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ORIGINAL ARTICLE

Gemcitabine, cisplatin, and dexamethasone (GDP) in combination with methotrexate and pegaspargase is active in newly diagnosed peripheral T cell lymphoma patients: a phase 2, single-center, open-label study in China

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Abstract

Peripheral T cell lymphomas (PTCL) are less responsive to anthracycline-containing regimen such as CHOP and carry a poor prognosis. In this prospective study, we investigated gemcitabine, cisplatin, and dexamethasone (GDP) combined with *methotrexate* (MTX) and pegaspargase (PEG-L) as front-line treatment in PTCL. Eligible newly diagnosed PTCL patients received 4 cycles of the GDP-ML chemotherapy every 28 days. After 4 cycles, responding patients continued to receive either autologous stem cell transplantation or the MTX/cytarabine (MA) regimen for consolidation. This trial is registered with www.chictr.org.cn (ChiCTR-ONC-12002055). A total of 65 patients were enrolled with a median follow-up of 38.5 months. The overall response rate (ORR) was 55.4%, and complete remission rate (CR) was 33.8%. The median overall survival (OS) was 16 months, and the 1-year and 2-year OS were 59.1% and 38.2%, respectively. The median PFS was only 8 months. The main adverse event was hematologic toxicity: 50% patients showed grade III/IV neutropenia. GDP-ML for the first-line treatment of PTCL patients is an effective induction regimen compared with standard CHOP, and the toxicity was more significant but acceptable. However, future studies exploring new drug combinations are warranted to overcome relapse after remission. ClinicalTrials.gov Identifier: NCT02987244

Keywords Peripheral T cell lymphoma · GDP · MTX · Pegaspargase · Overall response rate · Overall survival

Introduction

The prognosis of PTCL is far poorer than B cell lymphomas. The treatment strategy for peripheral T cell lymphomas (PTCLs) is still based on anthracycline-containing chemotherapy such as CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or CHOP-like regimens despite their outcome that was not satisfactory, and the long-term relapsing-free survival is less than 40% [1–3]. Given the uncommon frequency of PTCL and the highly heterogeneous nature of these diseases, there have been few randomized clinical trials evaluating the different front-line therapies for PTCL. In recent years, it has been reported that the short-term efficacy of gemcitabine, cisplatin, and dexamethasone (GDP) regimen as a salvage therapy for PTCL is 69%, and the 4-year survival rate reaches 68.2% [4]. The clinical efficacy of GDP regimen as a second-line treatment of T cell lymphoma has been widely recognized [5, 6]. MTX and pegaspargase (PEG-L) are both chemotherapeutic drugs with unique mechanism. MTX is widely applied in the treatment of the central nervous system lymphoma and acute lymphoblastic leukemia, whereas PEG-L can affect protein synthesis by hydrolyzing asparagine in tumor cells, and shows prominent effect on natural killer (NK)/T cell lymphoma [7, 8]. MA regimen (methotrexate/cytarabine) was widely used in PTCL, and MTX combined with CTX and dexamethasone was reported in 2015 [9]. Several retrospective studies demonstrated the efficiency of L-asparaginase in PTCL, especially in better short-term effect

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[10, 11]. Therefore, we added MTX and PEG-L to GDP regimen (GDP-ML) as first-line treatment of PCTL and conducted a prospective single-center single-arm phase II study (ChiCTR-ONC-12002055) to evaluate the efficacy and safety of GDP-ML regimen.

Materials and methods

Patient population

All enrolled patients were newly diagnosed with PTCL and treated at Peking Union Medical College Hospital. The inclusion criteria were as follows: [1] pathological confirmation of PTCL before the initial treatment; [2] age 18–70 years old; [3] Eastern Cooperative Oncology Group (ECOG) score ≤ 2; [4] renal function ≤ three times the upper limit of the normal range (ULN); and [5] total bilirubin (TBIL) ≤ three times ULN, alanine aminotransferase (ALT) ≤ three times ULN. The exclusion criteria were [1] phase I NK/T cell lymphoma, nasal type; [2] the proportion of bone marrow lymphoma cells exceeded 25%; [3] ALK-positive anaplastic large T cell lymphoma (ALCL); [4] central nervous system lymphoma; [5] accompanied uncontrolled active infection; and [6] pregnant or lactating women. The enrollment time was from March 2012 to December 2013. All patients provided a written informed consent before any study-related procedure was administered. The protocol was approved by the institutional review board before the study initiated.

