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ORIGINAL ARTICLE

Gemcitabine, dexamethasone, and cisplatin (GDP) as salvage chemotherapy for patients with relapsed or refractory peripheral T cell lymphoma—not otherwise specified

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Abstract Standard therapeutic options for patients with relapsed or refractory peripheral T cell lymphoma—not otherwise specified (PTCL—NOS) remain unclear. There are few large cohort studies specifically focused on gemcitabine-based chemotherapy for PTCL—NOS. We retrospectively reviewed patients with relapsed or refractory PTCL—NOS who received salvage GDP (gemcitabine, dexamethasone, and cisplatin) chemotherapy at the Cancer Hospital, Chinese Academy of Medical Sciences (CAMS) and Peking Union Medical College (PUMC), Beijing, China, from May 2008 to August 2014. Twenty-five patients were enrolled and analyzed. The median number of cycles of GDP chemotherapy per patient was four (range, 2–8 cycles). Overall response rate was 64.0% (16/25) with five achieved complete remission or complete remission unconfirmed. After a median follow-up of 9 months, median overall survival (OS) and progression-free survival after relapse or progression (second-PFS) were 9.3 and 5.4 months. One-year PFS rate and 1-year OS rate were 27.4% and 43.9%, respectively. Median second-PFS was significantly longer in patients sensitive to GDP than the ones resistant to the treatment (10.3 vs. 2.8 months, $p < .01$). In addition, the low International Prognostic Index, low Prognostic Index for T cell lymphoma, or normal level of LDH in serum was associated with favorable prognosis. Grade 3/4 adverse effect was observed in 10 of 25 patients treated with GDP including neutropenia (8/25), thrombocytopenia (5/25), and anemia (4/25). Taken together, our study suggests that GDP is an effective and optional salvage regimen for relapsed or refractory PTCL—NOS.

Keywords Peripheral T cell lymphomas—not otherwise specified · Chemotherapy · Gemcitabine

Introduction

Peripheral T cell lymphomas—not otherwise specified (PTCL—NOS) is a heterogeneous group of mature T cell malignancies excluded from the specifically defined entities. The frequency of the PTCL—NOS varies geographically, and it is the most common subtype in North America and Europe [1]. Patients often have B symptoms, generalized lymphadenopathy, bone marrow infiltration, and extranodal involvement. Because of the low incidence and evident heterogeneity of PTCL—NOS, substantial evidences are absent to guide the treatment up to now. In general, patients with PTCL—NOS were treated with anthracycline-containing chemotherapy such as CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or CHOP-like regimens which were well accepted in B cell Non-Hodgkin lymphomas [2]. However, this strategy was associated with short duration and frequent relapse [3]. Prognosis was usually poor and a 5-year overall survival (OS) rate was approximately 10–30% [3–7]. Therefore, more effective treatment strategies are highly in need.

In this study, we retrospectively reviewed a series of 25 relapsed or refractory PTCL—NOS patients who

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subsequently underwent GDP (gemcitabine, dexamethasone, and cisplatin) regimen. The clinical activities and treatment-related toxicities were evaluated, and possible prognostic factors were explored.

Materials and methods

Patients

Between May 2008 and August 2014, patients with PTCL—NOS who were consecutively treated at the Cancer Hospital, Chinese Academy of Medical Sciences (CAMS) and Peking Union Medical College (PUMC), Beijing, China, were reviewed. Patient selection criteria were as follows: (1) histological diagnosis of PTCL—NOS based on immunophenotypic and morphologic criteria according to the 2008 World Health Organization classification of lymphomas; neoplastic cells were negative for B cell antigens, such as CD20 and CD79α, but they were positive for CD3, CD4, CD8, and TCR β-chain (antibody βF1); and other pathological subtypes of PTCL were excluded; (2) Age ≥ 14 years; (3) Eastern Cooperative Oncology Group (ECOG) performance status 0–2; (4) measurable disease according to the International Workshop Criteria (IWC) [8]; (5) relapsed or refractory to prior systemic treatment; and (6) adequate hematologic, hepatic, and renal functions: absolute neutrophil count $\geq 1.5 \times 10^9$/L, platelet count $\geq 100 \times 10^9$/L, total bilirubin ≤1.5 × upper limit of normal, AST and ALT ≤2 × upper limit of normal, and creatinine ≤1.5 mg/dL. Patients who did not have complete clinical information or immunohistochemistry or who were lost to follow-up immediately after the treatment were excluded from this study. This study was a retrospective observational study, and patients' information was collected in the hospital database. There was no direct intervention in patients' treatment or care. Therefore, ethical approval and a patient's consent were not required.

