A multicenter retrospective study on the real-world outcomes of autologous *vs.* allogeneic hematopoietic stem cell transplantation for peripheral T-cell lymphoma in China

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Abstract

Background: There were few studies on real-world data about autologous hematopoietic stem cell transplantation (auto-HSCT) or allogeneic HSCT (allo-HSCT) in peripheral T-cell lymphoma (PTCL). This study aimed to investigate the clinical outcomes of patients who received auto-HSCT or allo-HSCT in China.

Methods: From July 2007 to June 2017, a total of 128 patients who received auto-HSCT ($n = 72$) or allo-HSCT ($n = 56$) at eight medical centers across China were included in this study. We retrospectively collected their demographic and clinical data and compared the clinical outcomes between groups.

Results: Patients receiving allo-HSCT were more likely to be diagnosed with stage III or IV disease (95% *vs.* 82%, $P = 0.027$), bone marrow involvement (42% *vs.* 15%, $P = 0.001$), chemotherapy-resistant disease (41% *vs.* 8%, $P = 0.001$), and progression disease (32% *vs.* 4%, $P < 0.001$) at transplantation than those receiving auto-HSCT. With a median follow-up of 30 (2–143) months, 3-year overall survival (OS) and progression-free survival (PFS) in the auto-HSCT group were 70%(48/63) and 59%(42/63), respectively. Three-year OS and PFS for allo-HSCT recipients were 46%(27/54) and 44%(29/54), respectively. There was no difference in relapse rate (34%[17/63] in auto-HSCT *vs.* 29%[15/54] in allo-HSCT, $P = 0.840$). Three-year non-relapse mortality rate in auto-HSCT recipients was 6%(4/63) compared with 27%(14/54) for allo-HSCT recipients ($P = 0.004$). Subanalyses showed that patients with lower prognostic index scores for PTCL (PIT) who received auto-HSCT in an upfront setting had a better outcome than patients with higher PIT scores (3-year OS: 85% *vs.* 40%, $P = 0.003$). Patients with complete remission (CR) undergoing auto-HSCT had better survival (3-year OS: 88% *vs.* 48% in allo-HSCT, $P = 0.008$). For patients beyond CR, the outcome of patients who received allo-HSCT was similar to that in the atuo-HSCT group (3-year OS: 51% *vs.* 46%, $P = 0.300$).

Conclusions: Our study provided real-world data about auto-HSCT and allo-HSCT in China. Auto-HSCT seemed to be associated with better survival for patients in good condition (lower PIT score and/or better disease control). For patients possessing unfavorable characteristics, the survival of patients receiving allo-HSCT group was similar to that in the auto-HSCT group.

Keywords: Peripheral T-cell lymphoma; Auto-HSCT; Allo-HSCT; PIT score; Remission status

Introduction

Peripheral T-cell lymphoma (PTCL) is a group of biologically and clinically heterogeneous malignancies. With geographical variations, PTCL represents <15% of all non-Hodgkin lymphoma (NHL) in Western countries,[1] with a high percentage of approximately 25% to 30% in East Asia where NK/T-cell lymphoma (NK/TCL) is more frequent.[2,3] PTCL not otherwise specified (PTCL-NOS), NK/TCL, anaplastic lymphoma kinase (ALK) positive or negative anaplastic large cell lymphoma (ALCL), and angioimmunoblastic T-cell lymphoma

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(AITL) account for >90% of PTCL in East Asia. Less frequent subtypes include hepatosplenic γ/δ lymphoma, enteropathy-type T-cell lymphoma, and subcutaneous-like T-cell lymphoma.

The prognosis of PTCL is generally unsatisfactory except for ALK-positive ALCL.[4-6] Despite the rapid progress in the knowledge of (epi)genetic findings of PTCL and the development of new drugs,[7,8] cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) or CHOP-like regimens remain the standard first-line therapy. Currently, there is no consensus for subsequent consolidations. Autologous hematopoietic stem cell transplantation (auto-HSCT) has been exploited as consolidation both in first remission and refractory/relapsed settings.[9-12] Allogeneic HSCT (allo-HSCT) is mainly tried in relapsed and refractory patients and shows promising results.[13-15] Key questions about the relative efficacy of auto-HSCT *vs*. allo-HSCT, identification of their optimal candidates, and optimal HSCT timing remain uncertain. Our study provides real-world data about auto-HSCT and allo-HSCT for PTCL in China.

Methods

Study design and population

A multicenter retrospective study was conducted to investigate the clinical outcomes of all consecutive patients with PTCL who received auto-HSCT or allo-HSCT from eight tertiary hospitals across China between July 2007 and June 2017. All diagnoses were confirmed and classified by pathologists at each institution, and they were further centrally reviewed again according to the 2016 edition of the World Health Organization classification of lymphoid neoplasms. Initial first-line regimens for all patients after diagnosis were six to eight cycles of CHOP or CHOP-like regimens. Response evaluations were usually performed after two to four cycles of chemotherapy. If no complete remission (CR) or partial remission (PR) was achieved, second-line regimens such as DHAP (dexamethasone, cytarabine, cisplatin), ICE (ifosfamide, carboplatin, etoposide), GDP (gemcitabine, dexamethasone, cisplatin), and GemOx (gemcitabine, oxaliplatin) were usually tried. Auto-HSCT was usually performed when one patient achieved CR/PR through chemotherapy. Allo-HSCT was often administered for patients with relapsed or refractory disease. The choice of one patient to receive auto-HSCT or allo-HSCT depended on age, Eastern Cooperative Oncology Group performance status, the availability of donors, the presence of unfavorable prognostic factors like advanced Ann Arbor stage, bone marrow involvement, and response to chemotherapy. After screening, a total of 128 patients were identified to receive auto-HSCT or allo-HSCT during the study period. No patients were found to receive prior auto-HSCT before allo-HSCT.