Study protocol

The enrolled patients were given 4 cycles of GDP-ML induction chemotherapy as follows: gemcitabine (1 g/m^2 day 1), cisplatin (75 mg/m^2 day 1), dexamethasone (40 mg days 1–4) and MTX (1 g/m^2 day 2), and PEG-L (3750 U day 5). Every 28 days was considered a treatment cycle. After 4 cycles, patients in complete remission (CR) or partial remission (PR) continued to receive consolidation chemotherapy with either autologous stem cell transplantation or MA regimen according to investigators' choices. Peripheral-blood stem cells were collected after 4 cycles, and conditioning regimen consisted of carmustine, etoposide, cytarabine, and melphalan (BEAM). MA regimen consisted of methotrexate (1.0 g/m^2) infused continuously for 24 h on day 1 and cytarabine (2.0 g/m^2) in a 3-h infusion repeated after 12 h on days 2 and 3. After 2 cycles of consolidation chemotherapy, the treatment ended. Patients who achieve disease progression (PD) or stable disease (SD) during the treatment were withdrawn from the trial and received salvage treatment. Follow-up procedures included a physical examination every 3 months for the first year and every 6 months thereafter for 3 years.

Efficacy evaluation

All patients received a full-body CT or PET/CT after 2, 4, and 6 cycles of treatment or 1 month after transplantation to assess the efficacy of the treatment. For efficacy evaluation, a revised response criteria for malignant lymphoma from 2007 [9] was applied. The main treatment endpoints included ORR, CR, and PR; secondary endpoints included PFS and OS. PFS was defined as the time from patient enrollment to tumor progression or death, and OS was defined as the time from patient enrollment to death caused by any adverse cause. All adverse reactions were recorded, and the corresponding evaluation and grading were performed in accordance with the Common Toxicity Criteria version 4.0 issued by the National Cancer Institute (NCI). October 25, 2016, was the time of the last follow-up included in this study.

Statistical analysis

All cases were analyzed on an intention-to-treat basis. Analyses of patient OS and PFS were conducted using the Kaplan-Meier method. Log-rank tests were performed to analyze the relationship between single factor and prognosis, and then Cox regression analysis was performed to analyze the relationship between multiple factors and prognosis; both analyses were performed with the forward stepwise method. p values of less than .05 were considered as statistically significant, from a two-tailed test. All data analyses were performed using the SPSS 20.0 software package (SPSS).

Results

Patient information

From March 2012 to December 2013, a total of 65 PTCL patients were enrolled. Baseline demographic and clinical characteristics of the patients are summarized in Table 1. There were 45 male and 20 female patients. The median age was 40 years old, and 11 (16.9%) were older than 60. The majority (84.6%) of patients were in advanced stage. Forty-two patients (64.6%) had B symptoms at the time of diagnosis; 38 patients (58.5%) showed elevated lactate dehydrogenase (LDH); 24 patients (36.9%) showed extranodal involvement more than 1 site; 13 patients (20%) showed bone marrow involvement; and 60% patients were determined to be high risk based on the International Prognostic Index (IPI).

