Annals of Hematology (2019) 98:1237–1247
https://doi.org/10.1007/s00277-018-3559-3

ORIGINAL ARTICLE

Outcomes of myeloablative peripheral blood stem cell transplantation for non-complete remission patients with relapsed/refractory peripheral T cell lymphomas

Zhenyang Gu[1] · Lu Wang[1,2] · Quanshun Wang[1] · Honghua Li[1] · Jian Bo[1] · Shuhong Wang[1] · Yu Zhao[1] · Fei Li[1] · Chunji Gao[1,2] · Daihong Liu[1] · Wenrong Huang[1,2]

Received: 16 July 2018 / Accepted: 15 November 2018 / Published online: 11 December 2018

Abstract

There was limited information about the efficacy of myeloablative allogeneic peripheral blood stem cell transplantation (allo-PBSCT) in non-complete remission (non-CR) patients with relapsed/refractory peripheral T cell lymphomas (PTCLs). We conducted a retrospective study of 21 consecutive non-CR patients with relapsed/refractory PTCLs who received myeloablative allo-PBSCT between January 2008 and June 2016. The median follow-up of survivors was 46.5 months (range, 14–105 months). The estimated 3-year relapse rate was 24% (95% CI, 9 to 43%). The 3-year non-relapsed mortality rate was 24% (95% CI, 9 to 44%). Overall, the estimated 3-year overall survival was 47% (95% CI, 25 to 66%). And the estimated 3-year progression-free survival was 46% (95% CI, 24 to 66%). Specifically, eight patients failed to achieve a CR at the first evaluation 3 months after allo-PBSCT and received withdraw of immunosuppression. Five patients also received donor lymphocytes infusions. Five (5/8, 62.5%) patients responded subsequently to these interventions (complete = 4, partial = 1). Overall, ten patients were alive at our last follow-ups, and durable CR were achieved in nine patients without further therapy. Five (50%) of these ten alive patients experienced chronic graft-versus-host disease (GVHD). Our favorable clinical outcomes suggested myeloablative allo-PBSCT was a valid therapeutic option for non-CR patients with relapsed/refractory PTCLs. The sustained CR after immunotherapeutic intervention and high prevalence of chronic GVHD in alive patients provided evidence of graft versus T cell lymphoma effects.

Keywords Peripheral T cell lymphoma · Relapsed/refractory · Allogeneic peripheral blood stem cell transplantation · Non-CR · Graft versus lymphoma effects

Introduction

Peripheral T cell lymphomas (PTCLs) are a broad group of heterogeneous malignancies. With a regional variation, PTCLs account for less than 15% of all non-Hodgkin's lymphomas (NHL) in Western countries [1]. However, its incidence is approximately 25–30% in East Asia [2]. Peripheral T cell lymphoma not otherwise specified (PTCL-NOS), NK/T cell lymphoma (NK/TCL), anaplastic large cell lymphoma (ALCL), and angioimmunoblastic T cell lymphoma (AITL) are the most common subtypes in East Asia. Less frequent subtypes include hepatosplenic γ/δ lymphoma (HSL), enteropathy-type T cell lymphoma, and subcutaneous-like T cell lymphoma.

Compared with aggressive B cell NHL, the prognosis of aggressive PTCLs was generally poor even when they were treated intensively [3–7]. CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone)-based chemotherapy was first-line therapy for most PTCL patients [7, 8]. However, there were no standards for subsequent consolidations. For patients who achieved a complete remission (CR) or partial response (PR) after first-line therapies, autologous hematopoietic stem

Zhenyang Gu and Lu Wang contributed equally to this work.

✉ Chunji Gao
gaochunji@hotmail.com

✉ Daihong Liu
daihongrm@163.com

✉ Wenrong Huang
huangwr301@163.com

[1] Department of Hematology, Chinese PLA General Hospital, No. 28 Fuxing Road, Beijing 100853, China

[2] Department of Hematology, Hainan Branch of General Hospital of PLA, Sanya 572013, Hainan, China

cell transplantation (auto-HSCT) was recommended for consolidation in most institutes [9]. Nevertheless, the vast majority of patients will eventually relapse after upfront chemotherapies, even when auto-HSCT was followed thereafter [10, 11]. The survival of patients with refractory or relapsed disease was disappointed. Median overall survival (OS) and progression-free survival (PFS) after first relapse or progression were only 5.5 and 3.1 months, respectively [12]. Allogeneic HSCT (allo-HSCT) was considered as a promising strategy for refractory/relapsed PTCLs. Several studies had shown the efficacy of allo-HSCT in PTCLs [13–18]. Given the progress in allogeneic transplantation techniques, we performed an observational retrospective study on 21 consecutive non-complete remission (non-CR) patients with relapsed/refractory PTCLs who received myeloablative allogeneic peripheral blood stem cell transplantation (allo-PBSCT) between January 2008 and June 2016 in Chinese People's Liberation Army (PLA) General Hospital.

Materials and methods

Study design and population

A retrospective study was conducted to investigate the clinical outcomes of patients with relapsed/refractory PTCLs who received allo-PBSCT in Chinese PLA General Hospital, a 4000-bed, tertiary care teaching hospital in Beijing, China, from January 2008 to June 2016. Only those patients who underwent myeloablative allo-PBSCT were included. Pathological diagnosis that had been made by hematopathologists in our hospital or reviewed by expert hematopathologists was only accepted. And patients with the diagnosis primary cutaneous lymphomas, lymphoblastic lymphomas, Sezary syndrome, or Mycosis fungoide were excluded. In order to focus on the outcomes of non-CR patients, relapsed/refractory patients who were in CR at the time of transplantation ($n = 2$) were excluded in our final analysis. Patients' records/information were anonymized and deidentified before analysis. The Medical Ethics Committee of PLA General Hospital reviewed and approved this study.

Demographic characteristics of patients included age at diagnosis and transplantation, gender, histopathologic subtype, disease status at and after transplantation, the number of cycles of chemotherapies before allo-HSCT, time from diagnosis to allo-HSCT, donor type, conditioning regimens, graft-versus-host disease (GVHD) prophylaxis, engraftment, and information on acute GVHD (aGVHD) and chronic GVHD (cGVHD), complications, and outcomes after allo-HSCT.

