Autologous Stem Cell Transplantation as the First-Line Treatment for Peripheral T Cell Lymphoma: Results of a Comprehensive Meta-Analysis

J. Yin J. Wei J.H. Xu Y. Xiao Y.C. Zhang

Department of Hematology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

For editorial comment see p. 112

Key Words

Autologous stem cell transplantation · Meta-analysis · Peripheral T cell lymphoma

Abstract

Objective: In view of the poor prognosis of most peripheral T cell lymphoma (PTCL) subtypes treated with conventional chemotherapy such as CHOP/CHOP-like regimens, high-dose chemotherapy followed by autologous stem cell transplantation (HDT/ASCT) seems a reasonable option in eligible patients. Nevertheless, owing to the small size of the study and the heterogeneity of most published series, a consensus on the role of ASCT as the first-line consolidation therapy for high-risk PTCL patients has not been reached so far. **Study Design:** We searched MEDLINE, EMBASE, EBSCO, Web of Science, clinicaltrials.gov and the Cochrane Library. Hazard ratio (HR) and 95% confidence intervals (CIs) were calculated by a fixed/random effect model. **Results:** Twenty-one studies were eligible. Although no statistical significance was observed in these studies, there was a trend toward survival advantage for the HDT/ASCT group as compared to the historical control group (HR 0.81, 95% CI 0.31–2.13). Statistical differences were confirmed in terms of overall survival (OS) between complete remission (CR) and non-CR patients (HR 3.17, 95% CI 0.92–5.42), patients with good and poor risk according to the International Prognostic Index (IPI; HR 0.36,

95% CI 0.22–0.60, I^2 49%) and Prognostic Index for PTCL (PIT; HR 0.31, 95% CI 0.17–0.58; HR 0.31, 95% CI 0.18–0.54). **Conclusion:** The clear and convincing proof of the effects of upfront HDT/ASCT still depends on sufficient large PTCL-restricted randomized trials in the future. Patients who failed to attain CR before transplant exhibited a worse prognosis; patients with good risk of IPI or PIT had a substantially better OS after ASCT.

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Introduction

Peripheral T cell lymphoma (PTCL) is a small heterogeneous subgroup of non-Hodgkin's lymphoma (NHL). Though clinical characteristics vary with different PTCL subgroups, patients with PTCL tend to have older age, higher frequency of constitutional symptoms, extranodal disease, a lower performance status, and an elevated serum lactate dehydrogenase (LDH) [1, 2]. The prognosis for most PTCL subtypes is generally poor with a 5-year survival of less than 30% and a median survival of 20–34 months [3]. Despite the disappointing outcome of anthracycline-based chemotherapy in PTCL patients compared to aggressive B cell NHL, such regimens, especially CHOP, have remained the standard treatment for PTCL [4–8]. In the largest study with 288 PTCL patients treated with dif-

ferent anthracycline-based regimens, the 5-year overall survival (OS) and event-free survival (EFS) were 41 and 33%, respectively, which were significantly worse than those of diffuse large B cell lymphomas (DLBCL) [5]. Similarly, some studies came to the conclusion that even intensified chemotherapy approaches failed to improve the outcomes of PTCL, and the 5-year OS remained between 25 and 40% [4, 9, 10]. Given the limited success of conventional chemotherapy in the majority of PTCL patients, high-dose chemotherapy followed by autologous stem cell transplantation (HDT/ASCT) has been investigated at many institutions worldwide. The impact of HDT/ASCT, which is considered the standard treatment in relapsed aggressive B cell lymphoma, has shown efficacy as a salvage therapy in PTCL [11–21]. However, this strategy as the first-line treatment is a matter of debate which has not been concluded yet because there have been no randomized prospective studies exclusively in patients with PTCL. In recent years, several retrospective and prospective trials have been published evaluating the role of ASCT as part of the first-line therapy in PTCL patients. However, these studies were limited by small sample sizes and case composition with various histologies [22–39]. Therefore, it is difficult to draw definitive conclusions regarding the efficacy of ASCT. Here, we perform a meta-analysis in order to determine whether PTCL patients could benefit from first-line therapy consolidation with ASCT.