The pathological types of the cases were predominantly PTCL, not otherwise specified (PTCL-NOS), including 22 cases (33.8%); there were 17 cases of extranodal natural killer/T cell lymphoma (ENKL), 10 cases (15.4%) of ALK negative anaplastic large T cell lymphoma (ALK− ALCL), 6 cases of angioimmunoblastic T cell lymphoma, four cases of

Table 1 Patients' characteristics

Characteristics	*n*	%
Age > 60 years	11	16.9
Female	20	30.7
Male	45	69.3
LDH level elevated	38	58.5
Extranodal involvement≥ 2	24	36.9
ECOG > 1	7	10.8
Clinical stage III/IV	55	84.6
B symptoms	42	64.6
Bone marrow involvement	13	20.0
IPI > 2	39	60.0
Pathological type		
PTCL, NOS	22	33.8
ALK− ALCL	10	15.4
ENKL	17	26.2
AITL	6	9.2
SPTCL	4	6.2
HSTL	1	1.5

subcutaneous panniculitis-like T cell lymphoma (SPTCL), and one case of hepatosplenic γδT cell lymphoma. The remaining five cases were unclassified (PTCL-u).

Efficacy

All enrolled patients completed a total of 215 GDP-ML induction chemotherapy cycles. Forty-four patients (67.7%) completed all four treatment cycles. Among patients withdrawn from the GDP-ML regimen, 15 (23.1%) died due to disease progression, and 4 died of concurrent infections. Two patients were lost to follow-up.

The ORR was 55.4% (36/65), including 22 (33.8%) cases of CR and 14 (21.5%) cases of PR. There were 5 (7.7%) cases of SD, and 24 (36.9%) cases of no remission (NR) (Table 2).

During the follow-up, no CNS relapsing or involvement occurred.

Recurrence and disease progression

After 4 cycles, 22 patients achieved CR. Among these, 10 underwent autologous stem cell transplantation, and one underwent allogeneic transplantation; these 11 patients all achieved disease-free survival. Nine patients were given MA regimen for consolidation, and 6 in sustained CR and 3 patients relapsed. Two patients died of other diseases.

Fourteen patients achieved PR after 4 cycles of GDP-ML. Ten of 14 relapse soon, and 9 died after failed salvage chemotherapy, and one achieved PR again. One patient received autologous transplantation and achieved CR, but relapsed after 8 months and died. Three NK/T cell lymphoma patients with received radiotherapy and achieved sustained CR.

Among the five cases of SD patients, two were lost to follow-up, one achieved CR after bortezomib combined salvage chemotherapy, and the remaining two patients died of disease progression.

After four treatment cycles, there were 24 cases of NR. Among these patients, only one NK/T cell lymphoma patient underwent radiotherapy and resulted in CR, and two patients received bortezomib in combination with chemotherapy and achieved sustained remission. The remaining 21 patients died within a short time period.

Long-term survival

Until October 25, 2016, the median follow-up time was 38.5 months (1–58 months); for the survivors, the follow-up time was 45 months. Two patients were lost to follow-up. At the end of the study, there remained 27 (41.5%) survivors, including 24 (36.9%) in CR. Thirty-six (55.4%) cases were dead, and six (9.2%) patients died of secondary infection; two died of cardiovascular diseases. The remaining 28 (43.1%)

Table 2 Response to treatment with different pathological types

Pathological type	CR (%)	PR (%)	SD (%)	NR (%)	ORR
PTCL, NOS	7 (31.8)	4 (18.2)	3 (13.6)	8 (36.4)	50%
ALK− ALCL	5 (50)	1 (10)	1 (10)	3 (30)	60%
ENKL	5 (29.4)	5 (29.4)	0	7 (41.2)	58.8%
AITL	2 (33.3)	2 (33.3)	0	2 (33.3)	66.6%
SPTCL	1 (25)	0	1 (25)	2 (50)	25%
HSTL	1 (100)	0	0	0	100%
T cell lymphoma, unclassified	1 (20)	2 (40)	0	2 (40)	60%
Total	22 (33.8)	14 (21.5)	5 (7.7)	24 (36.9)	55.4%

PTCL, NOS peripheral T cell lymphoma-not otherwise specified; *AITL* angioimmunoblastic T cell lymphoma; *ALK− ALCL* ALK negative anaplastic large cell lymphoma; *HSTL* hepatosplenic T cell lymphoma; *ENKL* extranodal NK/T cell lymphoma; *SPTCL* subcutaneous panniculitis like T cell lymphoma; *CR* complete response; *PR* partial response; *SD* stable disease; *NR* not remission; *ORR* overall response rate

patients all died of disease progression. Of the 65 patients, the median OS time was 16 months, and the 1-year and 2-year OS rates were 59.1% and 38.2%, respectively (Fig. 1); the median PFS time was 8 months, and the 1-year and 2-year PFS rates were 41.8% and 34.4%, respectively (Fig. 2).