Disease evaluation

Pretreatment evaluations included medical history, physical examination, complete blood cell count, serum biochemistry for hepatic and renal function, bone marrow examination, and computed tomography (CT) scan of neck, chest, abdomen, and pelvis. Positron emission tomography was recommended but not compulsory. Patients were staged based on the Ann Arbor staging system and scored by the International Prognostic Index (IPI) [1] and prognostic index for T cell lymphoma (PIT) [9].

Treatment protocol and dose modifications

GDP regimen was implemented in a 21-day cycle: gemcitabine (1000 mg/m^2 intravenously over 30 min on days 1 and 8), dexamethasone (20 mg/d orally on days 1–4 and days 11–14), and cisplatin (25 mg/m^2 intravenously over 60 min on days 1–3). Treatment responses were evaluated after every 2 cycles and at the end of treatment using the international criteria for lymphoma. After chemotherapy, patients could undergo additional palliative radiotherapy. The decision to enroll patients into radiotherapy was based on the physician's discretion, influenced by the patient's disease and performance status, and the patient's own willingness.

Doses of GDP were reduced according to severe hematologic or non-hematologic toxicities. If patients developed any grade 3 non-hematological toxicities (except alopecia) or grade 4 hematological toxicities, doses of gemcitabine and cisplatin were reduced by 25% in successive cycles. If the same grade 3 non-hematological toxicity or grade 4 hematological toxicity occurred again, doses were reduced by 50%. Chemotherapy was discontinued with the occurrence of any grade 4 non-hematological toxicities. Granulocyte colony stimulation factor was administered in cases where grade 4 neutropenia and leukopenia were observed.

Treatment response and toxicity assessment

Responses to chemotherapy were evaluated after every 2 cycles and at the end of the regimen, as well as every 2 or 3 months during the follow-up time. Complete remission (CR) was defined as disappearance of all previously measurable lesions and absence of any new tumor lesions. Complete remission unconfirmed (CRu) was defined as those patients who fulfill the criteria for CR above but with indeterminate bone marrow or with residual disease that decreased more than 75% in the product of two perpendicular diameters of each measurable lesion. Partial remission (PR) was defined as a decrease of at least 50% in size. Progressive disease (PD) was defined as greater than 25% increase in the product of the two diameters of at least one tumor or as the presence of a newly developed lesion. Stable disease (SD) was defined as any response that did not fall into the other defined categories.

Patients underwent clinical examination, routine complete blood counts, and biochemical tests before each new treatment cycle for toxicity evaluation. Treatment-related toxicities were assessed using the National Cancer Institute Common Toxicity Criteria, Version 3.0.

Statistical analysis

Overall response rate (ORR) was the percentage of patients who achieved CR, CRu, and PR. OS was calculated from the first day of GDP administration to the date of last follow-up or

death resulting from any cause. Second progression-free survival (second-PFS) was defined as the period from the first day of GDP administration to the date of disease progression, relapse, last follow-up, or death from any cause, whichever occurred first. All data were analyzed using SPSS 17.0. Survival analysis for OS and second-PFS were performed by the Kaplan-Meier methods. Comparisons of OS or PFS between groups were performed using log-rank test. A two-tailed $p < .05$ was considered statistically significant. Pearson χ^2 and Fisher's exact tests were used to compare the ORR of different groups.

Results

Patient characteristics

Twenty-five patients were reviewed in our study. Patient characteristics at the entry are listed in Table 1. Median age was 50 years (range 14–72 years). The ratio of male to female was 3.2:1. Enrolled patients represented a high-risk population: 92.0%(23/25) of them had advanced stage III/IV disease. 64.1% (16/25) of patients had a PIT score of ≥1, and 52% (13/25) had an IPI score of ≥2.

For all patients enrolled, CHOP or CHOP-like regimens had been given as first-line chemotherapy. All patients received GDP regimen as second- or third-line chemotherapy. After completion of GDP treatment, six patients received additional radiotherapy for local tumor persistence ($n = 4$) or disease relapse ($n = 2$). One patient achieved CRu from GDP regimen and subsequently underwent hematopoietic stem cell transplantation (HSCT). Other GDP responders refused HSCT for risk concern, ineligible physical condition, or economic reasons.

