Original Research

Outcomes of GDPT (gemcitabine, cisplatin, prednisone, thalidomide) *versus* CHOP in newly diagnosed peripheral T-cell lymphoma patients

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Abstract

Aim: To compare the outcomes of GDPT [gemcitabine (G), cisplatin (D), prednisone (P), thalidomide (T)] *versus* CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) in treating newly diagnosed PTCL (peripheral T-cell lymphoma).

Methods: An open-label prospective clinical trial with 153 newly diagnosed PTCL patients conducted between January 2010 and December 2018 was designed. Patients were randomly assigned to the GDPT (77 cases) and CHOP (76 cases) groups. Patients in each group were further divided into four subgroups: PTCL, not otherwise specified (PTCL-NOS); anaplastic large cell lymphoma (ALCL), angioimmunoblastic T cell lymphoma (AITL), and other types subgroup, in accordance with pathological patterns. Based on expression of *RRM1, TOP2A, TUBB3*, and *ERCC1*, patients were divided into groups with high and low gene expression levels. Clinical characteristics, side effects, efficacy, progression-free survival (PFS), and overall survival (OS) were compared.

Results: There were no significant differences in the basic clinical features or side effects between the GDPT and CHOP groups. The overall response rate (ORR) of the GDPT group was better than that of the CHOP group (66.3% *versus* 50.0%, $p=0.042$), as was the complete remission (CR) rate (42.9% *versus* 27.6%, $p=0.049$). Patients in the GDPT group had a longer PFS and OS than the CHOP group. The 4-year PFS and OS rates in the GDPT group were both superior to those in the CHOP group (63.6% *versus* 53.0% for PFS, $p=0.035$; 66.8% *versus* 53.6% for OS, $p=0.039$). In the GDPT group, the difference in CR between the four subgroups was statistically significant ($p=0.046$). In the CHOP group, differences in both CR and ORR among the four subgroups were statistically significant ($p<0.001$ and $p=0.005$, respectively). There were also statistically significant differences in CR between patients treated with CHOP and GDPT in the PTCL-NOS subgroup, AITL subgroup, and the other types subgroup ($p=0.015$; $p=0.003$; $p=0.005$, respectively). The data also showed a significant difference in OS among the four subgroups within the GDPT group ($p=0.001$). The OS of AITL was shorter than that of the other three subgroups. Four subgroups of CHOP showed a significant difference in PFS ($p=0.019$). There was no statistical association between responses and the gene expression levels of *RRM1, ERCC1, TUBB3*, and *TOP2A*.

Conclusion: The GDPT group had better response rates and prolonged patient PFS and OS. As a promising new regimen, GDPT is expected to become the first-line therapy for PTCL. New agents should be applied to patients who do not achieve good responses with previous treatment, such as those diagnosed with angioimmunoblastic T cell lymphoma.

Trial registration: This open randomized prospective clinical trial was registered at ClinicalTrials.gov (NCT01664975).

Keywords: CHOP, GDPT, genes, outcomes, peripheral T cell lymphoma

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Introduction

Peripheral T cell lymphoma (PTCL) originates from mature thymic T cells. This disease comprises a group of highly heterogeneous invasive non-Hodgkin lymphomas (NHL), with multiple subtypes such as anaplastic lymphoma kinase (ALK)-positive (+) anaplastic large cell lymphoma (ALCL), ALK-negative(−) ALCL, angioimmunoblastic T cell lymphoma (AITL), and PTCL not otherwise specified (PTCL-NOS).[1] Fewer patients are diagnosed PTCL compared with B cell lymphoma, and the former accounts for only 10% of NHL in western countries.[2] Previous studies have shown that PTCL accounts for nearly 25% of NHL cases in China, much higher than the global average.[3] At present, there is no consensus standard treatment for PTCL. Thus, treatment is based primarily on the experience of treating B cell lymphoma, which uses the CHOP regimen (cyclophosphamide, vincristine, doxorubicin, prednisone).[4] Other studies have revealed that the addition of etoposide can benefit young patients with PTCL.[5] The role of radiotherapy in PTCL has not been widely reported, and its significance and value remain controversial at present. The National Comprehensive Cancer Network (NCCN) guidelines recommend that apart from ALK (+) ALCL, PTCL patients who have been induced by induction therapy should be treated with autologous hematopoietic stem cell transplantation (ASCT). Even so, the overall response rate (ORR) of patients with PTCL remains low, prognosis is dismal, and patients with this disease readily relapse.[6] Many trials have demonstrated good outcomes using single-agent gemcitabine, or its combination with other drugs, for PTCL. Chemotherapy regimens including gemcitabine, cisplatin, and prednisone have previously been used to treat relapsed and refractory PTCL.[7,8] Thalidomide can suppress tumor growth by inhibiting angiogenesis, promoting apoptosis, inhibiting inflammatory responses, and regulating the immune system. However, there are no studies evaluating thalidomide combined with other agents for treating PTCL. Therefore, we undertook an open-label, prospective clinical study comparing the efficacy and adverse effects of gemcitabine, cisplatin, prednisone plus thalidomide (GDPT) regimen *versus* CHOP regimen in patients with newly diagnosed PTCL. It has been suggested that patients with low expression of *RRM1* and *ERCC1* in tumor tissues have better responses to cisplatin and gemcitabine, respectively.[9,10] Patients responding well to vinca alkaloids often have low expression of *TUBB3*.[11] Nevertheless, patients with

lower expression of *TOP2A* were partially resistant to anthracyclines.[12] In this study we sought to identify individualized treatments by detecting the expression of these four genes in PTCL patients and exploring potential associations of gene expression and responses to chemotherapy.