During whole following up, no CNS relapsing occurred.

Safety and adverse events

Hematologic toxicity was mainly manifested by neutropenia. Thirty-three patients (50.8%) had grade III/IV neutropenia in 68 treatment cycles, accounting for 31.6% of the total cycles. Thrombocytopenia were reported in 13 patients, and grade III/IV thrombocytopenia occurred in 5 patients (7.7%). Non-hematologic adverse events included: Serious infections occurred in eight patients (12.3%), and in six cases led to death (9.2%). Among them, two cases were caused by central nervous system infections (one case of bacterial infection and one case of fungal infection); two cases were caused by a Gram-negative bacilli bloodstream infection; two cases were mixed pulmonary infections. Coagulopathy caused by asparaginase was mainly hypofibrinogenemia. Eighteen (27.7%) patients developed a fall in fibrinogen levels, three of them were grade IV, and PEG-L was temporarily suspended. After fibrinogen concentrate infusion, hypofibrinogenemia was improved in all cases. No severe bleeding or thrombosis events occurred. In two cases, mild pancreatic enzyme elevated in two cases. Six (9.2%) cases occurred grade II/III alanine aminotransferase increase. In three cases experienced grade II/III transient creatinine increase, causing MTX suspended for 1 cycle (Table 3).

Univariate analyses of prognostic factors for OS and PFS

The remission status after induction chemotherapy

It was found that patients in CR after GDP-ML therapy were significantly longer OS than PR and NR groups. The 2-year OS rate of CR, PR, and PD group was 82.6% vs 22.5% vs 7.8% ($p < 0.001$) (Fig. 3).

Autologous transplantation

Twenty-three patients achieved CR after induction, 11 patients underwent autologous transplantation, and one received allogeneic transplantation. Eleven eligible patients did not receive autologous stem cell transplantation (ASCT) for different reasons: 2 patients were older than 65 years, 2 patients died of chemo-complications, 2 patients cannot harvest enough stem cells, 1 patient had an early relapsing before ASCT, and 5 patients refused ASCT for private reasons. The 2-year OS rate of transplantation group was 87.5%, and the median survival time was not reached. This was significantly better than the chemotherapy group: The 2-year OS rate of the chemotherapy