Baseline characteristics of patients were collected regarding age, gender, histological subtype, "B" symptoms, stage, international prognostic index and prognostic index score for PTCL-NOS (PIT), extranodal involvement at diagnosis, date of transplantation, the number of lines of chemotherapies before HSCT, time from diagnosis to HSCT, disease status at transplantation, donor type, conditioning regimens, graft-*vs*.-host disease (GVHD) prophylaxis, engraftment, and information on acute GVHD (aGVHD) and chronic GVHD (cGVHD), complications, response to transplantation, duration of responses, follow-ups, date, and causes of death, and other outcomes after HSCT.

Transplantation procedures

For auto-HSCT, patients were mobilized with high-dose chemotherapy and recombinant human granulocyte colony stimulating factor (filgrastim, Kirin, Tokyo, Japan). BEAM (carmustine, etoposide, cytarabine, melphalan) and CBV (cyclophosphamide, etoposide, and BCNU) were the most common conditioning regimens. All allo-HSCT included in our study were myeloablative. Three myeloablative conditioning regimens were mainly used[16]: (1) modified busulfan, cyclophosphamide (BuCy) regimen; (2) modified fludarabine, busulfan regimen: substitution of cyclophosphamide in BuCy with fludarabine; and (3) total body irradiation + cyclophosphamide (TBI + Cy) regimen. Patients received allografts from human leukocyte antigen (HLA)-matched donors, HLA-matched unrelated donors, or HLA-haploidentical donors. GVHD prophylaxis was cyclosporine A, methotrexate, and mycophenolate mofetil for HLA-matched transplantation; or in combination with antithymocyte globulin (thymoglobulin) in the haploidentical or unrelated donor transplantation setting.

Endpoints and definitions

The primary endpoints of this study were overall survival (OS) and progression-free survival (PFS). OS was calculated from the day of transplantation to the day of death from any cause, or last follow-up for survivors. PFS was defined as the date of transplantation to the date of disease relapse, progression, or death, or last follow-up for survivors without evidence of disease. Secondary endpoints were non-relapse mortality (NRM) and relapse (progression). NRM was defined as death from any cause related to transplantation without evidence of lymphoma progression. Time to relapse and time to NRM were calculated from the date of transplantation. Neutrophil engraftment was calculated from the day of transplantation 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 transplantation to the first day of 7 consecutive days with platelet count $>20 \times 10^9$/L, unsupported by platelet transfusion. The development of aGVHD and cGVHD (limited or extensive) was graded according to the international criteria.[17,18]

Responses to the treatment were evaluated according to the International Workshop NHL criteria.[19] Patients were evaluated using computed tomography (CT) scan, positron emission tomography-CT, or bone marrow aspiration and biopsy when necessary. Response evaluations were performed before and +3, +6, +9, +12 months after allo-peripheral blood stem cell transplantation, and thereafter semi-annually until 5 years after transplantation. The definitions of sensitivity to chemotherapy were as follows: primary sensitive was defined as CR or PR after

first-line chemotherapy; primary refractory, never reached CR or PR with first-line chemotherapy; relapse sensitive, achieved CR or PR again after salvage chemotherapy; relapse resistant, once getting CR or PR with primary chemotherapy but never achieved any CR or PR after progression or relapse with salvage chemotherapy.

Statistical analysis

Statistical descriptive analyses were used for baseline and transplantation characteristics. Categorical variables were calculated with the Chi-square test. Continuous variables were analyzed with the Mann-Whitney *U* test or *t*-test. The probability of survival (OS and PFS) was estimated with the Kaplan-Meier method with 95% confidence intervals (CIs) and statistical significance was compared using the log-rank test and or Cox regression. Cumulative incidences of NRM, relapse, and GVHD were calculated with competing risk analysis and compared with Gray test. A two-tailed $P < 0.050$ was considered to be significant. All analyses were performed with R software, version 2.12 (R Core Development Team, Vienna, Austria).

Results

Patient characteristics

A total of 128 patients with PTCL were included in this study. Seventy-two patients received auto-HSCT and 56 patients underwent allo-HSCT. Patient characteristics are shown in Table 1. As summarized in Table 1, NK/TCL ($n = 37$), ALK-positive ALCL ($n = 24$), PTCL-NOS ($n = 23$), and AITL ($n = 19$) were the dominant histological subtypes. There were no significant differences between auto-HSCT and allo-HSCT groups in terms of sex distribution, median age, the proportion of different histological subtypes, the proportion of patients with B symptoms at diagnosis, central nervous system and extranodal involvement at diagnosis, prognostic index (age-adjusted international prognostic index and PIT score), lines of prior therapy, and the interval between diagnosis and HSCT. Nevertheless, there were more unfavorable variables in the allo-HSCT group. Allo-HSCT recipients were more likely to be diagnosed with stage III or IV disease and bone marrow involvement, and they were less likely to be diagnosed with ALK-positive ALCL.