Materials and methods

Patients

From January 2010 to December 2018, 153 patients who met the inclusion criteria were admitted. They were all newly diagnosed with PTCL from the First Affiliated Hospital of Zhengzhou University. Inclusion criteria were as follows: (1) age from 18 to 70 years; (2) Eastern Cooperative s Group (ECOG) score ≤2 points; (3) estimated survival time greater than 3 months; (4) peripheral T cell lymphoma diagnosed by histopathology with reference to the 2008 WHO classification of lymphatic hematopoietic tumors; (5) no chemotherapy contraindications; (6) at least one measurable lesion according to the RECIST criteria; (7) no other serious disease; (8) available for follow up; (9) other anti-tumor agents were not used during this treatment, except symptomatic treatments; (10) patients understood the study and signed informed consent. Exclusion criteria: (1) patients who had other malignant tumors in the past; (2) patients with uncontrolled infections; (3) patients with a history of psychiatric disorders; (4) pregnant or lactating women; (5) patients with an involved central nervous system; (6) patients diagnosed with natural killer (NK)/T cell lymphoma, nasal type.

Treatment schedule

This open randomized prospective clinical trial was registered at ClinicalTrials.gov (NCT01664975). The research project was carried out in accordance with the Declaration of Helsinki and clinical practice guidelines, and was approved by the Local Ethics Committee of the Zhengzhou University and the Scientific Council of the Medical College (No. 2011ky003). All included patients were fully aware of the program and submitted written informed consent, which covered background, objective and method of the trial, precautions, possible benefits, adverse reactions and risks, security, information confidentiality, consultation and voluntary information. Enrolled patients were randomized into the CHOP and GDPT groups. GDPT includes gemcitabine 0.8 g/m² d1, 8, iv, 0.5 h; cisplatin 25 mg/m²

d1–3 iv; prednisone 60 mg/m² d1–5, po; thalidomide starting at 50 mg, then increasing by 50–200 mg every day if there are few side effects, taken before going to bed until the end of the project. The CHOP strategy comprised cyclophosphamide 750 mg/m² d1, iv; vincristine 1.4 g/m², the maximum dose is 2 mg, d1, iv; doxorubicin 50 mg/m² d1, iv; prednisone 60 mg/m² d1-5, po. Each cycle lasts 21 days. All patients were intended to receive six cycles. If patients progressed or experienced serious adverse reactions, the treatment was halted. In addition, chemotherapy drug dosages were to be reduced by 20% if the patients experienced a grade 4 adverse reaction during the therapy.

Clinical data

We searched the hospital medical records and obtained the patients' basic information, including general information: gender, age, date of diagnosis, pathological type, clinical stage (Ann Arbor stage), physical status score, ECOG score, international prognostic index (IPI) score, sites and number of extra nodal involvement, presence or absence of bone marrow invasion, B symptoms, as well as routine blood evaluations including lactate dehydrogenase (LDH), β2 microglobulin levels, liver function indicators including alanine transaminase (ALT), aspartate aminotransferase (AST), bilirubin element, and renal function indicators such as creatinine, urea, and others.

Gene detection

Tissues of the PTCL patients were obtained from the Department of Pathology, the First Affiliated Hospital of Zhengzhou University. A commercial company was contracted, and branched DNA liquid chip technology (bDNA-LCT) of SurPlexTM liquid chip was used to quantitatively detect mRNAs for *RRM1, TOP2A, TUBB3,* and *ERCC1*. A level above the normal value is defined as high expression; otherwise it was considered low expression. The link between expression of the four genes and patient prognosis was explored.

Efficacy evaluation

Efficacy was evaluated by imaging examination (referring to the International Lymphoma Working Group criteria) and was divided into four states: complete remission (CR), partial remission (PR), stable disease (SD), and disease progression (PD). The ORR includes CR and PR. After every two cycles of chemotherapy, an evaluation was performed. Adverse reactions such as digestive tract reactions, abnormal cardiac function, and venous thrombosis were all recorded.

Follow up

Patient progression and overall survival (OS) were obtained by telephone or hospital management system until 31 December 2018. Progression-free survival (PFS) refers to the span from the start of treatment to patient progression, whereas OS refers to the time from the start of treatment to death or last follow up.

Statistical methods

Statistical analysis was performed using SPSS 23.0 software. Quantitative variables and qualitative variables were compared using independent samples t test and the chi-square test, respectively. Survival analyses were estimated by using the Kaplan–Meier method with log-rank test. p values were considered statistically significant when less than 0.05.

Results

Basic features

In total, from January 2010 to December 2018, 153 patients who met the inclusion criteria entered the clinical trial, including 49 ALCL cases (32.0%), 37 AITL cases (24.2%), 31 PTCL-NOS cases (20.3%), and 36 others (23.5%). All patients were divided randomly into two groups, with 77 cases in the GDPT group and 76 cases in the CHOP group. At diagnosis, the median age of all patients was 51 years (ranging from 18 to 70). The male:female ratio was 1.89:1. The cases in stage I, II, III, and IV were 20 (13.1%), 20 (13.1%), 39 (25.5%), and 74 (48.4%), respectively. There were 69 patients (45.1%) with B symptoms, 65 patients (42.5%) with elevated LDH, 53 patients (34.6%) with increased β2 microglobulin, and 15 patients (9.8%) with bone marrow involvement. No significant differences were observed in clinical characteristics between the two groups (Table 1).