Methods

Literature Search Strategy

Studies were identified by searching MEDLINE, EMBASE, EBSCO, Web of Science, clinicaltrials.gov and the Cochrane Library. References mentioned in reviews and other published systematic reviews were also hand searched. All searches were conducted for the period between 1990 and 2012.

Study Selection

Studies were eligible for enrollment in the meta-analysis if they met all of the following criteria: (1) diagnoses were rendered according to the WHO classification; (2) the studies were published between January 1990 and July 2012 as an original article written in English; (3) the studies dealt with adult patients with PTCL followed by autologous stem cell transplantation; (4) the study patients were to be treated with HDT/ASCT as part of the first-line therapy; (5) the median follow-up time was at least 12 months; (6) the studies provided data on survival outcomes (OS) and/or hazard ratios (HRs) and 95% confidence intervals (95% CIs) for OS; (6) they were not presented as case reports, abstracts or reviews, and (7) they were published in full with available data, either published or retrieved through personal communication. Studies were carefully screened for possible duplication of study populations based on the participating institutions and period of presentation of patients.

Data Extraction

Two reviewers independently extracted data from the articles and subsequently compared the results. Any disagreement was solved by discussion. Extracted data included the name of the first author, year of publication, study name, PTCL subtype, number of patients, age, criteria for study entry, median follow-up time, disease status at diagnosis, disease status at ASCT, number of patients in different remission statuses at transplantation, and HRs and 95% CIs for OS. When the data required for the analysis could not be extracted from the articles, corresponding authors were contacted for missing data and additional information regarding the studies.

Outcomes Measures

OS were measured from the time of transplantation to death from any cause, and surviving patients were censored at last follow-up. Complete remission (CR) was defined as total disappearance of all evidence of tumor and partial remission (PR) as a >50% reduction in the sum of the products of the longest diameters of measurable lesions.

Statistical Analysis

The primary outcomes in our study were OS. HR was the preferred summary statistic for reporting time-to-event data. For most of the eligible studies, HRs for survival could not be directly extracted from the original articles. Accordingly, available data were extracted from the original paper to calculate HR and standard error using the method of Parmar et al. [40] and Tierney et al. [41]. For each analysis, a forest plot was generated to display results. Heterogeneity existed when the p value of Cochran's Q test was <0.1 and the I^2 statistic was >50% [42]. If significant heterogeneity existed, a random-effect model was used to pool the data; otherwise a fixed-effect model would be used. All meta-analyses were completed using Review Manager (v.5.1, The Cochrane Collaboration, Oxford, UK) and Stata v.11.0 software (College Station, Tex., USA). Statistical significance was defined as a p value <0.05 for all tests except those for heterogeneity and publication bias [43].

Results

Characteristics of the Studies

Our comprehensive search of MEDLINE, EMBASE, EBSCO, Web of knowledge, clinicaltrials.gov and the Cochrane Library identified 1,500 references as relevant. After screening the title and abstract of those studies, 1,318 studies were excluded because of duplication and irrelevance. After more detailed evaluation, 156 studies were excluded for not meeting the criteria (fig. 1). Ultimately, 21 studies with 1,021 PTCL patients who were treated with HDT/ASCT as part of the first-line therapy were used in the meta-analysis. All of the studies were published in full text. The characteristics of these 21 studies are described in table 1. Studies including both patients receiving ASCT as first-line and salvage therapy are listed

Fig. 1. Study selection for the systematic review and meta-analysis.

in the table representing the predominant group. The median age ranged from 36 to 59 years. The sample sizes ranged from 10 [23] to 166 [44] patients. In one study only patients with PR were included [45], and in another study the patients with CR were selected [29]. In the remaining studies, patients were enrolled irrespective of their remission status. A variety of induction, high-dose therapy regimens and conditioning regimens were used in the chemotherapy arms and transplantation (table 1).

Overall Survival

Among the 21 studies enrolled, the OS of patients receiving HDT/ASCT as part of front-line treatment ranged from 58% at 1 year to 34% at 12 years. The CR rate after ASCT ranged from 59 to 100%. Among the studies which provided both OS and its 95% CI, 5-year OS and its 95% CI were obtained from 5 studies [22, 29, 38, 44, 45]. The summary estimated 5-year probabilities of OS of patients who transplanted as front-line therapy was 62% (95% CI 0.44–0.80; fig. 2).