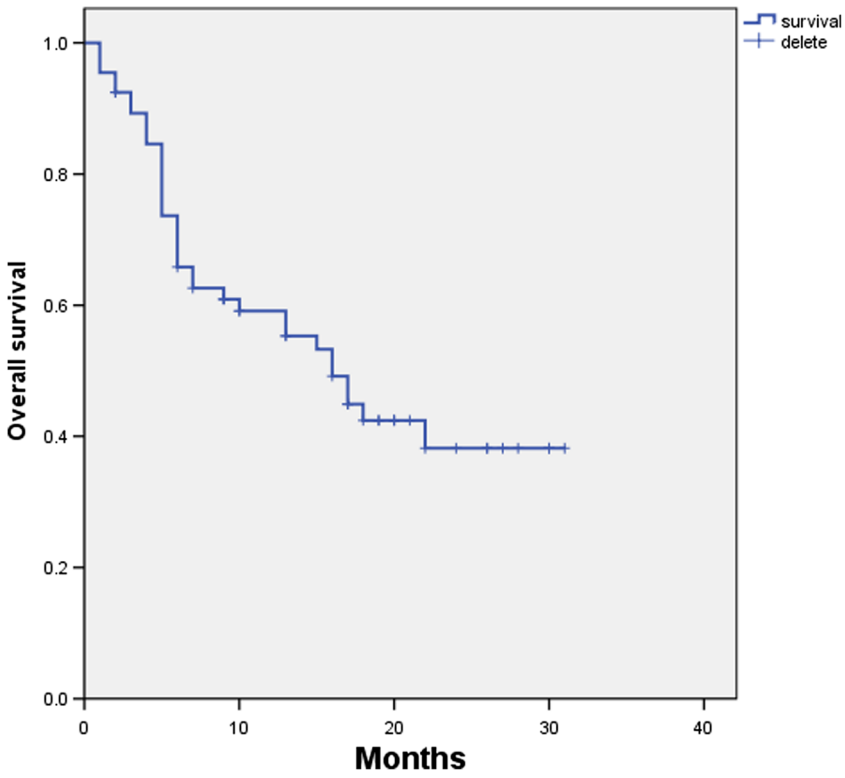

Fig. 1 The overall survival of 65 PTCL patients

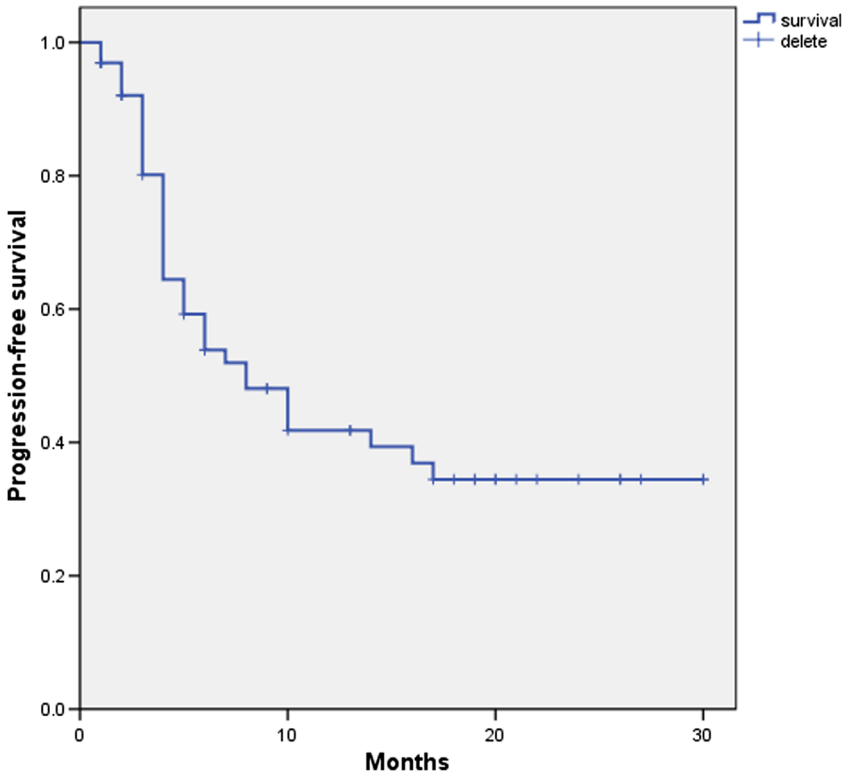

Fig. 2 The progression-free survival of 65 PTCL patients

group was 38.5%, and median survival time was 13 months ($p = 0.006$).

Pathological type and other variable

Different pathological types responded differently to the GDP-ML chemotherapy. The 2-year OS rates of SPTCL and ALK− ALCL patients were 75% and 53.3%, respectively. For patients with PTCL-NOS, the pathological type of which the proportion was the highest, the 2-year OS rate was only 31.2%, and the 2-year OS rate of ENKL patients was 30.9%. There was only one case of hepatosplenic T cell lymphoma; the patient underwent allogeneic transplantation in CR1 and achieved sustained remission. Due to limited sample size, there were no differences in 2-year OS between different pathological types ($p = 0.409$).

Younger patients (age < 40) had a better prognosis in PFS ($p = 0.040$) and OS ($p = 0.026$), but IPI score > 2, advanced stage, HLH, bone marrow involvement, and elevated LDH were not related with PFS or OS (see Table 4).