Responses and prognosis

The ORR of the GDPT group was 66.3%, which was significantly higher than that of the CHOP group (50.0%) ($p = 0.042 < 0.05$). The CR and PR rates of the GDPT group were 42.9% and

Table 1. Baseline characteristics of GDPT and CHOP group.

Characteristic	Number of patients (%)		p value
	GDPT (n = 77)	CHOP (n = 76)	
Age, years			
Median	52.0	48.5	0.059
(Range)	(18–70)	(18–70)	
Gender			0.819
Male	51 (66.2)	49 (64.5)	
Female	26 (33.8)	27 (35.5)	
Site of extranodal involvement			0.947
<2	46 (59.7)	45 (59.2)	
≥2	31 (40.3)	31 (40.8)	
Stage			0.492
I–II	22 (28.6)	18 (23.7)	
III–IV	55 (71.4)	58 (76.3)	
IPI			0.219
0–2	53 (68.8)	59 (77.6)	
3–5	24 (31.2)	17 (22.4)	
B symptoms present	34 (44.2)	35 (46.1)	0.814
Elevated serum LDH	31 (40.3)	34 (44.7)	0.575
Elevated serum β2 microglobulin	28 (36.4)	25 (32.9)	0.652
Bone marrow involvement	7 (9.1)	8 (10.5)	0.765
PTCL-NOS	19 (24.7)	12 (15.8)	0.096
AITL	22 (28.6)	15 (19.7)	
ALCL	18 (23.4)	31 (40.8)	
other types	18 (23.4)	18 (23.7)	

AITL, angioimmunoblastic T cell lymphoma; ALCL, anaplastic large cell lymphoma; CHOP, cyclophosphamide, vincristine, doxorubicin, prednisone; GDPT, gemcitabine, cisplatin, prednisone, thalidomide; IPI, International Prognostic Index; LDH, lactate dehydrogenase; PTCL-NOS, peripheral T cell lymphoma, not otherwise specified.
p: Chi-squared test.

with pathological patterns. In the GDPT group, the CR rates in PTCL-NOS, ALCL, AITL, and other types subgroup were 47.4%, 18.2%, 55.6%, and 55.6% (Table 3). The difference in CR among the four subgroups was statistically significant ($p = 0.046$), but there was no significant difference in ORR ($p = 0.437$). In the CHOP group, the differences in both CR and ORR among the four subgroups were statistically significant ($p < 0.001$ and $p = 0.005$, respectively). In addition, there were statistically significant differences in CR between patients treated with CHOP and GDPT in the PTCL-NOS subgroup, AITL subgroup, and other types subgroup ($p = 0.015$; $p = 0.003$; $p = 0.005$) (Table 3).

By December 2018, the median follow-up time among all the patients was 24 months (ranging from 1 to 101 months). PFS and OS in the GDPT group were longer than in the CHOP group; the 4-year PFS and OS rates of the two groups at 63.6% *versus* 53.0% and 66.8% *versus* 53.6%, respectively, with the GDPT group superior to the CHOP group (Figure 1). In the GDPT group, there were no significant differences in PFS among the four subgroups, whereas OS did show a significant difference ($p = 0.001$) (Figure 2). In contrast, the four CHOP subgroups showed significant differences in PFS ($p = 0.019$) but not OS (Figure 3). During follow up, eight patients accepted ASTC after chemotherapy. Four of them were from GDPT group, the remaining patients were from CHOP group. And only one patient from CHOP group died 6 months after transplantation.

Adverse events

All hematological and non-hematological adverse events during chemotherapy were recorded. The hematologic adverse events were mainly myelosuppressive, including leukopenia, anemia, and thrombocytopenia. The non-hematological side events included primarily digestive tract reactions, liver and kidney damage, cardiac dysfunction, neurotoxicity, and venous thrombosis. In the GDPT group, 25 patients (32.5%) developed 3/4-degree myelosuppression after chemotherapy, accompanied by fatigue and other related symptoms. A total of 38 cases (49.4%) developed mild-to-moderate anorexia, nausea, vomiting and other digestive tract reactions, which were tolerated after symptomatic treatments. While on the regimen, 26 (33.8%) and 10 (13.0%) patients,

23.4%, whereas rates of the CHOP group were 27.6% and 22.4%, respectively. The difference between the two groups was statistically significant (Table 2). The patients in each group were divided into four subgroups: PTCL-NOS, ALCL, AITL, and other types subgroup, in accordance

Table 2. Response rates of GDPT and CHOP group.

Response	Number of patients (%)		*p* value
	GDPT (*n* = 77)	CHOP (*n* = 76)	
CR	33 (42.9)	21 (27.6)	0.049
PR	18 (23.4)	17 (22.4)	
SD	0 (0.0)	2 (2.6)	
PD	26 (33.8)	36 (47.4)	
ORR	51 (66.3)	38 (50.0)	0.042

CHOP, cyclophosphamide, vincristine, doxorubicin, prednisone; CR, complete response; GDPT, gemcitabine, cisplatin, prednisone, thalidomide; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.
p: Chi-squared test.

Table 3. Response rates of subgroups treated with GDPT and CHOP.