All donors were mobilized with recombinant human granulocyte-colony stimulating factor (rhG-CSF, Filgrastim, Kyowa Kirin, Tokyo, Japan; 5 μg/kg/day). Peripheral blood stem cells were the sole source of graft collected with a COBE Blood Cell Separator (Spectra LRS; COBEBCT Inc., Lakewood, CO) after 4 consecutive days mobilization [19, 20]. Three myeloablative conditioning regimens were used [20]: (1) modified BuCy regimen: busulfan (9.6 mg/kg, IV, days −10 to −8), carmustine, (250 mg/m^2, day −5), cytarabine (4 g/m^2, days −7 to −6), cyclophosphamide (100 mg/kg, days −4 to −3); (2) modified FB regimen: substitution of cyclophosphamide in BuCy with fludarabine (150 mg/m^2, days −7 to −3); (3) TBI + Cy: total body irradiation (TBI, 8–10 Gy, days −7 to −6), cyclophosphamide (100 mg/kg, days −4 to −3). GVHD prophylaxis was cyclosporine A (CsA), methotrexate (MTX) based and mycophenolate mofetil (MMF) or in combination with ATG (Thymoglobulin, rabbit; Genzyme Europe B.V., Naarden, the Netherlands, 10 mg/kg, days −5 to −2) in haploidentical or unrelated donor transplantation setting. The dosage of CsA was 2 to 3 mg/kg per day, intravenously (IV) starting on day −7 until bowel function returned to normal, and then the patient was switched to oral CsA with trough levels targeted at 150 to 400 ng/ml. The dosage of MTX was 15 mg/m^2, administered IV on day 1, and 10 mg/m^2 on days +3, +6, and +11 after transplantation. MMF was administered orally, 15 mg/kg every 12 h, from day −1 to day −28 after transplantation.

We chose the 3-month (day +90) time point after transplantation to perform the first response evaluations [21]. For patients who achieved a CR, immune suppression was steadily tapered from 3 months after transplantation. For patients who were not in CR 3 months after transplantation, immunosuppression was reduced and stopped in a relatively short time, which were defined as "withdraw of immunosuppression (WOI)" here. Donor lymphocyte infusions (DLIs) were given for some patients, who relapsed or did not get CR after PBSCT, did not show any evidence of aGVHD, and agreed to receive DLIs. All infused cells for DLIs were rhG-CSF mobilized peripheral blood mononuclear cells. In patients with high risk of rapid growing tumor, chemotherapy was also exploited.

Definitions and statistics

Engraftment: neutrophil engraftment was defined as the number of days from allo-HSCT to the first day of 3 consecutive days with the neutrophil count in blood above 0.5×10^9/l. Platelet engraftment was defined as the number of days from all-HSCT to the first day of 7 consecutive days with platelet count was higher than 20×10^9/l, unsupported by platelet transfusion. aGVHD (grades I, II, III, or IV levels) and cGVHD (limited or extensive) were graded according to international criteria [22]. Responses to treatment were graded according to the International Workshop non-Hodgkin's lymphomas criteria [23, 24]. CR was defined to be the disappearance of all clinical, biologic, and radiologic disorders related to lymphoma. PR was defined as more than 50% reduction of the

Table 1 Clinical characteristic of patients with relapsed/refractory PTCLs who received myeloablative allo-PBSCT at Chinese PLA General Hospital between 2008 and 2016

Pt.	Age/sex	Type of disease	Cycles of chemo before HSCT	Time from Dx to HSCT	Status at HSCT	Years of HSCT	Donor type	Conditioning regimen	GVHD prophylaxis
1	51/M	PTCL-NOS	6	8	PD1	2008	HLA-matched sibling	TBI + CY	CSA + MTX + MMF
2	43/M	PTCL-NOS	5	10	PD2	2009	HLA-matched sibling	TBI + CY	CSA + MTX
3	43/F	PTCL-NOS	4	2	PR1	2008	HLA-matched sibling	TBI + CY	CsA + MTX
4	39/M	Nasal NK/TCL	5	7	PD1	2013	HLA-matched sibling	TBI + CY	CSA + MTX + MMF
5	33/M	Nasal NK/TCL	6	9	PD1	2013	HLA-matched sibling	BU/CY	CSA + MTX + MMF
6	44/F	PTCL-NOS	3	7	PD1	2010	HLA-matched sibling	FLU + BU	CSA + MTX + MMF
7	47/M	AITL	4	3	SD1	2010	HLA-matched sibling	TBI + CY	CSA + MTX + MMF
8	25/M	Non-nasal NK/TCL	6	7	PR1	2014	Haploidentical donor	BU/CY	CSA + MTX + MMF
9	47/M	AITL	4	5	PR1	2013	HLA-matched sibling	TBI + CY	CsA + MTX
10	31/M	PTCL-NOS	7	6	PD1	2015	Haploidentical donor	BU/CY	CSA + MTX + ATG
11	12/F	ALK-positive ALCL	6	9	PR1	2008	Matched unrelated	TBI + CY	CSA + MTX + MMF
12	30/M	Nasal NK/TCL	4	16	PR2	2010	HLA-matched sibling	BU/CY	CsA + MTX
13	17/M	HSL	4	4	PD1	2013	HLA-matched sibling	TBI + CY	CSA + MTX + MMF
14	33/M	PTCL-NOS	7	5	PR1	2013	HLA-matched sibling	TBI + CY	CSA + MTX + MMF
15	44/M	Non-nasal NK/TCL	6	6	PR1	2013	Haploidentical donor	TBI + CY	CSA + MTX + MMF + ATG
16	28/M	PTCL-NOS	8	13	PR2	2008	Haploidentical donor	TBI + CY	CSA + MTX + MMF + ATG
17	35/M	ALK-positive ALCL	10	13	PR2	2016	Haploidentical donor	BU/CY	CSA + MTX + MMF + ATG
18	27/F	Enteropathy-type T cell	11	10	PD1	2009	Matched unrelated	TBI + CY	CSA + MTX + MMF + ATG
19	37 M	PTCL-NOS	5	7	PD1	2011	HLA-matched sibling	TBI + CY	CSA + MTX + MMF
20	51/M	AITL	8	11	PD2	2008	HLA-matched sibling	BU/CY	CSA + MTX + MMF
21	44/F	ALK-negative ALCL	5	39	PD2	2013	HLA-matched sibling	TBI + CY	CSA + MTX + MMF + ATG

Pt. patients, *Chemo* chemotherapy, *HSCT* hematopoietic stem cell transplantation, *Dx* diagnosis, *GVHD* graft versus host disease, *M* male, *F* female, *nasal NK/TCL* nasal NK/T cell lymphoma, *PTCL-NOS* peripheral T cell lymphoma, not otherwise specified, *AITL* angioimmunoblastic T cell lymphoma, *ALCL* anaplastic large cell lymphomas, *ALK* anaplastic lymphomas kinase, *HSL* hepatosplenic gamma-delta T cell, *PR* partial remission, *PD* progression disease, *SD* stable disease, *TBI* total body irradiation, *CY* cyclophosphamide, *BU* busulfan, *FLU* fludarabine, *CsA* cyclosporine, *MTX* methotrexate, *MMF* mycophenolate mofetil, *ATG* anti-T cell globulin

tumor burden. Progressive disease (PD) was defined as more than 25% increase of the tumor mass or the onset of new tumor mass. Other cases were defined as stable disease (SD). All patients were evaluated by [^{18}F] fluorodeoxyglucose-positron emission tomography/computed tomography (PET/CT) and bone marrow aspiration or biopsy before and + 3, + 6, + 9, + 12 months after allo-PBSCT, and thereafter annually unless otherwise clinically indicated.