In the comparison of OS between the group of patients treated with up-front HDT/ASCT and with conventional chemotherapy alone, 4 studies with a total of 606 patients were used for meta-analysis [26, 32, 34, 36]. However, in the study reported by Niitsu et al. [34], the patients with chemotherapy alone were divided into CHOP and Cy-

cloBEAP subgroups, and the comparisons were drawn respectively. Therefore, a total of 5 sets of data were used for analysis. The random effect estimate of the HR for OS for the 4 studies was 0.81 (95% CI 0.31–2.13, I^2 77%). Although the survival benefits from the HDT/ASCT were unconfirmed by statistics ($p = 0.66$), the trend that HDT/ASCT achieved better therapeutic effect than chemotherapy alone is shown in figure 3.

Remission Status at Transplantation

Comparisons of OS among the patients with different remission statuses at transplantation were made in 8 studies [25–28, 31, 36–38]. The remission statuses at transplantation were assessed according to the International Working Group criteria [46]. Three studies with 149 PTCL patients were used in this meta-analysis and HR in multivariate analysis for OS between patients in CR and in non-CR at transplantation were provided [25, 37, 38]. The summary-estimated HR for OS was 3.17 (95% CI 0.92–5.42, I^2 0.0%). The patients in CR at the time of transplantation showed a definite survival advantage compared with patients in non-CR at transplantation ($p = 0.004$). In addition, the estimated HR for OS extracted from 3 studies [28, 36, 37] in patients in CR compared to patients in PR at transplantation was 0.73 (95% CI 0.36–1.48, I^2 0.0%) indicating that patients in CR at trans-

Fig. 2. Meta-analysis of 5-year OS of patients undergoing HDT/ASCT as the front-line therapy.

Fig. 3. Meta-analysis of the HRs of OS in patients with PTCL treated with HDT/ASCT in comparison with patients receiving conventional chemotherapy. Solid squares indicate the HRs of each study. The size of the squares is proportional to the sample size and the horizontal lines denote 95% CIs. The diamond shows the CI for the pooled HRs. HSCT = Hematopoietic stem cell transplantation.

plantation did not obtain better outcomes than patients in PR (fig. 4). In the remaining studies, 1 study provided HR in univariate analysis [36], 1 study compared OS between patients in CR1/PR1 and CR2/PR2 [38], and 3 studies provided comparisons between different statuses separately. Because of inconsistencies of grouping, these studies cannot be used for analysis.

Impact of Risk Factors on OS

Among the patients treated with HDT/ASCT, analysis of OS in terms of the International Prognostic Index (IPI) at diagnosis was reported in 9 studies [23, 25, 28, 30, 36–39, 45]. Six studies, including 347 patients, were enrolled in this meta-analysis [23, 28, 36, 38, 39, 45]. The summary-estimated HR for OS was 0.36 (95% CI 0.22–0.60, I^2

49%), as determined with the fixed-effect model, suggesting a significant survival advantage after transplantation for patients with low IPI risk compared to patients with high IPI risk ($p < 0.0001$; fig. 5).

Likewise, the Prognostic Index for PTCL (PIT) subgroup analyses were based on 4 studies according to stratification from the original articles [28, 29, 36, 37]. Two studies with 99 patients who received HDT/ASCT were used to analyze the OS in patients with PIT < 2 and patients with PIT ≥ 2 . Another 2 studies with 157 patients were used to compare the OS in patients with PIT < 3 and patients with PIT ≥ 3 . Among these, the study by Yang et al. [37] analyzed OS in patients with PIT 2–3 in comparison with patients with PIT 0 and PIT 1, respectively. The summary HRs for OS in patients with different PIT

Table 1. Studies on ASCT in PTCL as the first-line therapy**a** Retrospective studies