Table 1 Patient characteristics

Characteristics	*n*	%
Sex		
Male	19	76.0
Female	6	24.0
Age (years)		
<60	20	80.0
≥60	5	20.0
Ann Arbor stage		
I/ II	2	8.0
III/IV	23	92.0
ECOG score		
0–1	23	92.0
2	2	8.0
IPI score		
0–1	12	48.0
≥2	13	52.0
PIT score		
0	9	36.0
≥1	16	64.0
B symptoms		
No	14	56.0
Yes	11	44.0
Lactate dehydrogenase level		
Normal	16	64.0
Elevated	9	36.0
Bone marrow involvement		
Yes	3	12.0
No	22	88.0
Chemotherapy status		
Second line	23	92.0
>Second line	2	8.0
First-line treatment		
CHOP	7	28.0
CHOPE	18	72.0
Reasons to change prior regimen		
Relapsed	20	80.0
Refractory	5	20.0

ECOG Eastern Cooperative Oncology Group, *IPI* International Prognostic Index, *PIT* Prognostic index for T-cell lymphoma, *CHOP* cyclophosphamide, doxorubicin, vincristine and prednisone, *CHOPE* cyclophosphamide, doxorubicin, vincristine, prednisone and etoposide

Response and survival

A total of 96 cycles were administered for these 25 patients. The median number of cycles per patient was four (range, 2–8). All patients were evaluable for response to GDP chemotherapy. ORR was 64.0% (16/25). The rates of CR, CRu, PR, SD, and PD were 16% (4/25), 4% (1/25), 44% (11/25), 28% (7/25), and 8% (2/25), respectively.

At a median follow-up of 9 months (range 2–68 months), one case was lost to follow-up. Eighteen patients died from disease progression, and four were still alive with disease. It was worthy to note that the remaining two patients were surviving without evidence of detectable disease until the end of our observation in January 2015. Median second-PFS and OS were 5.4 (range 1.5–62.5 months) and 9.3 months (range 1.6–68.0 months). The 1-year and 2-year second-PFS rates were 27.4 and 9.1% (Fig. 1).The 1-year and 2-year OS rates were 43.9% and 25.1%, respectively (Fig. 2). The patient who underwent SCT survived 20 months and died of disease progression.

Patients who achieved remission with the treatment of GDP chemotherapy presented significantly longer median second-PFS than those who attained no response (SD plus

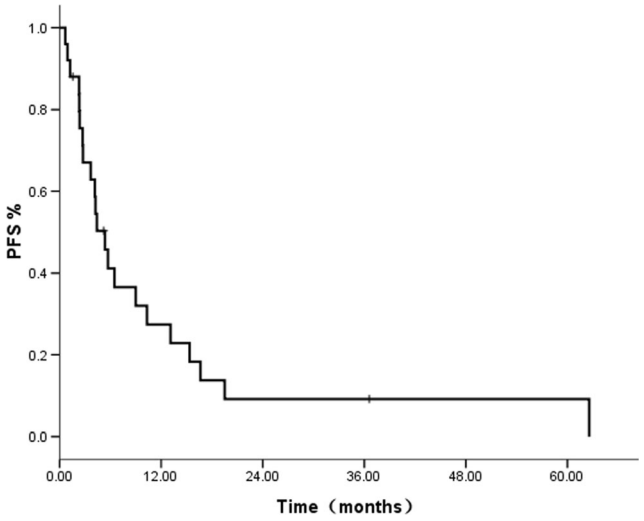

Fig. 1 Second progression-free survival (second-PFS) of patients treated with GDP regimen (n = 25) with relapsed or refractory peripheral T cell lymphoma—not otherwise specified (PTCL—NOS)

PD) (10.3 vs. 2.8 months, $p < .001$, Fig. 3). Good response (CR + CRu + PR) to GDP regimen had a tendency of prolonging OS, but there was no statistical significance possibly as a result of the small sample ($p = .077$). Univariate analysis was conducted, and it was found that elevated LDH ($p = .046$), IPI ≥2 ($p = .020$), and PIT ≥1 ($p = .036$) were all negatively associated with second-PFS. Our data showed no correlation between first-line treatment response and survival of GDP salvage regimen. No significant difference in outcome of response or survival was observed between relapsed and refractory groups.