Table 3 Toxicity profile of GDP-ML

	Grade 1–2	Grade 3	Grade 4	Grade 5
Acute renal toxicity	1 (1.5%)	2 (3.1%)		
ALT elevated	15 (23.1%)	2 (3.1%)	0	0
Anemia	31 (47.69%)	5 (7.7%)	0	0
Infection	14 (21.5%)	2 (3.1%)	0	6 (9.2%)
Fibrinogen decreased	15 (23.1)	2 (3.1%)	1 (1.5%)	0
Mucositis	8 (12.3%)	0	0	0
Nausea	18 (27.7%)	1 (1.5%)	0	0
Neutropenia	11 (16.9%)	23 (35.4%)	10 (15.4%)	0
Thrombocytopenia	8 (12.3%)	3 (4.6%)	2 (3.1%)	0
Vomiting	7 (10.7%)	1 (1.5%)	0	0

Data are *n* (%) for adverse events of grade 1–2 occurring in at least 10% of patients and all grade 3–5 events

Multivariate analyses of prognostic factors for OS and PFS

The COX multivariate regression analysis revealed that remission status after induction therapy was the only independent prognostic factor ($p = 0.005$) for OS. Also for PFS, the remission status was found to be the only independent prognostic factor ($p = 0.038$).

Discussion

The remission rate of T cell lymphoma after treatment using the CHOP induction regimen is currently less-than-ideal. The short-term ORR is 60–70% [2, 3], and the 5-year survival rate is 30–40% [2, 3]. The goal of the present prospective study was to evaluate the efficacy of a novel 5-drug combined induction regimen with different mechanisms. We hoped that

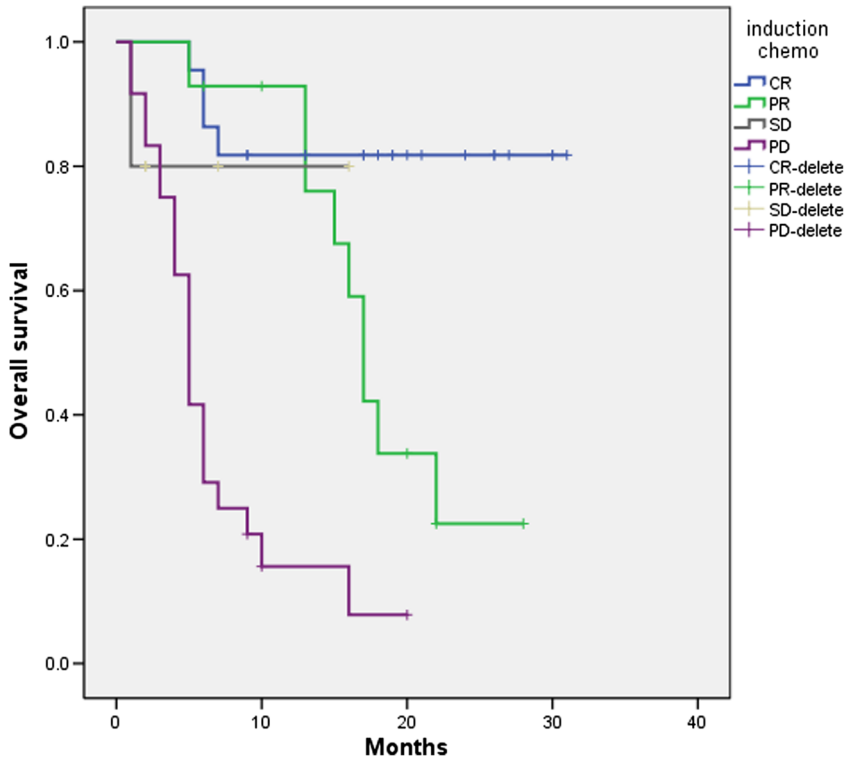

Fig. 3 The efficacy of induction chemotherapy and overall survival. CR complete response, PR partial response, SD stable disease, PD progressive disease

this regimen can increase remission rate and improve overall survival.