OS was calculated from the day of transplantation until date to death of any cause, or last follow-up for surviving patients. PFS was defined as the day of transplantation to relapse, progressive disease, or death, or last follow-up for surviving patients without disease progression. Non-relapse mortality (NRM) was defined as death from any cause related to transplantation without disease progression. Time to relapse and time to NRM were calculated from the date of transplantation.

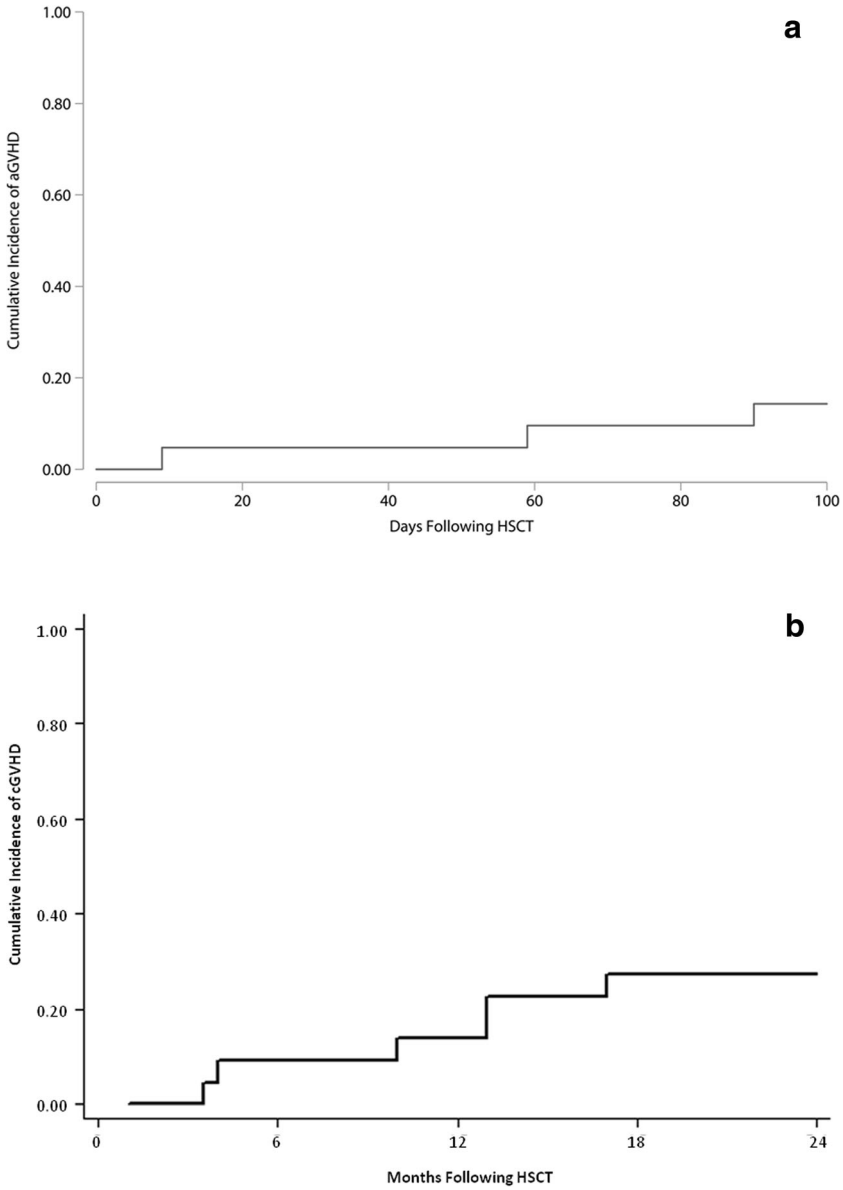

Fig. 1 Cumulative incidence of GVHD. The cumulative 100-day incidence of grades II–IV aGVHD was 14% (95% CI, 4–32%) (**a**). The estimated 2-year incidence of cGVHD were 29%, (95% CI, 12–48%) (**b**)

Descriptive tables were used to show demographic and transplant characteristics of patients included in this study. The probability of survival as a function of time was estimated using the Kaplan-Meier method with 95% confidence intervals (CIs) by SPSS, version 22.0 (SPSS, Chicago, IL). Cumulative incidences of NRM, relapse, and GVHD were estimated by competing-risk analysis using Gray's method by R software, version 2.12.

Results

Patient characteristics

A total of 21 patients were identified to meet the criteria: (1) relapsed after or were refractory to upfront chemotherapies; (2) underwent allo-PBSCT; (3) received @@myeloablative conditioning regimens; (4) did not achieve a CR at the time of transplantation. Their clinical characteristics were summarized in Table 1. There were 16 males (76%) and 5 females (24%). Their median age at allo-PBSCT was 37 years (range, 12 to 51 years). Most patients had been heavily treated before allo-PBSCT. Their detailed cycles of prior chemotherapies before allo-PBSCT were listed in Table 1, and their median number of prior cycles were 6 (range, 3 to 11). None of these patients received prior auto-HSCT. As to their disease status at the time of allo-PBSCT, 9 cases (43%) were in PR, whereas 12 cases (57%) were in SD/PD. Fourteen patients received their stem cells from HLA-matched sibling donors, five from haploidentical donors, and two from HLA-matched unrelated donors.