Treatment- and transplantation-related characteristics are listed in Table 2. The proportion of patients with PD in the allo-HSCT group was higher than that in the auto-HSCT group (32% *vs.* 4%, $P < 0.001$). And allo-HSCT recipients were more likely to be with the chemotherapy-resistant disease at the time of HSCT (41% *vs.* 8%, $P = 0.001$). Conditioning regimens in the auto-HSCT group consisted of BEAM, CBV, and TBI/Cy-based regimens in 89% of all patients. All the conditioning regimens in the allo-HSCT group were myeloablative. TBI/Cy and Bu/Cy based regimens accounted for >80% of all patients. Peripheral

Table 1: Main characteristics of 128 patients with PTCL who underwent HSCT in eight hospitals across China between July 2007 and June 2017.

Characteristics	Auto-HSCT ($n = 72$)	Allo-HSCT ($n = 56$)	Statistics	*P*
Sex			3.555	0.059*
Male	44 (61)	43 (77)		
Female	28 (39)	13 (23)		
Age at HSCT (years)	36.2 ± 12.8	33.6 ± 12.6	1.175	0.808†
Histology			9.162	0.103*
PTCL-NOS	11 (15)	12 (21)		
AITL	12 (17)	7 (13)		
ALK-positive ALCL	19 (26)	5 (9)		
ALK-negative ALCL	6 (8)	3 (5)		
NK/TCL	17 (24)	20 (36)		
Other	7 (10)	9 (16)		
B symptoms at diagnosis	42 (58)	38 (68)	1.548	0.213*
BM involvement at diagnosis	11 (15)	23 (41)	11.203	0.001*
CNS involvement at diagnosis	4 (6)	3 (5)	0.003	0.954*
Extranodal involvement at diagnosis	54 (75)	40 (72)	0.206	0.650*
aaIPI score ≥2	41 (57)	31 (55)	0.368	0.544*
PIT score ≥2	25 (37)	17 (34)	0.137	0.712*
Disease stage at diagnosis			4.496	0.027*
I–II	13 (18)	3 (5)		
III–IV	59 (82)	52 (93)§		
Lines of therapy before HSCT			0.124	0.725*
≤2	39 (54)	27 (48)		
>2	33 (46)	20 (36)‖		
Median time from diagnosis to HSCT (months)	9 (4–66)	6 (1–144)	1217	0.001‡

Values are presented as *n* (%), mean ± standard deviation, or median (range). *P value was analyzed by Chi-square test. †P values were calculated by *t*-test. ‡P value was analyzed by Mann-Whitney *U* test. §The staging information was unavailable for 1 patient in the allo-HSCT group; so, the total number of patients in this group was 55. ‖The information about previous lines of therapy before HSCT was unavailable for 9 patients in the allo-HSCT group; so, the total number of patients in this group was 47. aaIPI: age-adjusted International Prognostic Index; Auto-HSCT: Autologous hematopoietic stem cell transplantation; Allo-HSCT: Allogeneic HSCT; AITL: Angioimmunoblastic T-cell lymphoma; ALK-pos ALCL: Anaplastic lymphoma kinase positive anaplastic large cell lymphoma; ALK-neg ALCL: ALK-negative ALCL; ALK: Anaplastic lymphoma kinase; BM: Bone marrow; CNS: Central nervous system; PTCL-NOS: Peripheral T-cell lymphoma, not otherwise specified; PIT: Prognostic index for PTCL-NOS; NK/TCL: NK/T-cell lymphoma.

Table 2: Treatment- and transplantation-related characteristics of 128 patients with PTCL who underwent HSCT in eight hospitals across China between July 2007 and June 2017.

Characteristics	Auto-HSCT ($n = 72$)	Allo-HSCT ($n = 56$)	Statistics	P
Disease status at HSCT			30.947	<0.001*
CR	37 (51)	8 (18)		
PR	29 (40)	25 (46)		
SD	3 (4)	5 (9)		
PD	3 (4)	18 (32)		
Chemosensitivity status at HSCT			20.561	<0.001*
Primary sensitive	54 (75)	25 (45)		
Primary resistant	3 (4)	14 (25)		
Relapse sensitive	12 (17)	8 (14)		
Relapse resistant	3 (4)	9 (16)		
Conditioning regimens			79.711	<0.001*
TBI/Cy based	11 (16)	33 (60)		
BuCy based	2 (3)	12 (22)		
FB based	0	5 (9)		
BEAM	37 (52)	4 (7)		
CBV	15 (21)	0		
Others	6 (9)	1 (2)		
Unknown	1 (2)	1 (2)		
Donor HLA match	NA			
HLA-identical sibling		32 (57)		
Haplo-identical sibling		20 (36)		
Matched unrelated		4 (7)		
GVHD prophylaxis	NA			
CSA + MTX		6 (11)		
ATG + CSA + MTX		1 (2)		
CsA + MTX + MMF		26 (47)		
ATG + CSA + MTX + MMF		17 (31)		
Other		5 (9)		
Unknown		1 (2)		
Median follow-up of survivors (months)	23 (4–143)	39 (2–112)	745	0.215†