Subgroups	Responses (%)					
	GDPT		CHOP		*p* value	
CR	ORR	CR	ORR	CR	ORR	
PTCL-NOS	9 (47.4)	15 (78.9)	0 (0.0)	3 (25.0)	0.015	0.003
AITL	4 (18.2)	12 (54.5)	3 (20)	5 (33.3)	0.003	0.204
ALCL	10 (55.6)	12 (66.7)	16 (51.6)	23 (74.2)	0.790	0.574
Other types	10 (55.6)	12 (66.7)	2 (11.1)	7 (38.9)	0.005	0.095
p value	0.046	0.437	<0.001	0.005		

AITL, angioimmunoblastic T cell lymphoma; ALCL, anaplastic large cell lymphoma; CHOP, cyclophosphamide, doxorubicin, vincristine and prednisone; CR, complete response; GDPT, gemcitabine, cisplatin, prednisone and thalidomide; ORR, overall response rate; PD, progressive disease; PR, partial response; PTCL-NOS, peripheral T cell lymphoma, not otherwise specified; SD, stable disease.
p: Chi-square test.

respectively, had various degrees of liver and kidney function impairment, 1 (1.3%) patient developed heart failure, and 10 (13.0%) patients experienced numbness of the scalp, face, hands, and feet. In addition, 11 patients (14.3%) with unilateral limb swelling who showed venous thrombosis upon color Doppler examination. Low molecular weight heparin and other thrombolytic drugs were used. In the CHOP group, 14 (18.2%) patients developed pulmonary infection upon agranulocytosis. Some patients had mild constipation. The adverse reactions of all patients were transient and tolerated after symptomatic treatments. There were no statistical differences in adverse reactions between the two groups (Table 4).

Expression of ERCC1, RRM1, TUBB3, and TOP2A genes
Of the 153 patients, a total of 81 underwent gene testing. Among these, 42 patients in the GDPT group underwent *ERCC1* and *RRM1* gene testing, whereas 39 patients in the CHOP group underwent *TUBB3* and *TOP2A* gene testing. The expression level results are shown in Table 5. The data showed no statistical association between gene expression level and patient responses.

Discussion
PTCL is a highly heterogenous subgroup of invasive NHL derived from thymic mature T cells. The incidence rate of PTCL is lower than that of B cell lymphoma. The occurrence rate in European and American countries is low due to ethnic and geographical factors, and PTCL constitutes about 10–15% of NHL. However, the rate is higher in Asian countries, as previous research has shown that PTCL accounted for an estimated 25% of NHL cases in China.[3] Though the etiology of PTCL is not yet clear, it is likely related to viral infection, such as human T cell virus (HTLV) or Epstein-Barr virus (EBV), or perhaps other physical or chemical factors.[13]

PTCL generally occurs in the elderly, a population with a low cure rate and poor prognosis. Furthermore, patients with PTCL are often late stage with high IPI scores when they first manifest symptoms, and this disease shows a high rate of relapse.[14] Currently, the treatment of PTCL is the same as for diffuse large B cell lymphoma (DLBCL), which uses CHOP or CHOP-like regimens. Nevertheless, this regimen is not efficient, and most patients do not benefit from it.[15] Among 3287 PTCL patients diagnosed from 1992 to 1995 in 13 Surveillance, Epidemiology and End Results (SEER) registries who were treated with CHOP or CHOP-like regimens, the 5-year OS was reported at 37.5% for PTCL-NOS.[16] As reported, CHOP plus etoposide might improve 3-year event-free survival (EFS) and OS among younger patients.[17] It was illustrated that the poor efficacy of anthracycline-based chemotherapy may be mechanistically related to the P-glycoprotein-mediated multidrug resistance pathway.[18] P-glycoprotein (P-gy) is a multidrug resistance gene (MDR) encoding a transmembrane
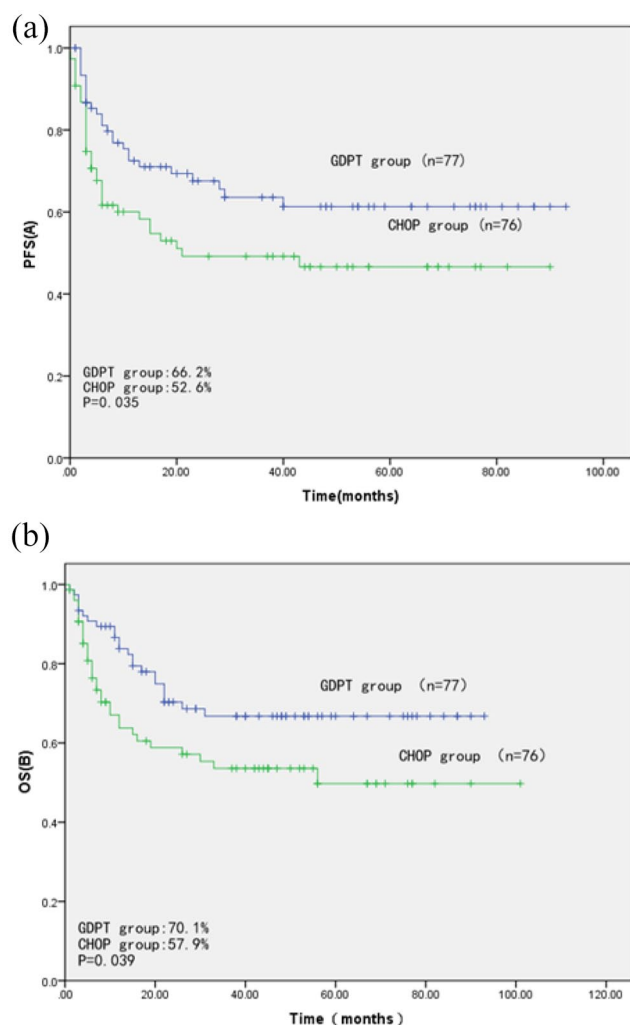
Figure 1. (A) PFS is shown for all patients; the GDPT group has a better PFS than the CHOP group ($p = 0.035$). (B) OS is shown for all patients; the GDPT group has a better OS than the CHOP group ($p = 0.039$).
CHOP, cyclophosphamide, vincristine, doxorubicin, prednisone; GDPT, gemcitabine, cisplatin, prednisone, thalidomide; OS, overall survival; PFS, progression-free survival.