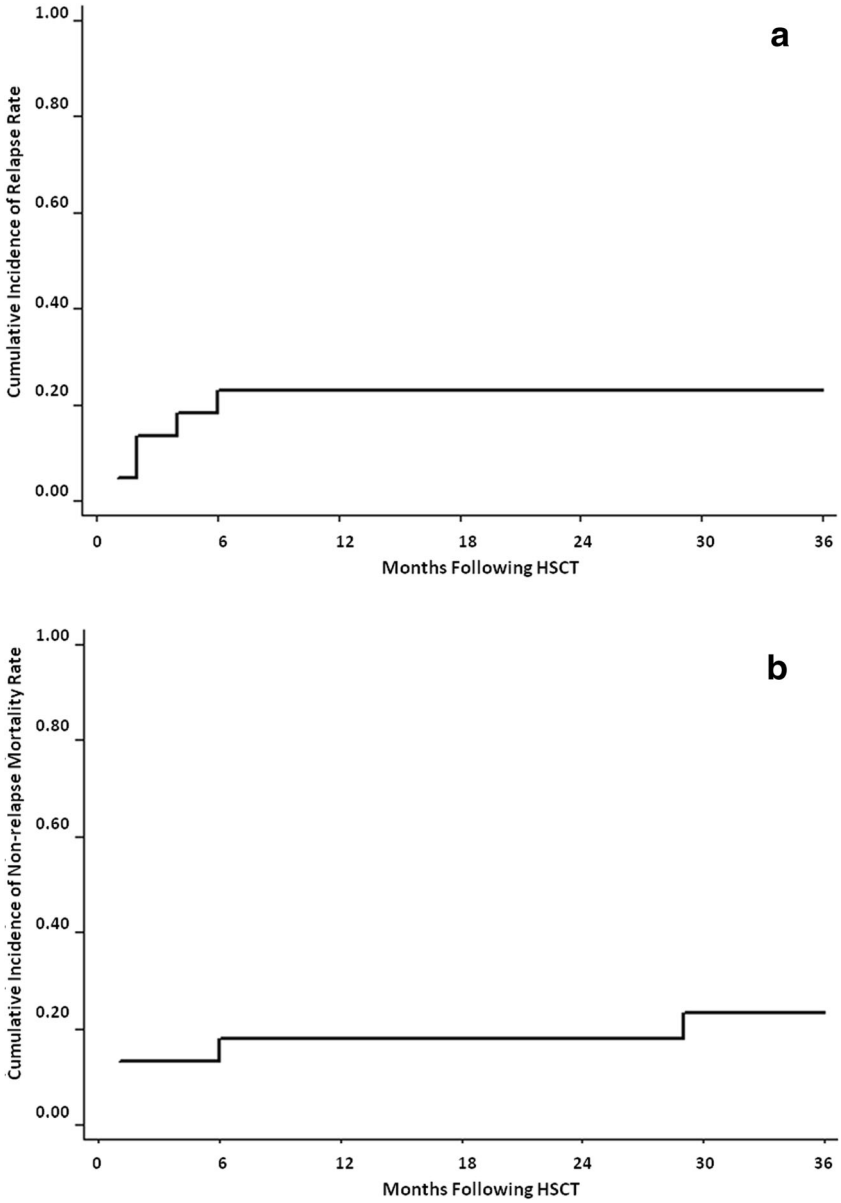

Fig. 2 The estimated 3-year relapse rate and NRM rate after allo-HSCT were 24% (95% CI, 9–43%) (**a**) and 24% (95% CI, 9–44%) (**b**), respectively

Engraftment and graft-versus-host disease

Engraftment was non-assessable in two patients: one patient died of hyper-acute GVHD on day + 13; the other patient died of bacterial infections on day + 9. One patient experienced graft failure and died of multiorgan failure 6 months after allo-HSCT. Overall, 18 patients achieved sustained engraftment and showed evidence of complete donor chimers on bone marrow aspirates 1 month after allo-PBSCT, using microsatellite polymerase chain reaction. The median time of neutrophil engraftment was 15.5 days (range, 9 to 22 days), and for platelets engraftment was 19 days (range, 12 to 35 days). Overall, three patients developed II to IV aGVHD, and the cumulative 100-day incidence of II to IV aGVHD was 14% (95% CI, 4 to 32%) (Fig. 1a). Four patients experienced limited cGVHD and three patients developed extensive cGVHD. The estimated 2-year incidence of cGVHD were 29%, (95% CI, 12–48%) (Fig. 1b). For the 10 patients who were alive at our last follow-ups, 5 patients (50%) experienced limited or extensive cGVHD.

Clinical outcomes and overall survival

The median follow-up of survivors was 46.5 months (range, 14–105 months). Five patients relapsed and died of lymphoma progression within 1 year after transplantation, with two patients died of early disease progression within 3 months. The estimated 3-year relapse rate was 24% (95% CI, 9 to 43%)

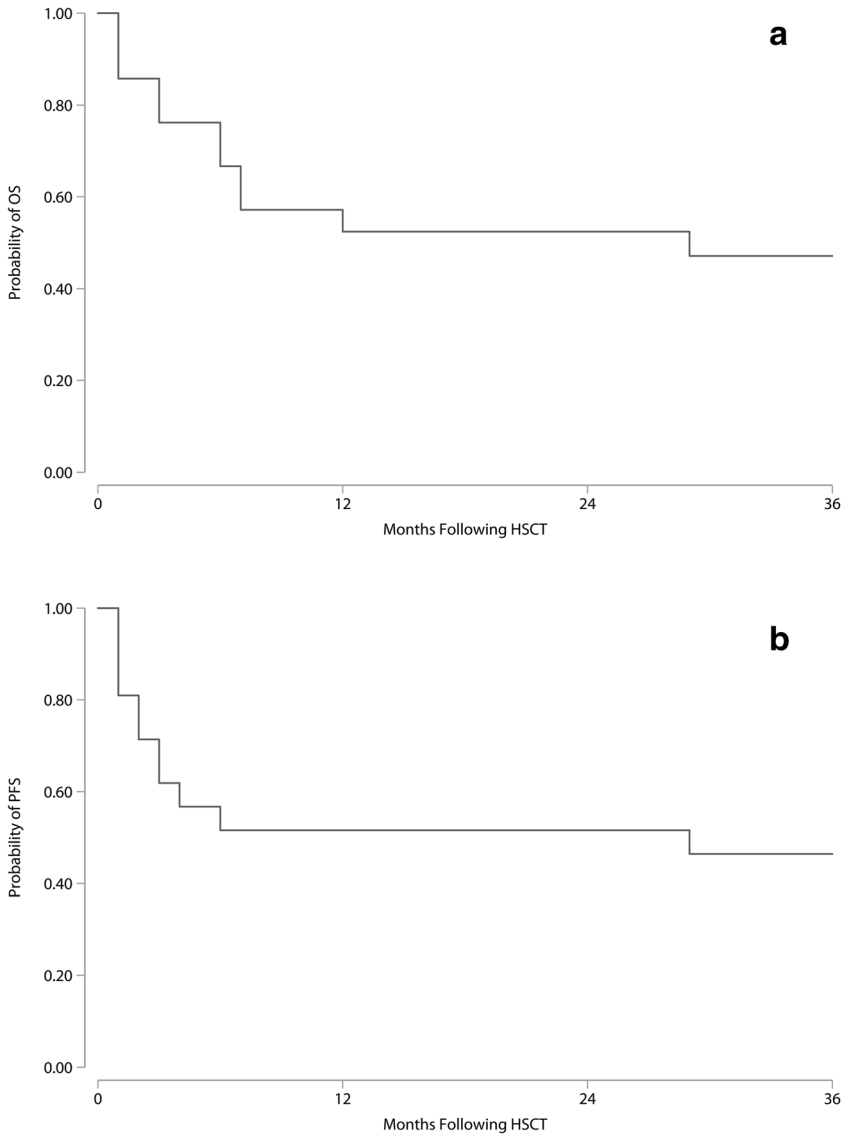

Fig. 3 The estimated 3-year OS was 47% (95% CI, 25–66%) (**a**). The estimated 3-year PFS was 46% (95% CI, 24–66%) (**b**)

(Fig. 2a). Six patients died of non-relapse reasons during our follow-ups. Causes of death were hyper-acute GVHD ($n = 1$), cGVHD ($n = 1$), cerebral hemorrhage ($n = 1$), and infections ($n = 3$, two bacterial and one fungi pneumonia). And the estimated 3-year NRM is 24% (95% CI, 9 to 44%) (Fig. 2b). Overall, the estimated 3-year OS was 47% (95% CI, 25 to 66%) (Fig. 3a). And the estimated 3-year PFS was 46% (95% CI, 24 to 66%) (Fig. 3b). There was no difference in OS for patients with different disease status at PBSCT (PR group versus PD group) ($p = 0.43$, Fig. 4).