Study	Year	PTCL subgroup	Type of study	n	Median age, years	Regimen	Conditioning regimen	CR, % before ASCT	after ASCT	Median follow-up, months	OS	
											years	%
Kahl et al. [23]	2002	PTCL-combined	inter-ventional	10	47	CHOP/CHOEP	BEAM/Dexa-BEAM+TBI	20	70	13.3	1	58
Schetelig et al. [19]	2003	AITL	inter-ventional	29	51	CHOP/CHOEP/VACOP-B/ ProMACE-CytaBOM/DHAP±VP16/ Dexa-BEAM/BCNU	BEAM/BEAM-like/ BUCY/ICE/ICE-like+TBI	45	76	60	5	44
Rodríguez et al. [45]	2003	PTCL-combined	inter-ventional	35	44	CHOP/MegaCHOP/MACOP-B	BEAM/BEAC/CVB+TBI	0	66	37.5	5	37
Bang et al. [24]	2005	NK/T nasal	inter-ventional	28	36	HDCT	BEAM/BEAC/CVB+TBI	61	71	12	3	42
Kim et al. [26]	2006	NK/T nasal	comparative	16	36	CHOP/de-CHOP/CHOP-RT/ DHAP/IMVP16Pd/VIPD-RT	BEAM/BEAC/CVB/CVT	56	75	22.4	2	71.3
Feyler et al. [27]	2007	PTCL-combined	inter-ventional	64	45	CHOP/CHOP-like	BEAM/BEAM-like+TIB	54		37	3	53
Rodríguez et al. [28]	2007	AITL	inter-ventional	19	46	CHOP/MegaCHOP/MACOP-B	BEAM/BEAC/CVB/Cy+TBI	58	79	25	3	60
Rodríguez et al. [29]	2007	PTCL-combined	inter-ventional	74	46	CHOP/anthracycline-based	BEAM/BEAC/CVB/ Cy+TBI	100		67	5	68
Kyriakou et al. [31]	2008	AITL	inter-ventional	146	53	HDCT	BEAM/BEAC/CVB/ MECET/BuEAM/Cy+TBI	48	70	31	2	67
Lee et al. [32]	2008	NK/T nasal	comparative	47	42	CHOP/deCHOP/velCHOP/MACOP-B/CEOP/ proMACE/EPOCH/COPBLAM/ESHAP/ DHAP/VIPD/ESHAP/IMEP/epi-COP/DeVIC	BEAM/BEAC/CVB/ MCEC/VCT/Cy+TBI	57	66	had not yet been reached	5	87.3
Niitsu et al. [34]	2008	PTCL-combined	inter-ventional	10		CHOP/CydoBEAP				72	5	60
Prochazka et al. [35]	2009	PTCL-combined	inter-ventional	18	59	PACEBO/IVAM/HAM	BEAM 200	61		25.7	2	71
Yang et al. [37]	2009	PTCL-NOS	inter-ventional	64	44	CHOP/IMEP/DHAP/ICE/ESHAP/EPOCH	BEAM/BuCyE+TBI	32.90		29.7	3	53
Prochazka et al. [39]	2011	PTCL-combined	inter-ventional	29	48	PACEBO/IVAM/HAM	BEAM 200		66	55.1	2	65
Numata et al. [38]	2010	PTCL-combined	comparative	39	49	CHOP+RT	MCEC+TBI	56	59	78	5	62.2

b Prospective studies

Study	Year	PTCL subgroup	Type of study	n	Going to transplant	median age, years	Regimen	Conditioning regimen	CR, %		median follow-up, months	OS	
									before ASCT	after ASCT		years	%
Deconinck et al. [22]	2000	ALCL	inter-ventional	15	15	39	CEEP/MINE	BEAM	73	100	68	5	87
Corradini et al. [25]	2006	PTCL-combined	inter-ventional	62	46	43	APO/DHAP/MACOP-B/Cy+VP16	mitoxantrone + melphalan	76	89	76	12	34
Rodríguez et al. [30]	2007	PTCL-combined	inter-ventional	26	19	44	MegaCHOP/IFE	BEAM	89	89	27	2	84
Mercadal et al. [33]	2008	PTCL-combined	inter-ventional	41	17	47	CHOP/ESHAP	BEAM/BEAC	49	51	34.8	4	39
Reimer et al. [36]	2009	PTCL-combined	inter-ventional	83	55	46.5	CHOP	Cy+TBI	73	87.3	33	3	71
d'Amore et al. [44]	2012	PTCL-combined	inter-ventional	166	115	57	CHOP/CHOEP-14	BEAM/BEAC	53	78	60.5	5	51

