EBMT. J Hematol Oncol. 2023;16(1):10.
28. Shimomura Y, Komukai S, Kitamura T, Sobue T, Akahoshi Y, Kanda J, et al. Effect of graft-versus-host disease on outcomes of HLA-haploidentical peripheral blood transplantation using post-transplant cyclophosphamide. Bone Marrow Transplant. 2024;59(1):66–75.
29. McCurdy SR, Kanakry CG, Tsai HL, Kasamon YL, Showel MM, Bolaños-Meade J, et al. Grade II acute graft-versus-host disease and higher nucleated cell graft dose improve progression-free survival after HLA-haploidentical transplant with post-transplant cyclophosphamide. Biol Blood Marrow Transplant. 2018;24(2):343–52.

30. Negrin RS. Graft-versus-host disease versus graft-versus-leukemia. Hematology Am Soc Hematol Educ Program. 2015;2015:225–30.
31. Teshima T, Hashimoto D. Separation of GVL from GVHD -location, location, location. Front Immunol. 2023;14:1296663.
32. Wachsmuth LP, Patterson MT, Eckhaus MA, Venzon DJ, Gress RE, Kanakry CG. Post-transplantation cyclophosphamide prevents graft-versus-host disease by inducing alloreactive T cell dysfunction and suppression. J Clin Invest. 2019;129(6):2357–73.
33. Edinger M, Hoffmann P, Ermann J, Drago K, Fathman CG, Strober S, et al. CD4+CD25+ regulatory T cells preserve graft-versus-tumor activity while inhibiting graft-versus-host disease after bone marrow transplantation. Nat Med. 2003;9(9):1144–50.
34. Kanakry CG, Ganguly S, Zahurak M, Bolaños-Meade J, Thoburn C, Perkins B, et al. Aldehyde dehydrogenase expression drives human regulatory T cell resistance to posttransplantation cyclophosphamide. Sci Transl Med. 2013;5(211):211ra157.

How to cite this article: Shimoni A, Peczynski C, Labopin M, Dominietto A, Koc M, Arat M, et al. Graft-versus-host disease is not associated with reduced incidence of relapse following haploidentical stem cell transplantation with post-transplant cyclophosphamide for acute lymphoblastic leukaemia: A study on behalf of the Acute Leukaemia Working Party of European Society for Blood and Marrow Transplantation. Br J Haematol. 2025;207(5):2041–2048. https://doi.org/10.1111/bjh.70101