protein that can mediate the pumping mechanisms underlying drug efflux. It can actively remove a drug that has accumulated in the cell to reduce intracellular drug concentrations. Through this mechanism, drugs such as vincristine and doxorubicin are pumped out of the cell or into membranous organelles. A decrease in intracytoplasmic drug concentration leads to reduced drug-mediated cytotoxicity. Studies have shown that the expression level of P-glycoprotein in peripheral T-cell lymphoma is negatively correlated with prognosis, which may be one possible reason for the poor therapeutic effect of CHOP.[19] Thus far, researchers worldwide are continuing to search for alternative options for curing PTCL.

Gemcitabine, which has no cross-resistance with the CHOP regimen, is a deoxypyrimidine analog with cell cycle specificity, acting mainly in S phase. The mechanism is to inhibit the activity of ribonucleotide reductase and reduce the concentration of intracellular nucleotides, resulting in the inhibition of cellular DNA synthesis and consequent cell apoptosis.[20] It has been previously reported that gemcitabine has antitumor effects by blocking the cell proliferation transition from G1 to S phase. Gemcitabine, which has a broad spectrum of antitumor indications, was originally applied to solid tumors.[21,22] In the late 1990s, it started to be used for NHL. Gemcitabine as single-agent therapy proved to be effective, and gemcitabine-based chemotherapy for patients with PTCL had an ORR of 85%.[23] Many clinical studies treated NK/T-cell lymphoma with the DDGP regimen including gemcitabine, which also achieved significant results.[24,25] Gemcitabine was reported to reverse the MDR caused by P-glycoprotein overexpression. MDR can mediate resistance to chemotherapeutic drugs, one of the leading causes of failure in first-line chemotherapy.[26] Hence, gemcitabine has become an ideal drug for PTCL. Cisplatin is a heavy metal complex that acts as a non-specific cell cycle inhibitor. A meta-analysis has shown that platinum-based regimens are superior to platinum-free regimens in the treatment of multiple cancer types.[27] Cisplatin can lead to intra- and inter-strand crosslinks, which can alter the structure of DNA. Thus, it exerts antitumor functions by impairing the function of DNA and inhibiting cell mitosis.[28] These alterations initiate the nucleotide excision repair (NER) and mismatch repair (MMR) systems, which represent one mechanism of cisplatin resistance. Besancon increased the expression of two key proteins in the NERDNA repair system, ERCC1 and XPA, upon pretreatment with gemcitabine followed by cisplatin. This caused increased formation of platinum adducts in DNA. Thereby, studies have concluded that cisplatin and gemcitabine exert synergistic anti-tumor effects.[29] Gemcitabine can overcome the cisplatin resistance caused by the up-regulation of DNA repair genes in tumor cells.