Cy = Cyclophosphamide; CEEP = cyclophosphamide, vindesine, epirubicin, prednisone; MINE = methotrexate, ifosfamide, mitoxantrone, etoposide; CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone; VACOP-B = etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin; MACOP-B = methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin; CHOE = cyclophosphamide, adriamycin, vincristine, etoposide, prednisone; ProMACE-CytaBOM = prednisone, doxorubicin, cyclophosphamide, etoposide, followed by cytarabine, bleomycin, vincristine and methotrexate with leucovorin rescue; BCNU = etoposide, cytarabine, melphalan; DHAP = dexa-methasone, cytarabine, cisplatin; Dexa-BEAM = dexa-methasone, carmustine, etoposide, cytosine arabinoside, melphalan; COPLAM = cyclophosphamide, vincristine, prednisone, bleomycin, doxorubicin, procarbazine; deCHOP = dose escalated CHOP; IMVP-16Pd = ifosfamide, methotrexate, etoposide, prednisone; VIPD = etoposide, ifosfamide, cisplatin, dexa-methasone; IFE = ifosfamide, etoposide; ESHAP = etoposide, methylprednisolone, cytarabine, cisplatin; velCHOP = velcade plus CHOP; CEOP = Cy, epirubicin, vincristine, prednisolone; epi-COP = epirubicin, Cy, vincristine, prednisolone; IMEP = ifosfamide, MTX, etoposide; DeVIC = carboplatin, etoposide, ifosfamide, dexamethasone; PACEBO = doxorubicin, cyclophosphamide, etoposide, bleomycin, vincristine, prednisone; IVAM = ifosfamide, etoposide, cytosine arabinoside, methotrexate, mesna prophylaxis, leucovorin rescue; HAM = cytosine arabinoside, mitoxantrone; ICE = ifosfamide, carboplatin, etoposide; EPOCH = cyclophosphamide, etoposide, vincristine, doxorubicin, methylprednisolone; APO = doxorubicin, vincristine, prednisone; CVB = carmustine, etoposide, cyclophosphamide; VCT = VP-16, cyclophosphamide, total body irradiation; BEAM = carmustine, etoposide, cytarabine, melphalan; BEAC = carmustine, etoposide, cytarabine, cyclophosphamide; TBI = total body irradiation; BuEAM = busulfan, etoposide, Ara-C, melphalan; BU = busulfan.

Fig. 4. a Meta-analysis of the HRs of OS in patients with PTCL in CR in comparison to non-CR patients at the time of transplantation. **b** Meta-analysis of the HR of OS in patients with PTCL in CR in comparison to PR patients at the time of transplantation.

Fig. 5. Meta-analysis of the HRs of OS in patients with good risk of IPI in comparison to patients with poor risk of IPI.

Fig. 6. Meta-analysis of the HRs of OS in patients from different PIT subgroups.

groups were 0.31 (95% CI 0.17–0.8, I^2 0%) and 0.31 (95% CI 0.18–0.54, I^2 24%), indicating that patients with lower scores of PIT had better outcomes compared with patients with higher scores of PIT (fig. 6).

Discussion

PTCL is less responsive to and has less frequent durable remissions with chemotherapy regimens such as CHOP and more intensive regimens such as hyper-CVAD. This meta-analysis reviewed 21 studies with 1,021 patients to evaluate the effects of HDT/ASCT in the first-line treatment in PTCL from different perspectives. The CR rate after ASCT ranged from 51 to 100%. The OS in those studies ranged from 58% at 1 year to 34% at 12 years. In this meta-analysis, a summary-estimated 5-year OS of 62% was revealed. Currently, some studies have suggested that HDT/ASCT might be superior to conventional chemotherapy [24, 27, 28, 32, 36, 37]. However, the studies supporting this were limited by small size and it is difficult to evaluate the clinical effect of HDT/ASCT from single-center research. Among the published studies which made comparisons between up-front HDT/ASCT and chemo-