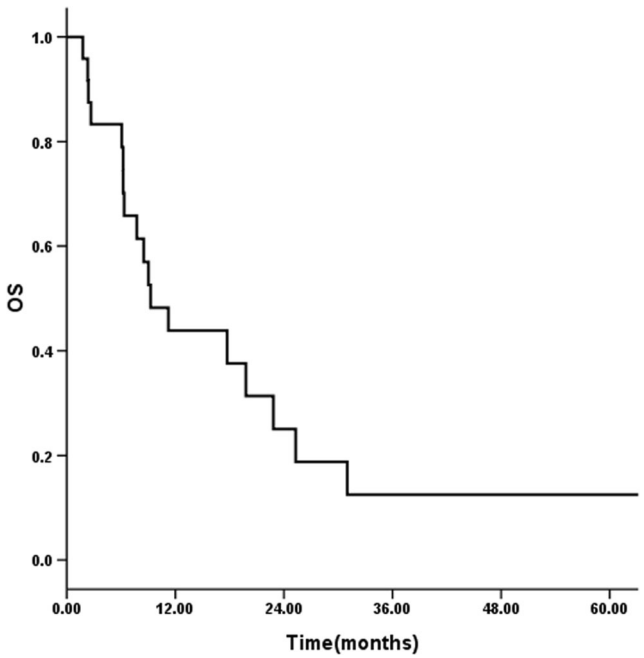

Fig. 2 Overall survival (*OS*) of patients treated with GDP regimen (n = 25) with relapsed or refractory peripheral Tcell lymphoma—not otherwise specified (PTCL—NOS)

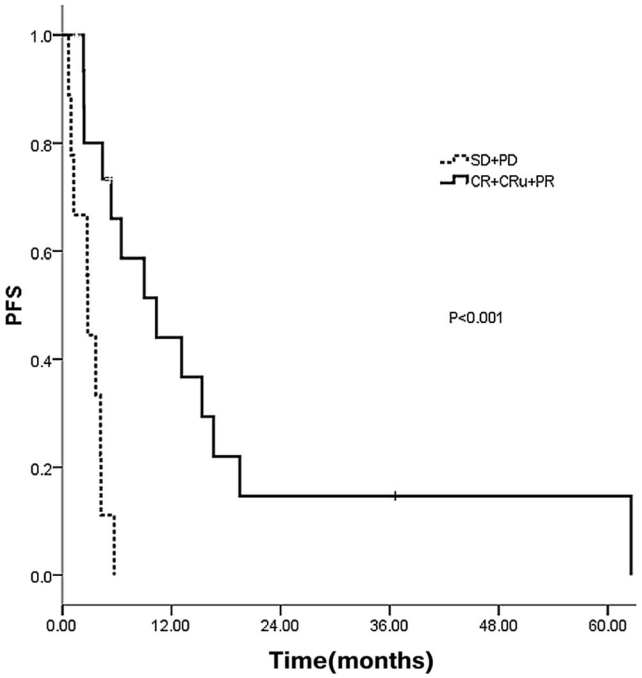

Fig. 3 Second progression-free survival (second-PFS) of patients treated with GDP chemotherapy (n = 25) with relapsed or progressive peripheral T cell lymphoma—not otherwise specified (PTCL—NOS) by response (median second-PFS: PR + CR + CRu, 10.3 months; PD + SD 2.8 months)

Safety

Treatment-related toxicities were summarized in Table 2. Grade 1–2 nausea and vomiting were the most common non-hematologic toxicities and observed in majority of our

Table 2 Toxicity profile

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
	n (%)			
Hematological				
Neutropenia	2 (8.0)	6 (24.0)	5 (20.0)	3 (12.0)
Febrile neutropenia	4 (16.0)	0	0	0
Thrombocytopenia	2 (8.0)	2 (8.0)	2 (8.0)	3 (12.0)
Anemia	8 (32.0)	2 (8.0)	1 (4.0)	3 (12.0)
Non-hematological				
Nausea/vomiting	16 (64.0)	7 (28.0)	2 (8.0)	0
Diarrhea	1 (4.0)	1 (4.0)	0	0
AST elevation	3 (12.0)	1 (4.0)	0	0
ALT elevation	1 (4.0)	1 (4.0)	1 (4.0)	0
Creatinine elevation	2 (8.0)	0	0	0
Hyperbilirubinemia	8 (32.0)	2 (8.0)	0	0
Fatigue	3 (12.0)	1 (4.0)	0	0
Peripheral neuropathy	2 (8.0)	0	0	0
Alopecia	2 (8.0)	0	0	0