Oncogenic pathways in PTCL, such as JAK-STAT, PI3K/AKT/mTOR, and RAS/RAF/MEK, provide a rationale for developing targeted therapies.[30] In addition, the NF-κB pathway is involved in lymphoma proliferation, apoptosis, and chemoresistance, and was reported to have a vital role in PTCL.[31] A multicenter, single-arm,
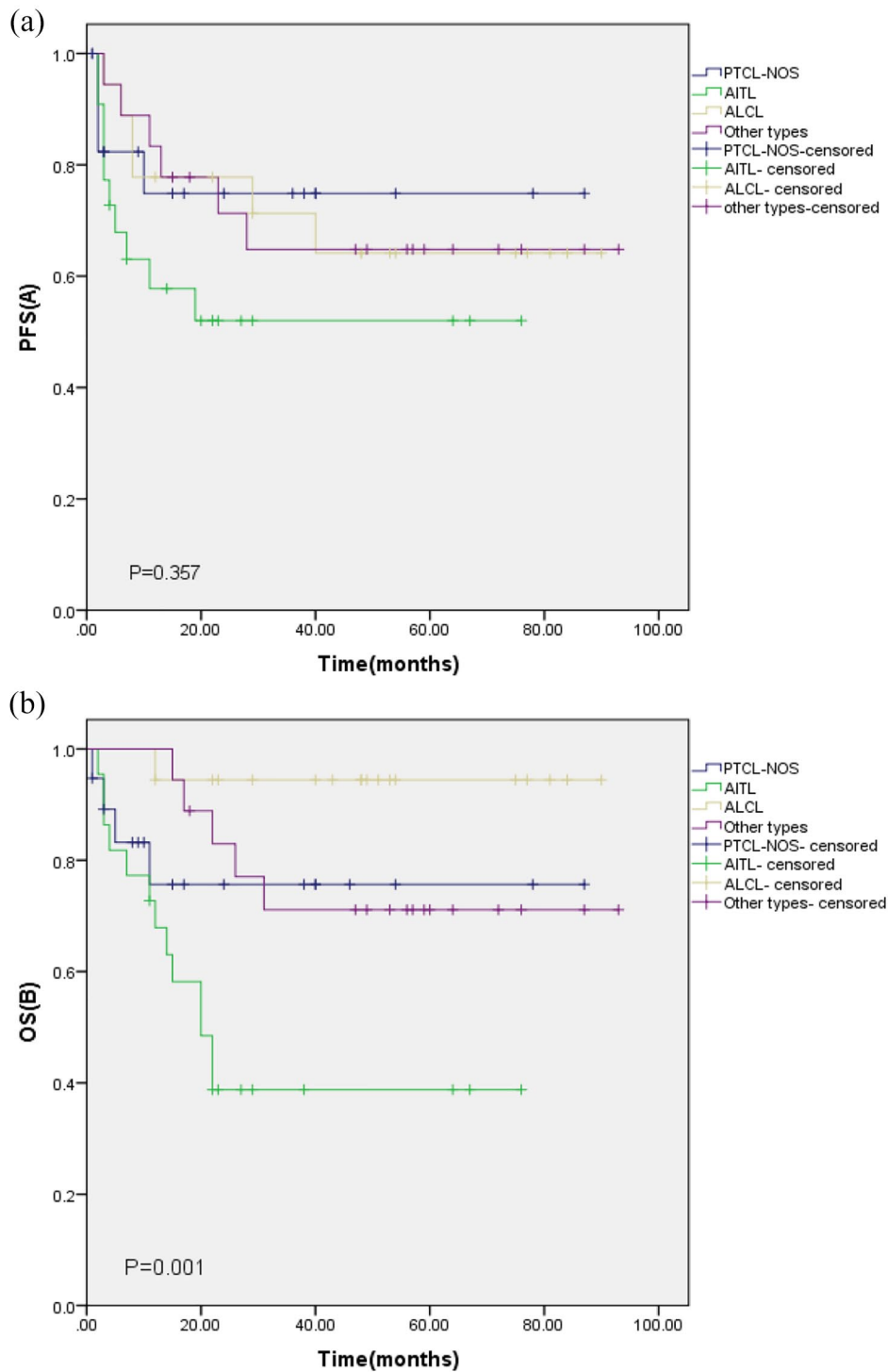
(a)

(b)

Figure 2. (A) PFS is shown for patients treated with GDPT, showing no significant difference between the four subgroups (*p* = 0.357). (B) OS is shown for patients treated with GDPT, showing significant difference between the four subgroups (*p* = 0.001).

CHOP, cyclophosphamide, vincristine, doxorubicin, prednisone; GDPT, gemcitabine, cisplatin, prednisone, thalidomide; OS, overall survival; PFS, progression-free survival.
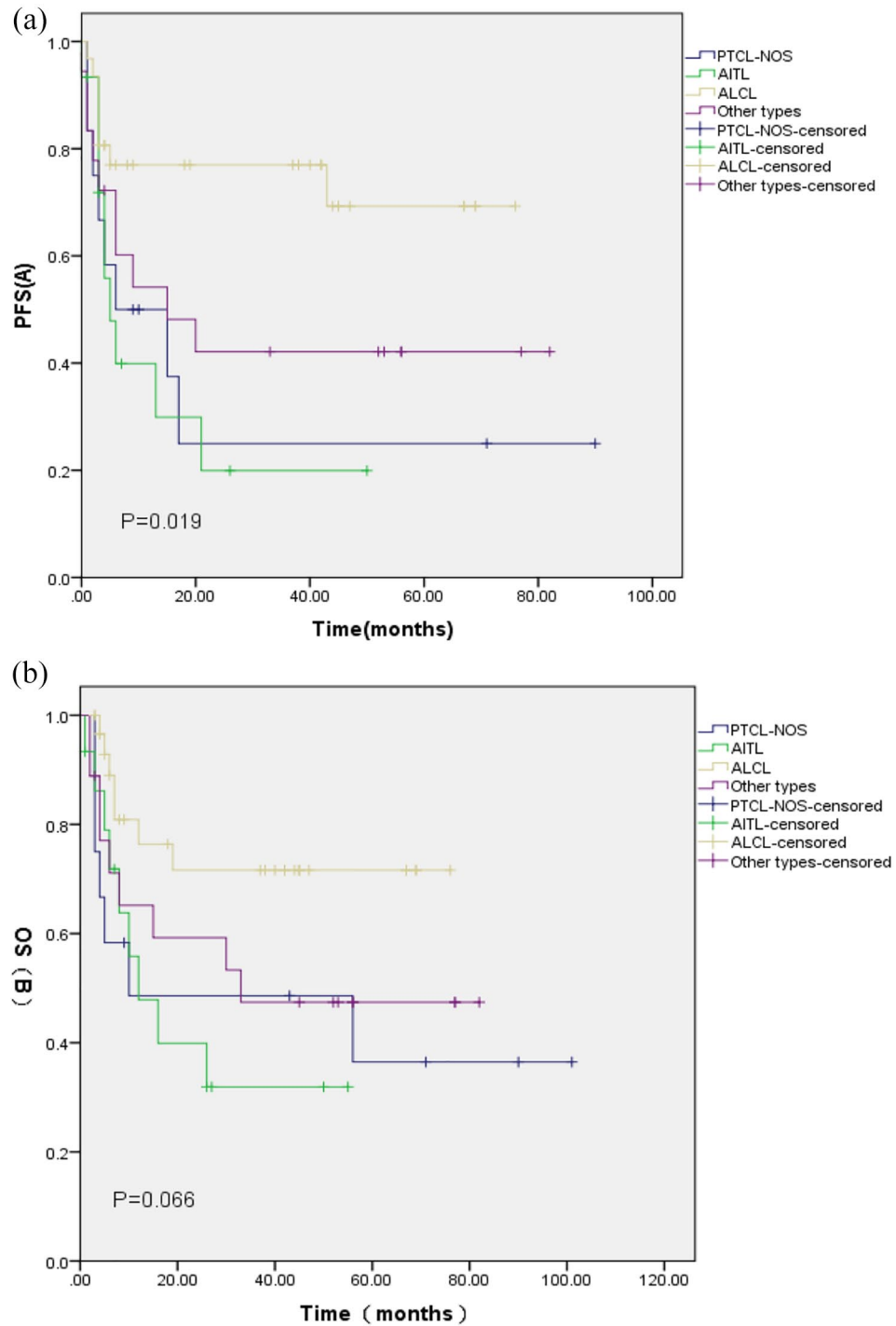
Figure 3. (A) PFS is shown for patients treated with CHOP, showing significant difference between the four subgroups (*p* = 0.0197). (B) OS is shown for patients treated with CHOP, showing no significant difference between the four subgroups (*p* = 0.066).