Responses to allo-PBSCT and immunotherapeutic interventions thereafter

The detailed responses of these 21 patients were shown in Table 2. Five patients died within 3 months after transplantation. Causes of death were disease progression (two patients), hyper-acute GVHD (one patient), infectious disease (one patient), and cerebral hemorrhage (one patient). First evaluation about their responses to allo-PBSCT was performed for the remaining 16 patients 3 months after transplantation: 8 patients achieved CR, and 8 patients were in PD/PR.

For the eight patients who achieved a CR at the 3-month evaluation after allo-PBSCT, immunosuppression was steadily tapered as usual from 3 months after transplantation. No extra interventions were used later. During our subsequent evaluations and follow-ups, five patients were still alive in a sustained CR; three patients died (one patient died of lymphoma progression 7 months after transplantation, one patient died of bacterial infection 6 months after transplantation, and one patient died of chronic GVHD 29 months after transplantation).

For the eight patients who did not get a CR at the 3-month evaluation after allo-PBSCT, WOI was initially used. Then,

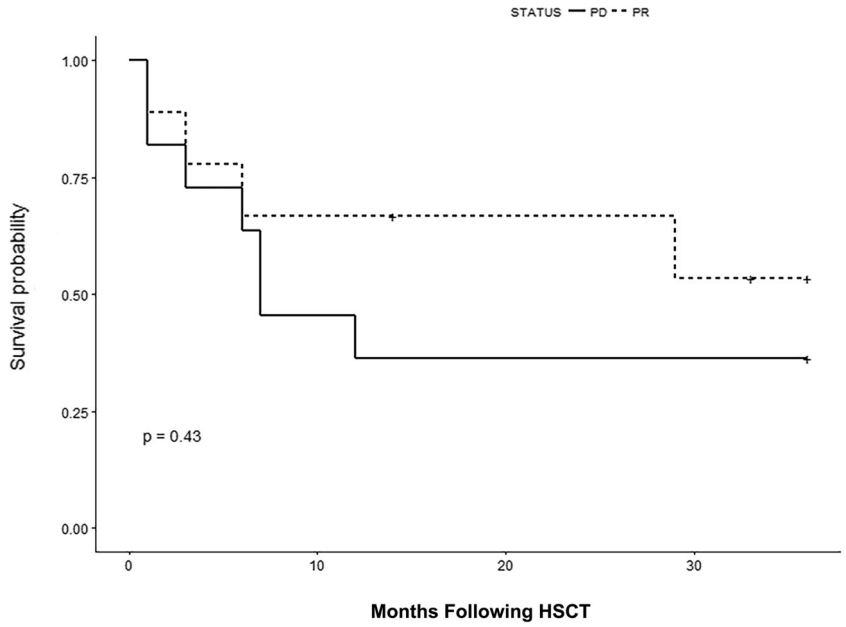

Fig. 4 Overall survival for patients with different disease status at HSCT (3-year OS: PR group versus PD group = 53% (95 CI, 28–100%) vs. 36% (95 CI, 17–79%), $p = 0.43$)

four patients also received additional DLIs. One patient received chemotherapy. And one patient received both DLIs and radiotherapy. During our subsequent evaluations and follow-ups, four patients were still in CR. One patient went into PR from PD. Three patients died of different reasons. The overall response rate of these eight patients to immunotherapeutic interventions was 62.5% (5/8).

For the five patients who received DLIs, they were all in PR or PD status during our first response evaluation 3 months after transplantation. During our subsequent follow-up and response evaluation, two patients went into CR from PR; one patient went into CR from PD; one patient went into PR from PD; one patient died of lymphoma progression. The overall response rate was 80% (4/5). Three of the five patients developed cGVHD after DLIs.

Discussion

While previous studies had shown promising results of allogeneic HSCT in the treatment of PTCLs [13–18, 25–27], most of these studies either included patients that were in CR at the time of allo-HSCT, or focused on patients receiving nonmyeloablative allo-HSCT. Our study confirmed the long-term disease control of myeloablative allo-PBSCT in non-CR patients with relapsed/refractory PTCLs. Overall, 48% (10/21) of the patients are alive at median follow-up of 46.5 months. And nine patients achieved durable CR without further therapy. We also assessed their responses after allo-PBSCT and further responses to immunotherapeutic interventions by either withdraw of immunosuppression or DLIs, somehow, demonstrating that the graft versus T cell lymphoma effects played a major role in the setting of myeloablative allo-PBSCT. The overall response rate to immunotherapeutic interventions was 62.5% (5/8). For the five patients who received additional DLIs, the overall response rate was 80% (4/5).

There were few reports on clinical outcomes of patients receiving myeloablative allo-PBSCT for relapsed/refractory PTCLs. Relapsed or refractory patients were very difficult to cure and long-term survival was dismal. In order to focus on the outcomes of non-CR patients with relapsed/refractory PTCLs, we excluded patients who were in CR at the time of transplantation. Nevertheless, we demonstrated a favorable OS and PFS in non-CR patients with relapsed/refractory diseases following myeloablative allo-PBSCT. Our OS (47%) was similar with previous studies [18, 26, 28]. Firstly, all these three studies include patients who were in CR at the time of transplantation. Secondly, the median cycles of prior chemotherapies before all-HSCT of these patients in these studies was less severe than that in our studies, which meant patients in our study had been more heavily treated and more resistant to chemotherapies. So, it was acceptable to achieve the similar survival in our study. Our results was slightly lower than OS (53–61%) in these studies [13, 17, 25, 27], and much lower than OS in Loirat's [14] (72.5%) and Corradini's [16] (81%) studies. One possible explanation was the differences in disease status at the time of transplantation. At least one third of patients in these three studies [13, 17, 25, 27] were in CR at the time of transplantation. In Loirat's study [14], allo-HSCT was undergone as the upfront treatments after induction chemotherapy. And only 22.5% (11/49) of the total patients in this study were in PD at the time of transplantation. In Corradini's study [16], 13 of the total 17 patients were in CR/PR at the time of transplantation. Twelve of 21 (57%) patients were in

Table 2 Responses and interventions and responses of patients with relapsed/refractory PTCLs after allo-PBSCT