In this study, the predominant subtype of PTCL was PTCL-NOS, accounting for nearly one third of all cases; the next was NK/T cell lymphoma, accounting for 26% of all cases. These proportions were similar to previous reports [3].

CHOP chemotherapy is the most commonly used first-line regimen for patients with PTCL, and the response rate was nearby 60%. Many efforts were made to find a better induction regimen, but none of them showed superior than CHOP. Various combinations of gemcitabine with platinum and steroid in relapsed or refractory peripheral T cell lymphoma have also been reported with encouraging results and acceptable toxicity, but the objective response rate varied a lot. In 2006, Kim et al. reported that in induction treatment of 26 PTCL Asian patients with CHOP combined with gemcitabine and etoposide, the short-term ORR was 77% and CR 61.5% [12]. In 2007, Arkenau et al. performed a retrospective analysis on 16 cases PTCL treated with gemcitabine, cisplatin, and methyl-prednisolone, and showed ORR 69% and CR 19% [4]. A very recent phase 2, multicenter, randomized, open-label study compared GEM-P (gemcitabine, methylprednisolone, and cisplatin) and CHOP regimen in untreated PTCL, and there was no difference in short-term efficiency (CR 62% vs 47%, $p = 0.164$) or long-term survival (2 year PFS 38.0% vs 36.0%, $p = 0.82$). Meanwhile, adverse events of grade 3 or worse were similar in both groups such as neutropenia, thrombocytopenia, and febrile neutropenia [13].

Table 4 Prognostic factors for progression-free survival and overall survival

Variate	PFS		OS	
	p value	OR	*p* value	OR
Age > 40	0.040	2.057	0.026	2.315
IPI > 2	0.898	0.955	0.254	0.663
Stage III/IV	0.532	1.401	0.811	1.137
HLH	0.179	1.695	0.116	1.866
Elevated LDH	0.058	2.093	0.072	2.100
BM involvement	0.908	0.949	0.333	1.490
CR status	0.001	0.233	0.002	0.216
ASCT	0.029	0.202	0.067	0.033

MTX is an efficient anti-tumor medication, and it is the backbone of pediatric leukemia therapy and essential element of NK/T cell lymphoma regimen. MTX can penetrate brain-blood-barrier and be widely used for preventing CNS relapsing in aggressive B cell lymphoma. Most PTCL patients were not in high risk of CNS relapsing (2–6%), except advanced ALK+ ALCL [14]. In our study, there were no CNS relapsing during whole follow-up, which may partly attribute to MTX administration.

Asparaginase was mostly used in the treatment of NK/T cell lymphoma, such as SMILE, pegaspargase, gemcitabine, and oxaliplatin (P-Gemox) regimens. Several retrospective studies in China had demonstrated the efficiency of L-asparaginase [10, 11]. In 2015, Xie reported that L-ASP

containing multidrug chemotherapy regimen in incipient PTCL showed a better short-term effect and controllable adverse reactions in 102 patients [10].

The ORR of GDP-ML regimen for whole series in this study was 55.4%, and CR was 33.8%. There was a difference in the ORR among PTCL subtypes, the ORRs were 50% in PTCL-NOS, 60% in ALK− ALCL, 66.6% in AITL, and 60% in PTCL-u. The efficiency was comparable with CHOP, GEM-P, and GDP regimen. Several reasons were related with the unsatisfied response rate: 23.1% patients had disease progression during chemotherapy—this was much higher than other studies; treatment-related toxicities and 9.2% died of concurrent infections.

Our regimen was similar with P-Gemox which was firstly reported in 2017 [15]. Among 17 ENKL patients, ORR was 58.8%, and 2-year OS was only 30.9%. Thus, both the short-term and the long-term efficacies were poorer than those of P-Gemox regimen, maybe the higher proportion of patients with stage IV disease in our group.