AST aspartate aminotransferase, *ALT* aspartate aminotransferase

patients. Severe (grade 3/4) neutropenia and thrombocytopenia occurred in eight patients (32.0%) and five patients (20.0%), respectively. Seven patients (26.0%) had liver dysfunction indicated by moderately elevated alanine aminotransferase and aspartate aminotransferase in serum. Two patients developed transient creatinine elevation. No allergic reaction was reported. Treatment-related death was not observed.

Discussion

Compared with B cell lymphomas, outcome of PTCL—NOS is fairly unfavorable [1, 4–7]. For newly diagnosed PTCL—NOS patients, participation in clinical trials is firstly recommended by the National Comprehensive Cancer Network (NCCN) guidelines. Anthracycline-based therapies, such as CHOP or CHOP-like regimens, are still the standard chemotherapy based on type II level of evidence [2]. However, no survival advantage was observed of anthracycline-based regimens over non-anthracycline-based therapies [10]. Besides, relapse rate was high with anthracycline-based regimens, and duration of remission was short, particularly in those with high-risk diseases [5]. In a Meta-analysis including 31 studies (13 prospective and 18 retrospective), 2912 patients with PTCL were treated with CHOP or CHOP-like regimens as first-line chemotherapy [3]. The CR rate was 36–66% with a relapse rate of 20–43%. However, the result of this meta-analysis was heterogeneous for that PTCL—NOS was included into PTCL with other different pathological subtypes and they were analyzed as a whole cohort.

Similarly, there is no well-accepted salvage treatment for relapsed or refractory PTCL—NOS. High-dose chemotherapy and autologous stem cell transplantation (HDT/ASCT) are recommended to eligible PTCL [11]. Many studies have been conducted to access the role of HDT/ASCT, but no definite conclusions are drawn [12]. Moreover, patients may not reach

Table 3 Overview of literatures on new drugs in relapsed or refractory peripheral T cell lymphoma

Studies	Regimens	Phase	PTCL (*n*)	PTCL—NOS (*n*)	Median age (year)	$\frac{\text{ORR}}{\text{CR/CRu+PR}}$ (%) for PTCL	$\frac{\text{ORR}}{\text{CR/CRu+PR}}$ (%) for PTCL—NOS	Median PFS (*m*)	Median OS (*m*)	DOR (*m*)
O'Connor et al. (2011) [22]	Pralatrexate	II	111	59	58	$\frac{29}{11+18}$	$\frac{32}{\text{NR+NR}}$	3.5	14.5	10.1
Zinzani et al. (2005) [23]	Alemtuzumab	II	10	6	65	$\frac{60}{20+40}$ (MF + NOS)	$\frac{50}{17+33}$	NR	NR	7.0
Y. Shi et al. (2015) [24]	Chidmide	II	83	27	53	$\frac{28}{14+14}$	$\frac{22}{7+15}$	2.1	21.4	9.9
Coiffier et al. (2014) [25]	Romidepsin	II	130	90	61	$\frac{25}{15+10}$	$\frac{29}{14+15}$	20 for responders	30 for responders	28 for responders
O'Connor et al. (2015) [26]	Belinostat	II	120	77	62	$\frac{26}{11+15}$	$\frac{23}{\text{NR+NR}}$	1.6	NR	8.3
Francine et al. (2015) [27]	Belinostat	II	24	13	64	$\frac{25}{9+16}$	NR	2.7	NR	3.6
Franck et al. (2013) [28]	lenalidomide	II	54	20	65	$\frac{22}{11+11}$	NR	2.5	3.6	NR
Gandhi et al. (2013) [29]	Bendamustine	II	60	23	66	$\frac{50}{28+22}$	NR	3.6	6.3	3.5
Dong	GDP	–	25	25	50	$\frac{64}{20+44}$	$\frac{64}{20+44}$	5.34	9.27	–

a remission adequate for transplantation and prognosis is dismal with the ineligible patients. For years, different research centers have been exploring relatively more effective but less toxic salvage alternations for PTCL. However, large-scale prospective clinical trials in relapsed or refractory PTCL—NOS are relatively few.