Pt.	Responses 3-month after HSCT	Interventions	Later responses	aGVHD	cGVHD	Survival (months)	Causes of death
1	–	–	–	–	–	1	Die of infection
2	–	–	–	Yes	–	1	Die of hyper-acute GVHD
3	–	–	–	–	–	1	Died of cerebral hemorrhage
4	CR	–	CR	No	No	44+	
5	CR	–	CR	No	Extensive cGVHD	47+	
6	CR	–	CR	No	–	79+	
7	CR	–	CR	No	No	84+	
8	CR	–	CR	No	No	33+	
9	CR	–	CR	No	Extensive cGVHD	29	Died of chronic GVHD
10	CR	–	PD	No	No	7	Die of disease,
11	CR	–	CR	No	No	6	Die of infection
12	PD	–	–	No	–	3	Die of disease
13	PD	–	–	No	–	3	Die of disease
14	PR	WOI + DLI	CR	No	Limited cGVHD	46+	
15	PR	WOI + DLI	CR	No	Limited cGVHD	44+	
16	PD	WOI + DLI	CR	No	No	105+	
17	PD	WOI + DLI + Radio	PR	Yes	Extensive cGVHD	14+	
18	PD	WOI	CR	Yes	Extensive cGVHD	97+	
19	PR	WOI + DLI	PD	No	No	12	Die of disease
20	PR	WOI	PR	No	Extensive cGVHD	7	Died of fungi infection
21	PD	WOI + Chemo	PD	No	No	6	Die of disease

Pt. patients, *PTCLs* peripheral T cell lymphomas, *HCT* hematopoietic stem cell transplantation, *aGVHD* acute graft versus host disease, *cGVHD* chronic graft versus host disease, *CR* complete remission, *PR* partial remission, *PD* progression disease, *DLI* donor lymphocyte infusion, *WOI* withdrawal of immunosuppression, *Chemo* chemotherapy, *Radio* radiotherapy

PD at the time of transplantation in our study, and the duration of follow-up in our study was longer than that in Corradini's study (a median of 3 versus 2 years). Overall, it was very encouraging to achieve the 3-year OS (47%) in a group of non-CR patients with relapsed/refractory PTCLs.

Early myeloablative allo-HSCT was associated with high prevalence of regimen-related toxicity and transplantation-related mortality. And nonmyeloablative or reduced intensity conditioning regimens was accompanied by higher relapse rates. Most of previous studies performed to date included lots of patients that received allo-HSCT before 2005 [16–18, 25–28]. Improvement in supportive care measures and better management in the treatment of GVHD had greatly reduced overall mortality from 41 to 26% in the period 2003–2007, as compared with 1993–2007 period [29]. And in our study, we focused on patients that received allo-PBSCT after 2008. And our 3-year NRM rate was as low as 24%. The incidence of II–IV aGVHD (14%) and 2-year cGVHD (29%) was both acceptable and comparable with previous studies [18, 30]. The fact that ATG were used for GVHD prophylaxis in six patients in our study contributed to the lower incidence of II–IV aGVHD here. The 3-year relapse rate in this study was 24%, lower than those in previous studies that combined myeloablative and nonmyeloablative allo-HSCT for patients with PTCLs [17, 26, 28]. Myeloablative conditioning regimen and peripheral grafts used in our study somehow both contributed to reduce relapse rates.

The efficacy of allo-HSCT depended on two effects: the antitumor effects of conditioning regimens given before transplantation and the immune-mediated graft versus tumor effects by allo-reactive lymphocytes of the grafts [31]. Based on our results that eight patients achieved CR 3 months after allo-HSCT with myeloablative conditioning regimens, it was very reasonable to conclude that non-CR relapsed/refractory PTCLs could have been susceptible to the high-dose cytotoxic chemotherapy or radiotherapy in myeloablative conditioning regimens. During our subsequent evaluations and follow-ups, five of these eight patients were alive in sustained CR. We

would rather believe this was due to the combined effects of conditioning regimens and the graft versus T cell lymphoma effects. But the sustained CR was probably depending on the sole effects of the conditioning regimens. That was why myeloablative allo-HSCT suffers from lower relapse rates. To further detect whether there was a graft versus T cell lymphoma effect, we also analyzed patients that were in PR or PD 3 months after transplantation. Five out of eight patients showed responses to immunotherapeutic interventions (WOI and DLIs). Although the sustained CR in patients who in PR 3 months after allo-HSCT could be a continued response of the conditioning regimens. The observation that two patients who were in PD 3 months after allo-HSCT also achieved sustained CR after immunotherapeutic interventions provided solid evidence for the existence of graft versus T cell lymphoma effect. Similar results had been observed in the setting of nonmyeloablative allo-HSCT in patients with PTCLs [16, 17] and patients with B cell lymphomas [21]. Four out of five patients (80%) in our study responded to DLIs, providing further evidence for the existence of graft versus lymphoma effects. In addition, chronic GVHD was also thought to be another kind of evidence for graft versus lymphoma effects. In our study, 50% of all patients who were alive until our last follow-up experienced limited or extensive chronic GVHD.

Conclusions

In summary, our results, together with the studies cited above, demonstrated the long-term disease control of myeloablative allo-PBSCT in non-CR patients with relapsed/refractory PTCLs. Our further analysis on the responses to immunotherapeutic interventions provided evidence for the existence of graft versus T cell lymphoma effects, which also played an important role in the setting of myeloablative allo-PBSCT. However, there were several inherent limitations in our study, such as the retrospective nature, the small number of patients, and the heterogeneity in pathological subtypes. Considering that the feasibility and safety of myeloablative allo-PBSCT are increasing with the progress in supportive care measures and better management of complications in modern transplantation techniques, more patients with PTCLs can be cured with allo-PBSCT. Nevertheless, further prospective studies were really needed to evaluate allo-PBSCT for the treatment of PTCLs.

Authors' contributions Chunji Gao, Daihong Liu, Wenrong Huang designed the study and initiated this work; Data was obtained by Zhenyang Gu, Lu Wang, Quanshun Wang, Honghua Li, Jian Bo, Shuhong Wang, Yu Zhao, Fei Li, Chunji Gao, Daihong Liu, Wenrong Huang. Monitoring and all statistical analyses were performed by Zhenyang Gu, Lu Wang, Chunji Gao, Daihong Liu, Wenrong Huang. Zhenyang Gu wrote the paper; all the authors were involved in the interpretation of the results; read, gave comments, and approved the final version of the manuscript; had full access to the data in the study; and take responsibility for the accuracy of the data analysis.

Compliance with ethical standards

Conflict of interest All authors did not have any grants for this manuscript. All authors declared that they had no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The Medical Ethics Committee of PLA General Hospital reviewed and approved this study.

Informed consent Informed consent was obtained from all individual participants included in the study.

Consent for publication All authors agree that this manuscript can be published in Journal of Experimental & Clinical Cancer Research.

Availability of data and material All data and material are available in this manuscript.