CHOP, cyclophosphamide, vincristine, doxorubicin, prednisone; GDPT, gemcitabine, cisplatin, prednisone, thalidomide; OS, overall survival; PFS, progression-free survival.

Table 4. Main adverse effects between GDPT group and CHOP group (%).

Toxicity	Grade 3/4 myelosuppression	Digestive tract toxicity	Hepatic dysfunction	Renal dysfunction	Cardiac toxicity	Neurological toxicity	Venous thrombosis
GDPT (n = 77)	25 (32.5)	38 (49.4)	26 (33.8)	10 (13.0)	1 (1.3)	10 (13.0)	11 (14.3)
CHOP (n = 76)	19 (25.0)	28 (36.8)	25 (32.9)	10 (13.2)	3 (3.9)	9 (11.8)	4 (5.3)
p value	0.308	0.118	0.909	0.975	0.305	0.83	0.061

CHOP, cyclophosphamide, vincristine, doxorubicin, prednisone; GDPT, gemcitabine, cisplatin, prednisone, thalidomide.
p: Chi-squared test.

Table 5. Gene expression in patients of GDPT and CHOP group.

Group and gene	Response	Number of patients		p value
		Low expression	High expression	
GDPT group (n = 42)				
ERCC1	CR+PR	7	11	0.856
	SD+PD	10	14	
RRM1	CR+PR	8	10	0.650
	SD+PD	9	15	
CHOP group (n = 39)				
TOP2A	CR+PR	8	11	0.648
	SD+PD	7	13	
TUBB3	CR+PR	13	5	0.708
	SD+PD	14	7	

CHOP, cyclophosphamide, doxorubicin, vincristine and prednisone; CR, complete response; GDPT, gemcitabine, cisplatin, prednisone and thalidomide; PD, progressive disease; PR, partial response; SD, stable disease.
p: Chi-square test.

phase II trial suggested that combined treatment of bortezomib and CHOP is an effective regimen for advanced-stage PTCL.[32] Therefore, therapy targeting this pathway has become a potential path for PTCL treatment. Thalidomide is an agent that can inhibit angiogenesis and inflammatory responses, promote apoptosis, and regulate the immune microenvironment. It has a suppressive effect on the NF-κB pathway by inhibiting VEGF. Huang *et al.* demonstrated that thalidomide has therapeutic effects *via* induction of intracellular reactive oxygen species (ROS) in gemcitabine-resistant cells.[33] And there is a synergistic effect between the two agents. Inhibition of this pathway improves the tumor-killing ability of gemcitabine.

In brief, these four agents can exert synergistic antitumor effects without increased side effects. Until now, there have been no clinical trials comparing the efficacy and adverse events of the GDPT regimen and the CHOP regimen in the treatment of newly diagnosed PTCL. So we designed and conducted an open, randomized prospective clinical trial. The experimental GDPT group regimen consisted of gemcitabine, cisplatin, prednisone, and thalidomide, whereas the control group was the standard CHOP regimen. PTCL is heterogenous with more than 20 subtypes, all of which were randomly allocated to the GDPT and CHOP group. The pathological types were not exactly the same between the two groups. In our mid-term results, the 2-year PFS

and OS rates were better in the GDPT group than in the CHOP group (57% *versus* 35% for 2-year PFS, $p = 0.0035$; 71% *versus* 50% for 2-year OS, $p = 0.0001$).[34] Previous patients were followed up and new patients were enrolled. Years later, we continued to observe that the responses of the GDPT group were superior to the CHOP group ($p = 0.042$). Moreover, GDPT prolonged patients' PFS and OS ($p = 0.035$; $p = 0.039$). There were eight patients in all treated with ASCT after chemotherapy. And only one patient from the CHOP group died 6 months after transplantation. NCCN guidelines recommended that PTCL patients should be treated with ASCT after being induced by induction chemotherapy, apart from ALK (+) ALCL. Patients treated with GDPT showed a better response rate than those treated with CHOP in the PTCL-NOS subgroup, AITL subgroup, and the other types subgroup. Therefore, we recommend GDPT as first-line regimen for patients diagnosed with the above pathological types. Besides, patients treated with GDPT in the AITL subgroup had worse outcomes compared with those in the PTCL-NOS, ALCL, and other types subgroup. AITL is a distinct subtype of PTCL with unique pathologic and clinical features. But treatment of relapsed and refractory disease remains a challenge. Fu *et al.* reported that, in AITL, the combination of chidamide and chemotherapy was significantly more effective than that of the single chemotherapy group.[35] Thus, it is essential to consider this before initiating chemotherapy for this pathologic type. Perhaps the group of patients diagnosed with AITL should be treated with targeted drugs earlier. Studies have aided in determining which drugs or regimens were most appropriate for patients with AITL by identifying markers of response or resistance.[36]