Values are presented as *n* (%) or median (range). *P value was analyzed by Chi-square test. †P values were calculated by Mann-Whitney *U* test. Auto-HSCT: Autologous hematopoietic stem cell transplantation; Allo-HSCT: Allogeneic HSCT; ATG: Antithymocyte globulin; Bu/Cy: Busulfan, cyclophosphamide; BEAM: semustine/carmustine, etoposide, cytarabine, melphalan; CBV: Cyclophosphamide, etoposide, and BCNU; CR: Complete remission; CSA: Cyclosporine; FB: Fludarabine, busulfan; GVHD: Graft-*vs*.-host disease; HLA: Human leukocyte antigen; MTX: Methotrexate; MMF: Mycophenolate mofetil; NA: Not available; PTCL: Peripheral T-cell lymphoma; PD: Progression disease; PR: Partial remission; SD: Stable disease; TBI/Cy: Total body irradiation, cyclophosphamide.

blood was the sole graft source for all patients. Thirty-two (57%) of the 56 allo-HSCT recipients received their grafts from HLA-matched siblings, 20 patients (36%) from HLA haploidentical siblings, and four patients (7%) from HLA-matched unrelated donors.

General clinical outcomes

The median follow-up period for survivors was 30 months (range, 2–143 months). After excluding 11 patients who were lost to follow-up, clinical outcomes about the remaining 117 patients were finally analyzed. The engraftment of neutrophil and platelets in the auto-HSCT were both shorter than those in the allo-HSCT group (neutrophil engraftment: 10 days [range, 9–19 days] in auto-HSCT *vs*. 13 days [range, 9–27 days] in allo-HSCT, $P < 0.010$; platelets engraftment: 12 days [range, 6–46 days] in auto-HSCT *vs*. 15 days [range, 9–38 days] in allo-HSCT, $P < 0.010$). For the allo-HSCT group, the cumulative incidence of grade I to IV aGVHD at 100-day was 35% (95% CI, 22%–48%) [Supplementary Figure 1A, http://links.lww.com/CM9/A617]. The cumulative incidence of limited and extensive cGVHD at 2 years was 40% (95% CI, 26%–52%) [Supplementary Figure 1B, http://links.lww.com/CM9/A617].

The 3-year OS and PFS in the auto-HSCT group were 70% (48/63) (95% CI, 58%–85%) and 59%(42/63) (95% CI, 47%–76%). And the 3-year OS and PFS in patients receiving allo-HSCT were 46%(27/54) (95% CI, 34%–63%) and 44%(29/54) (95% CI, 32%–60%), respectively [Figure 1A and 1B]. Three-year NRM for allo-HSCT recipients was 27%(14/54) (95% CI, 16%–40%) compared with 6%(4/63) (95% CI, 2%–14%) for auto-HSCT recipients ($P = 0.004$) [Figure 1C]. There was no difference in relapse rates between these two groups (29%(15/54) [95% CI, 17%–42%] in allo-HSCT *vs*. 34%(17/63) [95% CI, 20%–48%] in auto-HSCT, $P = 0.840$) [Figure 1D]. As for causes of death [Supplementary Table S1, http://links.lww.com/CM9/A617], lymphoma progression was the most common reason in both groups.