Gemcitabine is an analog of cytosine arabinoside inhibiting DNA synthesis and ribonucleoside reductase of tumor cells [13]. It has shown antineoplastic activities in PTCL—NOS as a monoagent therapy. Zinzani assessed the long-outcomes of gemcitabine among 20 pretreated PTCL—NOS patients in a retrospective study [14]. All patients were diagnosed with stage III/IV disease. The median number of prior systemic treatments was three. Gemcitabine was given on days 1, 8, and 15 on a 28-day schedule (1200 mg/m^2/day) for a total of 3 to 6 cycles. ORR was 55% with CR rate of 30%.

Gemcitabine-based regimens, such as GemOD (gemcitabine, oxaliplatin, and dexamethasone), GEM-P (gemcitabine, cisplatin, and methylprednisolone), and PEGS (cisplatin plus etoposide plus gemcitabine plus solumedrol), have been investigated as second- or third-line chemotherapies in relapsed or refractory PTCL [15–18]. ORR was reported at a range of 38 to 73% and CR rate 10 to 38% in these regimens. In our previous study, which had been cited by the NCCN guideline, GDP regimen produced an ORR of 83% in 26 PTCL patients (including 9 PTCL—NOS, ORR = 100%) [19]. In a Korean research by Byeong-Bae Park, salvage GDP regimen was administered among 27 relapsed or refractory PTCL patients (PTCL—NOS, n = 14). The ORR was 72% with 48% CR rate [20]. This present article focused on relapsed or refractory PTCL—NOS subtype and analyzed the efficacy of GDP regimen. ORR was 64%, and the CR/CRu rate was 20%. Given that GDP was given as third-line salvage chemotherapy in two patients in our study, response rate was encouraging. Although it may be hard to make a direct comparison, GDP in our study may achieve a comparable ORR with CHOP or CHOP-like chemotherapies and other gemcitabine-based regimens.

In this study, median second-PFS and OS were 5.37 and 9.27 months. Survivals in our study were slightly better than the data reported by Vivien Mak [21], who retrospectively reviewed 153 patients with relapsed or refractory PTCL (PTCL—NOS, n = 79). Second-line chemotherapies in his study included ICE (ifosfamide, etoposide, and carboplatin), cyclophosphamide and/or doxorubicin-containing regimens, and single-agent chemotherapy (alkylators, etoposide). Median second-PFS and OS were 3.1 and 5.5 months for PTCL and 3.8 and 6.5 months for PTCL—NOS, respectively, in his report. Median PFS of salvage GEM-P, GemOX, and other gemcitabine-base regimens in PTCL were reported 4.1–8.0 months [15–18]. Survival statistics of our salvage GDP regimen were encouraging, and GDP may potentially be an alternative and optional therapy for relapsed or refractory PTCLNOS.

Novel approaches are being investigated mainly among relapsed or refractory PTCL patients with particularly unfavorable prognostic features, including palatrexate [22], alemtuzumab [23], chidamide [24], romidepsin [25], belinostat [26, 27], lenalidomide [28], and bendamustine [29]. Outcomes of monoagent chemotherapy are summarized in Table 3. No definite superiority on ORR, PFS, or OS are concluded. However, combination therapies of new drugs are supposed to improve responses and duration of responses. New approaches like lenalidomide and romidepsin (NCT01755975), romidepsin with ICE, or gemcitabine are undergoing in treating patients with relapsed or refractory aggressive mature T cell lymphoma [30]. Phase II and III trials assessing CHOP plus romidepsin or brentuximab vedotin are also being explored [5]. New combination strategies may be the frontier domains for relapsed or refractory PTCL—NOS, and further randomized controlled trials are warranted.

Generally, GDP regimen was well-tolerated in our study, and the primary toxicity was myelosuppression. Neutropenia and thrombocytopenia were the main toxicities leading to the delay of the treatment. Hematological toxicities were mild and manageable with growth factors utilization or blood component transfusion. Importantly, there was no toxic death or related life-threatening complications occurred.

This study is limited by its retrospective nature, nonrandomized design, and small sample size. Given the rarity of this disease and consequent lack of prospective data, the present study provides evidence to confirm GDP regimen as effective treatment in relapsed or refractory PTCL—NOS considering its safety profile and clinical activity. Further prospective studies are needed to validate the results.

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

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