In our study, among 36 patients who achieved initial remission after GDP-ML induction, 12 (33.3%) relapsed within 6 months, and 2-year PFS were 34.4%, respectively. In a previous study on 340 PTCL patients (T and NK/T cell lymphoma), although the CR rate of induction chemotherapy was 56%, the 5-year RFS was only 22% [3]. In a study of induction chemotherapy using bortezomib combined with CHOP conducted in Korea as described above [16], half of the patients relapsed within 3 years. Relapsing was the main concern in PTCL treatment, and this cannot be overcome by traditional chemotherapy including this regimen. Novel agents such as histone deacetylase inhibitors should be administrated as maintenance to decrease relapsing.

It should be noted that GDP-ML is associated with significant toxicities, particularly neutropenia. Fifty percent of the patients showed grade III/IV neutropenia. The infection incidence caused by neutropenia was 33.8%, and treatment-related mortality (TRM) was 9.2%. Compared with GDP regimen, grade 3/4 neutropenia occurred in 16.3–32% patients and no treated-related death was observed [17, 18]. In our study, no prophylactic G-CSF was administered to decrease the incidence and duration of severe neutropenia. So, the high TMR was not only related to intensive chemotherapy but also to no prophylactic G-CSF. The thrombocytopenia cases were mostly grade I/II. Renal injury and nausea were common side effects which induced by MTX and cisplatin, and there were only two transient episodes of grade 3 renal injury. Hypofibrinogenemia occurred in 27.7% patients and can be corrected by fibrinogen infusion easily. No allergy reaction, pancreatitis, diabetes, thrombosis, and bleeding events occurred during total 215 cycles. Thus, GDP-ML regimen with prophylactic G-CSF may have lower infection incidence and can be an alternative choice of CHOP.

Although our data show that GDP-ML has efficacy in terms of response and survival in peripheral T cell lymphoma, but, it was comparable with CHOP for treatment-naive patients with this disease, without superiorities in efficiency and safety. In the future, adding G-CSF may reduce the toxicities and TRM. Also, when front-line anthracycline-based chemotherapy is contraindicated to avoid cardiotoxicity, this regimen can be an alternative option.

We explored prognostic factors. Univariate analysis showed that younger patients (< 40 years) had significantly better PFS and OS than elder patients. This might be explained by the good tolerance and physical status in younger patients. CR status after induction chemotherapy was the strongest factor which improved significantly PFS and OS. The 2-year OS rate of the CR group was 82.6%, whereas that of the PR group was only 22.5% ($p < 0.001$).

Many studies have reported favorable outcomes in patients with PTCL undergoing HDT/ASCT during first-line or subsequent lines of therapy. But, a report from Memorial Sloan-Kettering Cancer Center showed a potential benefit of non-CHOP induction therapy followed by consolidative transplant in PTCL, NOS, but ASCT was not an independent factor [19]. There are no clear data to support ASCT in ENKL, and 26.2% patients were ENKL in our study. These may explain why there was no difference between ASCT and non-ASCT group in our study. Multivariate COX regression analysis revealed that only CR status was the only independent factor in both PFS and OS. For the limited number of patients for subtypes other than PTCL-NOS, there was no significant prognostic difference between subtypes.

However, the limitations of our study also need to be acknowledged. Firstly, for the limited number of patients and the big proportion of patients who did not complete induction, the outcome analysis was underpowered. Secondly, half of CR patients did not undergo ASCT, and this was a related bias in PFS and OS analysis.

Conclusion

In this preliminary study, the 5-drug combination regimen including gemcitabine, dexamethasone, cisplatin, PEG-L, and MTX was an effective induction regimen with significant toxicity. Combined with prophylactic G-CSF in the future, it could be an alternative choice of CHOP. Our results also showed the importance of obtaining early CR in PTCL prognosis. The main concern was early relapsing after induction, even 5-drug combination regimen with unique mechanism cannot overcome, new therapeutic targets still are urgent needs in order to break the bottleneck of T cell lymphoma treatment, and a prospective trial of CHOEP combination with histone deacetylase inhibitor is ongoing in our center.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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