Abbreviations aGVHD, acute GVHD; AITL, angioimmunoblastic T cell lymphoma; ALCL, anaplastic large cell lymphoma; Allo-HSCT, allogeneic HSCT; allo-PBSCT, allogeneic peripheral blood stem cell transplantation; auto-HSCT, autologous hematopoietic stem cell transplantation; cGVHD, chronic GVHD; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CIs, confidence intervals; DLIs, donor lymphocyte infusions; GVHD, graft versus host disease; HSL, hepatosplenic γ/δ lymphoma; NHL, non-Hodgkin's lymphomas; NK/TCL, NK/T cell lymphoma; non-CR, non-complete remission; NRM, non-relapse mortality; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; PTCLs, peripheral T cell lymphomas; PTCL-NOS, peripheral T cell lymphoma not otherwise specified; SD, stable disease

References

1. The Non-Hodgkin's Lymphoma Classification Project (1997) A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. Blood 89(11):3909–3918
2. Park S, Ko YH (2014) Peripheral T cell lymphoma in Asia. Int J Hematol 99(3):227–239. https://doi.org/10.1007/s12185-014-1520-3
3. Bellei M, Foss FM, Shustov AR, Horwitz SM, Marcheselli L, Kim WS, Cabrera ME, Dlouhy I, Nagler A, Advani RH, Pesce EA, Ko YH, Martinez V, Montoto S, Chiattone C, Moskowitz A, Spina M, Biasoli I, Manni M, Federico M, International TcPN (2018) The outcome of peripheral T-cell lymphoma patients failing first-line therapy: a report from the prospective, international T-cell project. Haematologica 103(7):1191–1197. https://doi.org/10.3324/haematol.2017.186577
4. Vose J, Armitage J, Weisenburger D, International TCLP (2008) International peripheral T-cell and natural killer/T-cell lymphoma study: pathology findings and clinical outcomes. J Clin Oncol 26(25):4124–4130. https://doi.org/10.1200/JCO.2008.16.4558
5. Nickelsen M, Ziepert M, Zeynalova S, Glass B, Metzner B, Leithaeuser M, Mueller-Hermelink HK, Pfreundschuh M, Schmitz N (2009) High-dose CHOP plus etoposide (MegaCHOEP) in T-cell lymphoma: a comparative analysis of