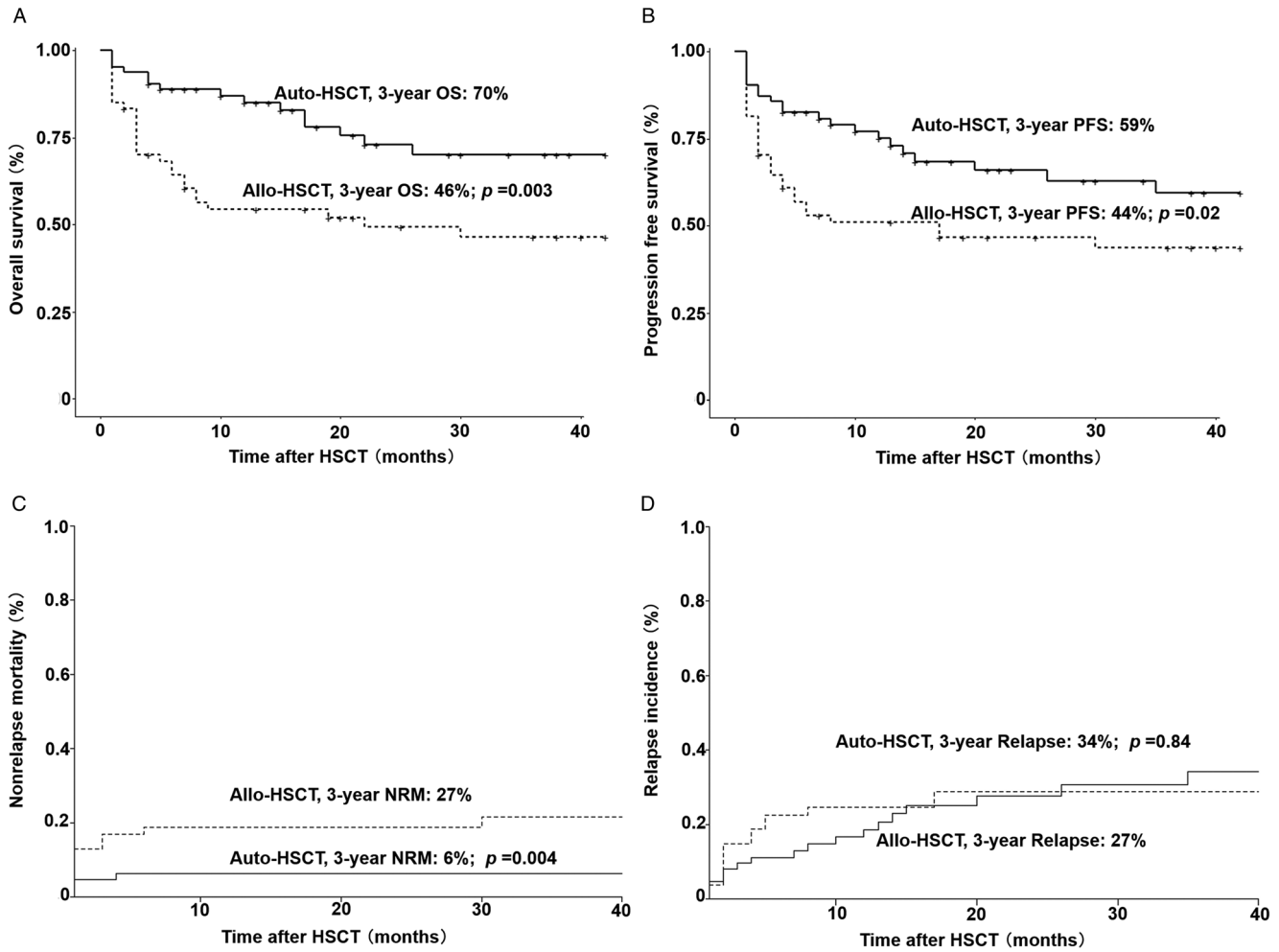

Figure 1: Kaplan-Meier survival estimates for 3-year OS (A) and PFS (B) for patients who underwent auto-HSCT *vs.* those for patients who underwent allo-HSCT. Cumulative incidence of NRM (C) and relapse rates (D). Auto-HSCT: Autologous hematopoietic stem cell transplantation; Allo-HSCT: Allogeneic HSCT; NRM: Non-relapse mortality; OS: Overall survival; PFS: Progression-free survival.

Subgroup analyses

Subgroup analysis about patients with different prognostic indexes was first performed. For patients who received auto-HSCT group in the upfront setting, the survival of patients with PIT 0 or 1 was significantly better than that in patients with PIT 2 or higher (3-year OS: 85% *vs.* 40%, $P = 0.003$; 3-year PFS: 75% *vs.* 36%, $P = 0.006$) [Figure 2A and 2B]. For patients with PIT 2 or higher who received auto-HSCT or allo-HSCT in upfront settings, there was no difference both in 3-year OS (40% *vs.* 34%, $P = 0.590$) [Figure 2C] and PFS (36.4% *vs.* 35.7%, $P = 0.850$) [Figure 2D]. When specifically checking their baseline characteristics, patients who received upfront allo-HSCT had more patients with stage IV disease (93% [13/14] *vs.* 71% [12/17] in patients who received upfront auto-HSCT), more patients in PD/SD (36% [5/14] *vs.* 6% [1/17] in patients who received upfront auto-HSCT), and more bone marrow involvement (79% [11/14] *vs.* 35% [6/17] in patients receiving upfront auto-HSCT) (data not shown).

According to the disease status before transplantation, patients in CR undergoing auto-HSCT had the best 3-year OS (88% *vs.* 48% in allo-HSCT; $P = 0.008$) [Figure 3A]. But there was no significant difference in PFS (73% *vs.* 54%; $P = 0.150$) [Figure 3B]. It may be because of the small number of patients ($n = 7$) in CR who received allo-HSCT. After excluding patients with CR, 29 patients received auto-HSCT and 47 patients received allo-HSCT. There was no difference both in 3-year OS (51% *vs.* 46%; $P = 0.300$) [Figure 3C] and PFS (46% *vs.* 42%; $P = 0.490$) [Figure 3D] between these two groups. While specifically examining the clinical characteristics of patients less than CR, allo-HSCT recipients had more patients with advanced stages (85% with stage III–IV disease compared with 48% in the auto-HSCT group), more bone marrow involvement (40% *vs.* 17% in the allo-HSCT group) (data are not shown).