therapy alone in PTCL patients, 4 studies with a total of 128 PTCL patients treated with up-front HDT/ASCT and 468 patients who received conventional chemotherapy were enrolled in this analysis. Therefore, we combined these 4 studies to perform a meta-analysis. Unfortunately, according to our pooled results, no significant difference existed for HDT/ASCT to improve OS. Nevertheless, a trend of advantage for the patients with HDT/ASCT over those with chemotherapy alone can be seen in figure 2. The studies reported by Lee et al. [32] and Reimer et al. [36] with larger sample sizes provided statistics to prove the survival benefits from HDT/ASCT in comparison to chemotherapy alone. The study by Reimer et al. [36] was one of the first prospective multicenter trials that evaluated the role of HDT/ASCT as upfront therapy for PTCL. Eighty-three patients with primary diagnosed PTCL were enrolled and the median age was 46.5 years (range 30–65). Sixty-two patients had advanced disease (Ann Arbor stage III or IV) and 49 patients complained of ‘B’ symptoms. The treatment regimen consisted of four to six cycles of CHOP followed by HDT/ASCT. With a median follow-up of 33 months, the 3-year OS rate was 71% for patients who underwent ASCT compared with only 11% for patients who did not undergo ASCT. This study excluded anaplas-

tic lymphoma kinase (ALK)-positive anaplastic large cell lymphoma (ALCL) cases so that a potential OS bias toward a survival benefit caused by including ALK-positive ALCL could be ruled out. In the study reported by Lee et al. [32], a total of 47 patients who underwent ASCT were compared with 107 matched controlled cases. The median age was 47 years (range 17–80). All clinical parameters except age and initial Ann Arbor stage were relatively well balanced between the control group and the study group. Although the median survival time was not determined for the HDT/ASCT group after a median follow-up of 116.5 months, the impact of HDT/ASCT on the survival of patients was significantly improved with a 2.1-fold reduced risk of death. There were limited cases treated with HDT/ASCT in the studies reported by Kim et al. [26] and Niitsu et al. [34]. The study reported by Kim et al. [26] included 16 extranodal NK/T cell lymphoma patients who received HDT/ASCT and 246 patients who did not receive transplantation. At diagnosis, half of the patients were at an advanced stage (Ann Arbor stage III–IV). The median age was 36 years (range 17–54). The estimated 2-year OS was $71.3 \pm 12.4\%$ in patients with HDT/ASCT and $56.5 \pm 3.3\%$ in the 246 patients who did not receive HDT/ASCT. Also, in the study reported by Niitsu et al. [34], CHOP therapy was performed in 55 cases in patients with PTCL-U or angioimmunoblastic T cell lymphoma, CycloBEAP therapy in 32 cases and ASCT in 10 cases. The 5-year OS among those who received CHOP therapy, CycloBEAP therapy or ASCT was 25.7, 61.7 and 60%, respectively. Although no statistical significance was observed in these studies, the authors regarded that there was a trend toward survival advantage for the HDT/ASCT group as compared to the historical control group. Furthermore, in the largest study with 288 PTCL patients treated with different anthracycline-based regimens, the 5-year OS was 41% [5], and according to a published meta-analysis of front-line anthracycline-based chemotherapy regimens for PTCL, which included 31 studies, the 5-year OS for all PTCL patients ($n = 1,691$) was 36.6% (95% CI 31.5–42.0) [47]. Compared with the 5-year OS of 65% in this meta-analysis, it seems that the up-front ASCT provides a better survival outcome. Although a statistical survival benefit of HDT/ASCT as the first-line therapy could not be proven in this meta-analysis, evidences to support the survival advantages of up-front HDT/ASCT are beginning to emerge as more clinical studies are reported. In general, the clear and convincing proof about the effects of up-front HDT/ASCT still depends on sufficient PTCL-restricted randomized trials with large size being carried out in the future.

Despite the fact that there was no evidence for HDT/ASCT to improve OS in patients, there were some differences between risk groups stratified according to disease status at transplantation, the IPI and PIT. Good-risk patients, i.e. those with low or low-intermediate risk according to IPI and PIT and those achieving CR before transplantation, showed evidence for improved OS with HDT/ASCT.

The outcomes after HDT/ASCT always correlate with the disease status at the time of transplantation, which can be regarded as a significantly independent prognostic factor [13, 25, 28, 29, 31, 36, 37]. The achievement of CR before transplantation was a strong predictor of survival benefit. Our meta-analysis strengthens the proposal that survival outcomes are dismal if the patient failed to attain CR before transplantation. We also found that patients in CR and patients in PR at transplantation showed no statistical difference in OS. Consequently, patients with PTCL should be brought into remission with optimal chemotherapeutic regimens. When this is attained, the use of ASCT to consolidate responses could lead to good long-term post-transplant survival. In cases where remission cannot be attained, ASCT rescues only a handful of patients. Hence, novel treatment concepts incorporating novel agents and dose-dense regimens are needed to increase the CR rate prior to transplantation.