The primary adverse events during chemotherapy were myelosuppression, including leukopenia, anemia, and thrombocytopenia. Blood cell counts returned to normal levels by administering granulocytecolony stimulating factor, thrombopoietin, interleukin-11, or even the infusion of blood components. The decrease in granulocytes was likely to result in granule-deficient fever. Indeed, some patients even experienced severe lung infections. Antibiotics were indispensable for preventing the spread of infection. Accordingly, granulocytecolony stimulating factor could be applied to patients in advance to prevent fourth-degree myelosuppression. To avoid liver damage, hepatoprotective drugs such as glutathione and compound glycyrrhizin

were applied prior to treatment initiation. According to medical records, patients with GDPT were prone to experience numbness of the face, hands, and feet during chemotherapy. Considering the neurotoxicity of thalidomide, mecobalamin and ganglioside could be used to relieve symptoms. It is well known that anthracyclines in the CHOP regimen are cardiotoxic, and dexfenamine should therefore be used in advance to protect the myocardium. All patients had mild-to-moderate, and tolerable, adverse reactions. The two regimens did not cause serious complications or increase patient death rates. The adverse reactions in the GDPT group were not significantly different from those in the traditional CHOP group.

Some scholars have used the *ERCC1* and *RRM1* genes to predict outcomes of patients with solid tumors treated with cisplatin and gemcitabine. Low expression of *TOP2A* and high expression of *TUBB3* may be related to the resistance mechanism of PTCL to CHOP chemotherapy. In order to evaluate this association, the efficacy of PTCL patients with high and low tumor tissue gene expression levels after CHOP and GDPT treatment were compared. The results showed that gene expression was not related to patient prognosis, with no statistical difference observed. These negative results might due to the small sample size and should be further explored. As a new biomarker, *p38MAPK* has been found to associate with drug resistance. Also, other reports have shown that patients who express *GATA-3* will have a poor prognosis, even after stem cell transplantation following a good response.[37] Some PTCL patients have specific genetic mutations (*TET2, DNMT3A*, etc.), and these mutations may be the molecular basis for treatment with histone deacetylase inhibitors. However, in addition to the originally identified *TOP2A, RRM1, TUBB3*, and *ERCC1* gene associations, or those with *p38MAPK, GATA-3, TET2*, and *DNMT3A*, further research is needed to identify strategies for individualized treatment.

Novel targeted drugs have emerged in recent years, bringing new hope for the treatment of PTCL. For example, chidamide is a histone deacetylase inhibitor developed in China. It is a selective inhibitor of the phenylamide HDAC subtype, which increases the acetylation level of chromatin histones by inhibiting this HDAC subtype. In turn, this triggers epigenetic chromatin remodeling, which inhibits cell cycle progression and induces apoptosis of tumor cells. Refractory or relapsed patients

with low IPI scores, patients intolerant or unsuitable for conventional chemotherapy, or those who have achieved clinical remission are advised to take single chidamide. For recurrent or refractory patients with medium- to high-risk IPI scores, combination of chidamide with chemotherapy or other drugs is recommended. Chidamide can be combined with the GDP regimen or specifically with the immunomodulator lenalidomide/thalidomide. Immunotherapy has shown significant progress in various fields in recent years. Immunological checkpoint inhibitors enhance anti-tumor immune responses by regulating T cell activity. The widespread use of PD-1 and PD-L1 inhibitors in the treatment of relapsed/refractory lymphoma has demonstrated good efficacy and tolerance, bringing in a new era of lymphoma treatment.

Additionally, other targeted drugs are gradually being applied to PTCL, such as the histone deacetylase inhibitor Romidepsin, Belinostat, the antifolate preparation pralatrexate, anti-CD30 drug conjugate Brentuximab vedotin (BV), anti-CD52 drug conjugate Alemtuzumab, immunomodulatory agent lenalidomide, PI3K inhibitor Duvelisib, etc. The therapeutic effect of a single agent or its combination with the GDP program needs further investigation.[38–40] Molecular biologic classification technique (MICM) typing can guide the selection of targeted drugs, which improves patient response rates. In the future, increased study of the genetic mutations in lymphoma patients is needed to guide clinical treatment.

Conclusion

This clinical trial showed that patients in the GDPT group had better response rates than the CHOP group, and the GDPT regimen could improve patient responses and prolong PFS and OS. Within the GDPT group, the AITL subgroup had a worse outcome than the other subgroups, and, thus, improved treatment options are necessary. As a new promising chemotherapy regimen, GDPT is expected to be the first-line for PTCL, but it also needs further confirmation in future large-scale and multi-center clinical studies. The expression levels of *TUBB3, ERCC1, RRM1,* and *TOP2A* genes were not statistically related to patient prognosis, and thus further research is needed to find other relevant biomarkers. We believe the near future will gradually bring more and better-targeted drugs applied to PTCL.

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