According to the different histology of patients between these two groups, subgroup analyses were also performed. Given the good prognosis of ALK-positive ALCL and that there were more ALK-positive ALCL in the auto-HSCT group, we first excluded ALK-positive ALCL patients in both groups. Patients in the auto-HSCT group ($n = 50$) still had better 3-year OS (71% *vs.* 50%, $P = 0.010$) [Supplementary Figure 2A, http://links.lww.com/CM9/A617] than that in the allo-HSCT group ($n = 49$), with

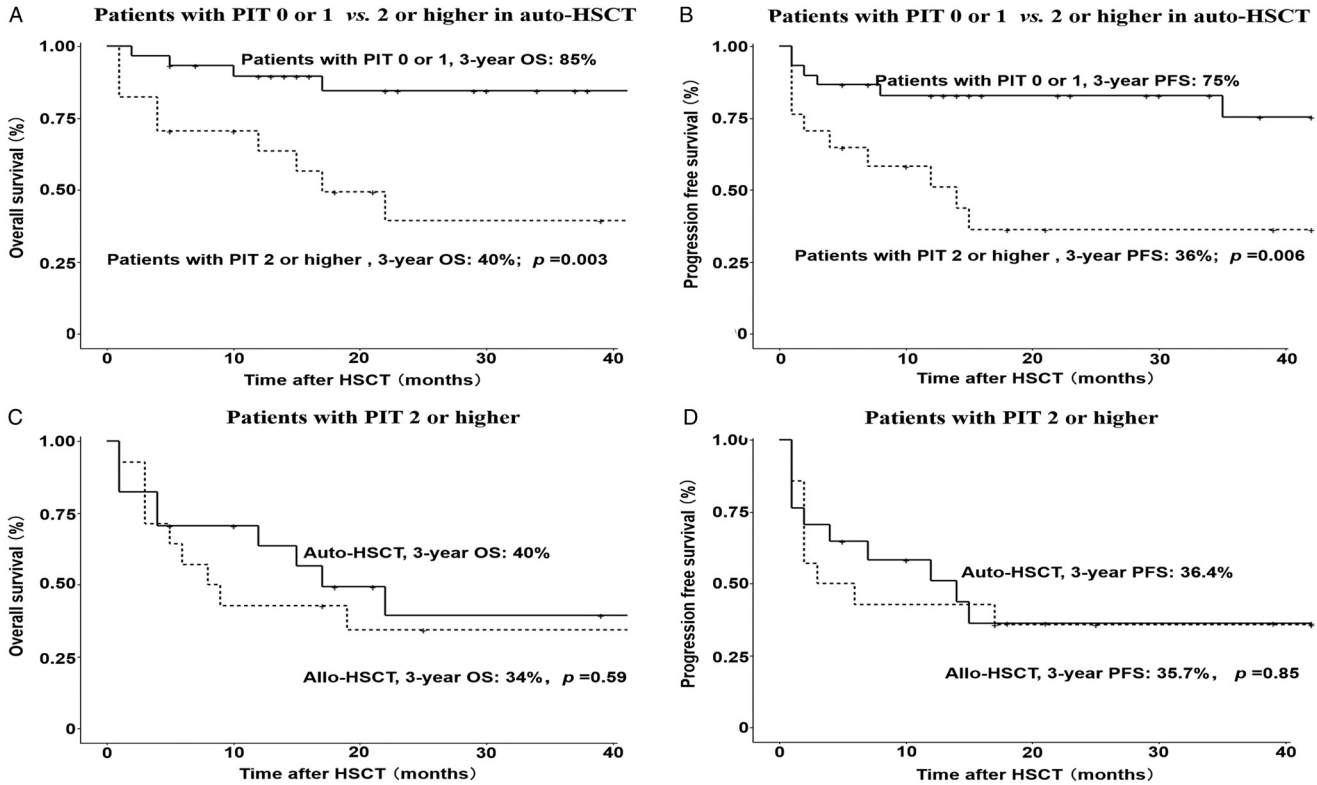

Figure 2: For patients who received auto-HSCT group in the upfront setting, the survival of patients with PIT 0 or 1 was significantly better than that of patients with PIT 2 or higher (3-year OS: 85% [95% CI, 72%–100%] *vs.* 40% [95% CI, 20%–77%], $P = 0.003$; 3-year PFS: 75% [95% CI, 59%–97%] *vs.* 36% [95% CI, 19%–71%], $P = 0.006$) (A) and (B). For patients with PIT 2 or higher who received auto-HSCT or allo-HSCT in upfront settings, there was no difference both in 3-year OS (40% [95% CI, 20%–77%] *vs.* 34% [95% CI, 16%–72%], $P = 0.590$) (C) and PFS (36.4% [95% CI, 18.6%–71.4%] *vs.* 35.7% [95% CI, 17.7%–70%], $P = 0.850$) (D). Auto-HSCT: Autologous hematopoietic stem cell transplantation; Allo-HSCT: Allogeneic HSCT; CI: Confidence interval; OS: Overall survival; PIT: Prognostic index score for PTCL-NOS; PFS: Progression-free survival.

no difference in PFS (56% *vs.* 46%, $P = 0.080$) [Supplementary Figure 2B, http://links.lww.com/CM9/A617].

Discussion

The efficacy of first-line chemotherapy is far from optimal for most PTCL subtypes until today. HSCT is a valuable option to achieve longer survival or even cure this disease. In this study, we report the real-world data about the outcomes of a multicenter retrospective study of 128 patients who underwent HSCT in eight hospitals across China. To our knowledge, this is one of the largest reports in the Mainland of China. In general, the survival of patients in the auto-HSCT group is better than that in the allo-HSCT group. NRM is as expected to be lower in the auto-HSCT group. Relapse rates are similar. It is difficult to draw conclusions because of the baseline differences between these two groups. Compared with patients in the auto-HSCT group, patients undergoing allo-HSCT are more likely to be diagnosed with ALK-negative ALCL, advanced stage, bone marrow involvement, or relapsed/refractory disease status before transplantation. We further compared the survival of patients in different subgroups. First, we find that patients with lower PIT score who received auto-HSCT group in the upfront setting have a better outcome than patients with higher PIT score. Second, patients with CR undergoing auto-HSCT have the best outcome (3-year OS: 88% *vs.* 46% in the allo-HSCT group). For patients beyond CR, their survival is similar. When further checking the baseline characteristics, more unfavorable clinical features are found in the allo-HSCT group. Our real-world data suggest that auto-HSCT seemed to be associated with better survival for patients in good condition (lower PIT score and or better disease control). For patients with unfavorable clinical characteristics, allo-HSCT group seems to be a better choice.