IPI was originally developed for the aggressive B cell lymphomas and is commonly used in PTCL. PIT was specifically developed for PTCL. Both IPI and PIT have shown prognostic value in PTCL and determine the outcome of patients with PTCL in many studies [2, 48–55]. OS benefit from HDT/ASCT was mainly demonstrated for high/intermediate-risk patients but not for low-risk patients compared with chemotherapy. In this meta-analysis, statistical differences obtained from enrolled studies showed that patients with good risk of IPI or lower scores of PIT before transplantation showed considerably better outcomes after ASCT. Nevertheless, these results can be understood with the fact that high-risk patients remain at high risk even after ASCT. In the studies reported by Kim et al. [26] and Lee et al. [32], further analyses of OS between HDT/ASCT and chemotherapy subgroups were performed in terms of good and poor risk of IPI. Despite high-risk IPI groups that underwent HDT/ASCT having more prolonged survival, no statistical significance was revealed. These results were inconsistent with those of previous studies. The limitation that PIT and IPI subgroup comparisons are hampered by their variety of grouping should be taken into consideration. In addition, given that the IPI and PIT failed to demonstrate

prognostic value in some studies [13, 27, 30], a new prognostic model was developed by the International Peripheral T Cell Lymphoma Project (IPTCLP). Definite survival benefit of HDT/ASCT either in high-risk or low-risk patient subgroups needs more randomized trials to be proven to be true, and the prognostic value of IPI and PIT for PTCL should be further studied. However, the latest and largest multi-center clinical trial, reported by d'Amore et al. [44], found the IPI to prognosticate effectively in angioimmunoblastic T cell lymphoma and PTCL-NOS, but not in ALK-negative ALCL. Furthermore, considering individual clinicopathologic features, those significantly affecting OS and/or progression-free survival at both univariate and multivariate levels were female sex and ALCL histology associated with favorable outcome, and age, bone marrow involvement and PS ≥ 2 as adverse prognosticators.

There are some limitations of our meta-analysis. First of all, since this meta-analysis was mainly based on retrospective studies, results can only be suggested and not proven. Further prospective studies would therefore be necessary. Secondly, we failed to get all the details of the patients that were available from the published studies or through contacting the authors, meaning we only used abstracted data although those details would have provided a more robust estimate of the efficacy of up-front HDT/ASCT. Our meta-analyses pooled the best available data from existing publications on the treatment of PTCL and the random effects model was chosen to enhance the stability of the statistics. However, we did not perform Jadad scoring of individual trials in this meta-analysis because there were no randomized PTCL-restricted clinical trials and most series were of a small size [56]. As a result,

heterogeneity problems were inevitable. We did not take the impact of the histological subtype on ASCT under consideration. Thus, our comparison is biased by this lack of information. In addition, some studies included ALCL patients with ALK+ or patients with NK/T cell lymphoma, who generally showed favorable outcomes. Taking this into account, there would be a tendency to bias OS toward a benefit. Finally, studies reporting positive or significant findings are more likely to be published than those reporting nonsignificant results. Therefore, publication bias is a major concern in all meta-analyses. To better define the role of HDT/ASCT, the data from the unpublished trials should be made available for a more complete assessment of the treatment effect.

In conclusion, up-front HDT/ASCT failed to show a survival benefit in PTCL patients compared with conventional chemotherapy alone based on our statistical results. However, HDT/ASCT is considered a reasonable approach in eligible patients with PTCL, especially in patients achieving CR after induction therapy. Also, low PIT or IPI score could be regarded as favorable prognostic factors for OS. Taking into account that most of these studies had heterogeneous weakness and different trial designs, definitive treatment recommendations would seem to depend on large-scale, high-quality multinational randomized PTCL-restricted clinical studies.

Acknowledgments

The authors would like to thank Dr. Peter Reimer for providing detailed information regarding the survival analysis of his study.

This study was supported by two grants from the National Science Foundation of China (30971293 and 30670897).

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