patients treated within trials of the German High-Grade Non-Hodgkin Lymphoma Study Group (DSHNHL). Ann Oncol 20(12):1977–1984. https://doi.org/10.1093/annonc/mdp211
6. Savage KJ, Chhanabhai M, Gascoyne RD, Connors JM (2004) Characterization of peripheral T-cell lymphomas in a single North American institution by the WHO classification. Ann Oncol 15(10):1467–1475. https://doi.org/10.1093/annonc/mdh392
7. Rodriguez J, Munsell M, Yazji S, Hagemeister FB, Younes A, Andersson B, Giralt S, Gajewski J, de Lima M, Couriel D, Romaguera J, Cabanillas FF, Champlin RE, Khouri IF (2001) Impact of high-dose chemotherapy on peripheral T-cell lymphomas. J Clin Oncol 19(17):3766–3770. https://doi.org/10.1200/JCO.2001.19.17.3766
8. Armitage JO (2017) The aggressive peripheral T-cell lymphomas: 2017. Am J Hematol 92(7):706–715. https://doi.org/10.1002/ajh.24791
9. Schmitz N, Lenz G, Stelljes M (2018) Allogeneic hematopoietic stem cell transplantation for T-cell lymphomas. Blood 132(3):245–253. https://doi.org/10.1182/blood-2018-01-791335
10. Rodriguez J, Conde E, Gutierrez A, Lahuerta JJ, Arranz R, Sureda A, Zuazu J, Fernandez de Sevilla A, Bendandi M, Solano C, Leon A, Varela MR, Caballero MD, Grupo Espanol de Linfomas/Trasplante Autologo de Medula Osea SLABMTSG (2007) The adjusted International Prognostic Index and beta-2-microglobulin predict the outcome after autologous stem cell transplantation in relapsing/refractory peripheral T-cell lymphoma. Haematologica 92(8):1067–1074
11. Corradini P, Tarella C, Zallio F, Dodero A, Zanni M, Valagussa P, Gianni AM, Rambaldi A, Barbui T, Cortelazzo S (2006) Long-term follow-up of patients with peripheral T-cell lymphomas treated up-front with high-dose chemotherapy followed by autologous stem cell transplantation. Leukemia 20(9):1533–1538. https://doi.org/10.1038/sj.leu.2404306
12. Mak V, Hamm J, Chhanabhai M, Shenkier T, Klasa R, Sehn LH, Villa D, Gascoyne RD, Connors JM, Savage KJ (2013) Survival of patients with peripheral T-cell lymphoma after first relapse or progression: spectrum of disease and rare long-term survivors. J Clin Oncol 31(16):1970–1976. https://doi.org/10.1200/JCO.2012.44.7524
13. Huang H, Jiang Y, Wang Q, Guo L, Jin Z, Fu Z, Han Y, Sun A, Liu W, Ruan J, Wu D (2017) Outcome of allogeneic and autologous hematopoietic cell transplantation for high-risk peripheral T cell lymphomas: a retrospective analysis from a Chinese center. Biol Blood Marrow Transplant 23(8):1393–1397. https://doi.org/10.1016/j.bbmt.2017.04.021
14. Loirat M, Chevallier P, Leux C, Moreau A, Bossard C, Guillaume T, Gastinne T, Delaunay J, Blin N, Mahe B, Dubruille V, Augeul-Meunier K, Peterlin P, Maisonneuve H, Moreau P, Juge-Morineau N, Jardel H, Mohty M, Moreau P, Le Gouill S (2015) Upfront allogeneic stem-cell transplantation for patients with nonlocalized untreated peripheral T-cell lymphoma: an intention-to-treat analysis from a single center. Ann Oncol 26(2):386–392. https://doi.org/10.1093/annonc/mdu515
15. Kyriakou C, Canals C, Finke J, Kobbe G, Harousseau JL, Kolb HJ, Novitzky N, Goldstone AH, Sureda A, Schmitz N (2009) Allogeneic stem cell transplantation is able to induce long-term remissions in angioimmunoblastic T-cell lymphoma: a retrospective study from the lymphoma working party of the European group for blood and marrow transplantation. J Clin Oncol 27(24):3951–3958. https://doi.org/10.1200/JCO.2008.20.4628
16. Corradini P, Dodero A, Zallio F, Caracciolo D, Casini M, Bregni M, Narni F, Patriarca F, Boccadoro M, Benedetti F, Rambaldi A, Gianni AM, Tarella C (2004) Graft-versus-lymphoma effect in relapsed peripheral T-cell non-Hodgkin's lymphomas after reduced-intensity conditioning followed by allogeneic transplantation of hematopoietic cells. J Clin Oncol 22(11):2172–2176. https://doi.org/10.1200/JCO.2004.12.050
17. Le Gouill S, Milpied N, Buzyn A, De Latour RP, Vernant JP, Mohty M, Moles MP, Bouabdallah K, Bulabois CE, Dupuis J, Rio B, Gratecos N, Yakoub-Agha I, Attal M, Tournilhac O, Decaudin D, Bourhis JH, Blaise D, Volteau C, Michallet M, Societe Francaise de Greffe de Moelle et de Therapie C (2008) Graft-versus-lymphoma effect for aggressive T-cell lymphomas in adults: a study by the Societe Francaise de Greffe de Moelle et de Therapie Cellulaire. J Clin Oncol 26(14):2264–2271. https://doi.org/10.1200/JCO.2007.14.1366
18. Dodero A, Spina F, Narni F, Patriarca F, Cavattoni I, Benedetti F, Ciceri F, Baronciani D, Scime R, Pogliani E, Rambaldi A, Bonifazi F, Dalto S, Bruno B, Corradini P (2012) Allogeneic transplantation following a reduced-intensity conditioning regimen in relapsed/refractory peripheral T-cell lymphomas: long-term remissions and response to donor lymphocyte infusions support the role of a graft-versus-lymphoma effect. Leukemia 26(3):520–526. https://doi.org/10.1038/leu.2011.240
19. Maris MB, Niederwieser D, Sandmaier BM, Storer B, Stuart M, Maloney D, Petersdorf E, McSweeney P, Pulsipher M, Woolfrey A, Chauncey T, Agura E, Heimfeld S, Slattery J, Hegenbart U, Anasetti C, Blume K, Storb R (2003) HLA-matched unrelated donor hematopoietic cell transplantation after nonmyeloablative conditioning for patients with hematologic malignancies. Blood 102(6):2021–2030. https://doi.org/10.1182/blood-2003-02-0482
20. Huang WR, Li HH, Gao CJ, Bo J, Li F, Dou LP, Wang LL, Jing Y, Wang L, Liu DH, Yu L (2016) Haploidentical, unmanipulated G-CSF-primed peripheral blood stem cell transplantation for high-risk hematologic malignancies: an update. Bone Marrow Transplant 51(11):1464–1469. https://doi.org/10.1038/bmt.2016.166
21. Bishop MR, Dean RM, Steinberg SM, Odom J, Pavletic SZ, Chow C, Pittaluga S, Sportes C, Hardy NM, Gea-Banacloche J, Kolstad A, Gress RE, Fowler DH (2008) Clinical evidence of a graft-versus-lymphoma effect against relapsed diffuse large B-cell lymphoma after allogeneic hematopoietic stem-cell transplantation. Ann Oncol 19(11):1935–1940. https://doi.org/10.1093/annonc/mdn404
22. Przepiorka D, Weisdorf D, Martin P, Klingemann HG, Beatty P, Hows J, Thomas ED (1995) 1994 Consensus conference on acute GVHD grading. Bone Marrow Transplant 15(6):825–828
23. Cheson BD, Horning SJ, Coiffier B, Shipp MA, Fisher RI, Connors JM, Lister TA, Vose J, Grillo-Lopez A, Hagenbeek A, Cabanillas F, Klippensten D, Hiddemann W, Castellino R, Harris NL, Armitage JO, Carter W, Hoppe R, Canellos GP (1999) Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group. J Clin Oncol 17(4):1244. https://doi.org/10.1200/JCO.1999.17.4.1244
24. Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ, Coiffier B, Fisher RI, Hagenbeek A, Zucca E, Rosen ST, Stroobants S, Lister TA, Hoppe RT, Dreyling M, Tobinai K, Vose JM, Connors JM, Federico M, Diehl V, International Harmonization Project on L (2007) Revised response criteria for malignant lymphoma. J Clin Oncol 25(5):579–586. https://doi.org/10.1200/JCO.2006.09.2403
25. Shustov AR, Gooley TA, Sandmaier BM, Shizuru J, Sorror ML, Sahebi F, McSweeney P, Niederwieser D, Bruno B, Storb R, Maloney DG (2010) Allogeneic haematopoietic cell transplantation after nonmyeloablative conditioning in patients with T-cell and natural killer-cell lymphomas. Br J Haematol 150(2):170–178. https://doi.org/10.1111/j.1365-2141.2010.08210.x
26. Jacobsen ED, Kim HT, Ho VT, Cutler CS, Koreth J, Fisher DC, Armand P, Alyea EP, Freedman AS, Soiffer RJ, Antin JH (2011) A large single-center experience with allogeneic stem-cell transplantation for peripheral T-cell non-Hodgkin lymphoma and advanced mycosis fungoides/Sezary syndrome. Ann Oncol 22(7):1608–1613. https://doi.org/10.1093/annonc/mdq698

27. Goldberg JD, Chou JF, Horwitz S, Teruya-Feldstein J, Barker JN, Boulad F, Castro-Malaspina H, Giralt S, Jakubowski AA, Koehne G, van den Brink MRM, Young JW, Zhang Z, Papadopoulos EB, Perales MA (2012) Long-term survival in patients with peripheral T-cell non-Hodgkin lymphomas after allogeneic hematopoietic stem cell transplant. Leuk Lymphoma 53(6):1124–1129. https://doi.org/10.3109/10428194.2011.645818
28. Kanakry JA, Kasamon YL, Gocke CD, Tsai HL, Davis-Sproul J, Ghosh N, Symons H, Bolanos-Meade J, Gladstone DE, Swinnen LJ, Luznik L, Fuchs EJ, Jones RJ, Ambinder RF (2013) Outcomes of related donor HLA-identical or HLA-haploidentical allogeneic blood or marrow transplantation for peripheral T cell lymphoma. Biol Blood Marrow Transplant 19(4):602–606. https://doi.org/10.1016/j.bbmt.2013.01.006
29. Gooley TA, Chien JW, Pergam SA, Hingorani S, Sorror ML, Boeckh M, Martin PJ, Sandmaier BM, Marr KA, Appelbaum FR, Storb R, McDonald GB (2010) Reduced mortality after allogeneic hematopoietic-cell transplantation. N Engl J Med 363(22):2091–2101. https://doi.org/10.1056/NEJMoa1004383
30. Hamadani M, Benson DM Jr, Hofmeister CC, Elder P, Blum W, Porcu P, Garzon R, Blum KA, Lin TS, Marcucci G, Devine SM (2009) Allogeneic stem cell transplantation for patients with relapsed chemorefractory aggressive non-hodgkin lymphomas. Biol Blood Marrow Transplant 15(5):547–553. https://doi.org/10.1016/j.bbmt.2009.01.010
31. Horowitz MM, Gale RP, Sondel PM, Goldman JM, Kersey J, Kolb HJ, Rimm AA, Ringden O, Rozman C, Speck B et al (1990) Graft-versus-leukemia reactions after bone marrow transplantation. Blood 75(3):555–562