The efficacy of auto-HSCT had been evaluated both in retrospective and prospective studies, with reported 3- to 5-year OS ranging from one-third to more than two-thirds.[12,20-23] The huge variability in survival rate was related to the heterogeneity in baseline characteristics of patients included in the above studies. Among the baseline factors, remission status before HSCT was the most important factor affecting post-HSCT survival. The 3-year OS in our study was 70% (58–85%). This was higher than the OS (59%) in the study by the Center for International Blood and Marrow Transplant Research (CIBMTR), where 64 patients (56%) were in CR at transplantation.[21] Also, the 5-year OS was only 46% in the largest Asian study, which comprised 104 (77%) patients in CR/PR.[20] It can be partially explained by three reasons. First, over 90% of patients (66/72) undergoing auto-HSCT were in CR (37) or PR (29) at transplantation in our study. Second, the percentage of ALK-positive ALCL patients (19/72) was higher than that (12/135) in the Asian study. Third, the median follow-up time was only 23 (4–143) months, which was shorter than that in the above studies.

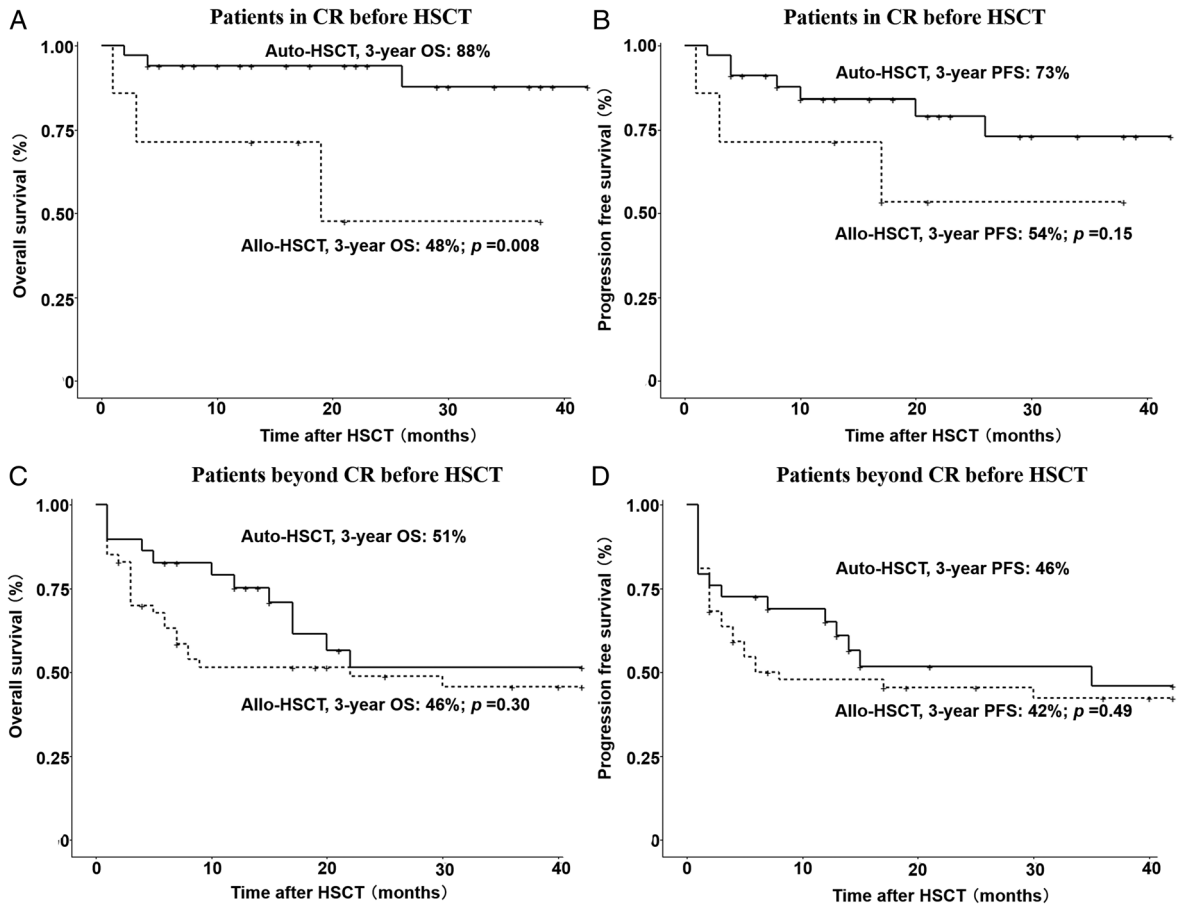

Figure 3: For patients in CR, the outcome of patients undergoing auto-HSCT had the best 3-year OS (88% [95% CI, 75%–100%] *vs.* 48% [95% CI, 19%–100%], $P = 0.008$) (A); but there was no significant difference in PFS (73% [95% CI, 57%–94%] *vs.* 54% [95% CI, 26%–100%], $P = 0.150$) (B). For patients beyond CR, there was no difference both in 3-year OS (51% [95% CI, 35%–77%] *vs.* 46% [95% CI, 33%–64%], $P = 0.300$) (C) and PFS (46% [95% CI, 30%–71%] *vs.* 42% [95% CI, 30%–60%] $P = 0.490$) (D) between the auto-HSCT and allo-HSCT groups. Auto-HSCT: Autologous hematopoietic stem cell transplantation; Allo-HSCT: Allogeneic HSCT; CR: Complete remission; CI: Confidence interval; OS: Overall survival; PFS: Progression-free survival.

Another question was which part of patients can benefit from auto-HSCT. The prognostic Index attained at diagnosis was not so important for patients who received HSCT in relapsed settings. So, we only checked the role of PIT score in the upfront setting. We found that patients with lower PIT scores who received auto-HSCT group in the upfront setting had a better outcome. But for the prognosis of patients with PIT 2 or higher was very poor, which was consistent with Shigeo's study.[24] So, it was reasonable to avoid auto-HSCT for patients with higher PIT score in the upfront setting.

Because of the fact that the vast majority of patients will eventually relapse after upfront chemotherapies, even when auto-HSCT were followed thereafter,[25,26] or remained refractory at the beginning, allo-HSCT was mostly performed in the relapsed or refractory setting. About one-half of patients could achieve long-term survival through allo-HSCT, which was confirmed in large retrospective studies from CIBMTR,[21] Europe,[13] and Asia.[20] Nevertheless, there were all kinds of heterogeneity in histologic subtypes, stages, remission status at transplantation, the intensity of conditioning regimens, donor types, and GVHD prophylaxis among previous reports. In our study, over 90% of patients (52/56) in the allo-HSCT group were diagnosed with advanced stages. And >80% of patients (48/56) were non-CR at transplantation. The 3-year OS of allo-HSCT recipients was 46% (34%–63%), which was similar to previous studies. In particular, all allo-HSCT in our study were myeloablative conditioning regimens. Few studies were focusing on patients who received myeloablative conditioning regimens. There were two studies about the impact of regimens intensities on survival. But both studies failed to find a significant difference either in toxicity or survival between myeloablative and reduced conditioning regimens.[13,21] With progress in supportive care, GVHD prophylaxis, and donor selection system, 20 patients in our study received HLA-haploidentical HSCT.

Because of the inherent toxicity of conditioning regimens and GVHD along with allo-HSCT, NRM in the allo-HSCT group was as expected higher than that (27% *vs.* 6%) in the auto-HSCT group. But there was no difference in relapse rates (29% *vs.* 34% in auto-HSCT). One possible explanation was that approximately 40% of patients (23/56) were in progressive status before transplantation. Allo-HSCT in our study, like most previous studies, often performed as a salvage treatment, compromising the effectiveness of allo-HSCT. As for causes of death,

lymphoma progression or relapse was the leading factor in both groups, which indicated that prevention of relapse was also very important in the allo-HSCT.

More practical issues for physicians were how to choose the type of HSCT, HSCT timing, and identification of optimal candidates. With huge heterogeneity in disease itself and results of previous studies, there was no consensus about this issue until today. Hopefully with evidence from both retrospective and prospective cohort studies, auto-HSCT was recommended as consolidation in most institutes for patients who achieved a CR or PR after first-line therapies.[22,27] Two recent prospective studies also failed to demonstrate that allo-HSCT could achieve better survival than auto-HSCT for patients in the first remission.[28,29] Allo-HSCT for patients in the first remission remained controversial until today. To further explore this issue, we assessed the survival of patients according to the disease status at transplantation. Consistent with the literature, patients with CR can benefit from auto-HSCT. For patients beyond CR, more unfavorable clinical features were found in the allo-HSCT group. But its survival was comparable to that in the auto-HSCT group. Based on the evidence and results above, we are proposing that it is advisable to choose auto-HSCT for patients with CR. And for patients beyond CR but also possessing other unfavorable clinical characteristics, it was more plausible to proceed allo-HSCT. This was just our scenario. It was urgently to be confirmed in further prospective or randomized studies.

There were several limitations in this study. First, the basal characteristics and prognosis of patients who were unable to undergo transplantation were not included in this study. It cannot reflect the whole clinical picture of PTCL. Second, due to the retrospective design and small size of this study, the conclusions should be interpreted with caution. Nevertheless, our real-world data indicated that these two treatment strategies remained valuable treatment options both in first-line and relapsed/refractory settings. For patients in good condition through first-line chemotherapy (like lower PIT score and or good disease control), it was wise to choose auto-HSCT. And it is more plausible to choose allo-HSCT for patients with worse disease control and (or) unfavorable clinical characteristics. Prospective studies are still urgently needed to compare the relative efficacy of these two treatment platforms and identify their ideal candidates.

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Conflicts of interest

None.

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