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ORIGINAL PAPER

Assessment of gemcitabine, cisplatin and methylprednisolone (GEM-P) combination treatment for non-Hodgkin T cell lymphoma

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Abstract T cell lymphoma is rare with few dedicated studies and no consensus regarding optimal treatment. We undertook a retrospective hospital review to assess the efficacy of gemcitabine, cisplatin and methylprednisolone (GEM-P) combination therapy. Twenty-nine patients were followed up for a median duration of 28 months. Twenty-three patients received standard GEM-P. Due to hearing impairment, 3 patients had cisplatin substituted with carboplatin and 1 with oxaliplatin. In 2 cases, rituximab was added to GEM-P in view of the presence of EBV + B cell clones. Overall response rate (RR) [complete response (CR) + partial response (PR)] was 73 % (95 % CI range 54–86 %). 11/29 (38 %) achieved CR and 10/29 (35 %) had PR. In first-line treatment, 4/10 patients achieved CR and 4/10 had PR relating to a RR of 80 %. CR was seen in 4/9 (45 %), 2/8 (25) and 1/2 (50 %) patients treated in the second, third and fifth-sixth line respectively. Thus, GEM-P was found to be effective as first-line or salvage therapy in T cell lymphoma.

Keywords Chemotherapy · Cisplatin · Gemcitabine · Lymphoma · Methylprednisolone · T cell

Introduction

Peripheral T cell lymphomas are a rare and heterogeneous group comprising around 10–15 % of all lymphomas. Patients commonly present in the advanced stages, and prognosis is generally poor with a 5-year survival of around 30 % [1]. Despite subtypes like cutaneous anaplastic large cell lymphoma (ALCL) and systemic anaplastic lymphoma kinase-1 (ALK1) positive ALCL which may respond better to chemotherapy and achieve a better outcome [2], compared to their B cell counterparts, the majority of T cell lymphoma patients have a significantly worse 5-year overall survival [1, 3, 4]. Without data to suggest that other treatments are more effective, patients continue to commonly receive CHOP-type (cyclophosphamide, doxorubicin, vincristine and methylprednisolone) regimens [5, 6]. In the first-line setting, CHOP-based therapy has been reported to elicit a CR rate of 60 % [6]. However, there are advocates for non-CHOP-based chemotherapy in relapsed or refractory lymphoma, and studies show gemcitabine combined with vinorelbine [7] or cisplatin [8] could achieve a CR rate of between 30 and 40 % in the small T cell subpopulation. In relapsed or refractory patients, single agent gemcitabine achieved a CR rate of between 20 and 23 % and PR rate of between 28 and 40 % with a 13.5-month median duration of response [9, 10]. A previous article reported 16 patients treated with GEM-P achieving an ORR of 69 % (95 % CI range 41.4–89.0), where 3 patients (19 %) achieved CR and 8 (50 %) PR [11].

Patients and methods

Selection of cases

We carried out a 10-year retrospective review of all T cell lymphoma patients treated with GEM-P. Review Board approval was obtained (Project reference number: LYM 042), and individual patient consent was not deemed to be necessary by the committee. Patients were identified by

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diagnosis key word from the histopathology database and cross-referenced against our pharmacy database having received gemcitabine plus platinum. Clinical data including demographics, tumor subtype, stage, treatment received, toxicity, imaging and histological response, time of relapse and overall survival were extracted from the hospital electronic patient record (EPR) system and recorded on a separate database. Data were censored for survival on the date of last follow-up with our institution or on the date of last contact with the general practitioner.

Chemotherapy regimen

The GEM-P regimen consisted of an intravenous infusion of gemcitabine 1,000 mg/m^2 given on days 1, 8 and 15 with cisplatin 100 mg/m^2 on day 15 in a 28-day cycle. Cisplatin was given 4 h after gemcitabine administration and over 4 h with pre- and post-hydration. Methylprednisolone 1,000 mg was administered intravenously on day 1 and then orally from days 2–5 of each cycle. In patients with pre-existing tinnitus, cisplatin was replaced by oxaliplatin 100 mg/m^2 or carboplatin AUC 5. Where Epstein–Barr virus B cell clones were expressed (EBV +), rituximab 375 mg/m^2 (days 1 and 15) was added to the combination (R-GEM-P).

Evaluation of toxicity on study

The Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 was used for assessing biochemical and hematological toxicities. Full blood count, urea and electrolytes and liver function tests were performed prior to each treatment and between sessions if an abnormal results were found. Non-hematological or non-biochemical toxicities were monitored during clinic visits and information obtained from the EPR. Details of toxicities were recorded until 28 days after the last session of GEM-P.

Evaluation of response

All patients had a baseline CT prior to start of therapy. PET-CT scanning was introduced during the later period of the study. During treatment, patients were assessed clinically, and CT scans were planned after at least every two cycles until maximum response was achieved on CT. Post-treatment PET-CT scans and repeat bone marrow trephine were performed to confirm response as appropriate. The International Working Group recommendations [12] introduced in 1999, followed by the Revised Response Criteria for Malignant Lymphoma [13] in 2007, were correspondingly adopted in the evaluation of response during this review period. Where both post-therapy CT and PET-CT scans were available for assessment of treatment response, overall response was based on the PET-CT result.

Statistical methods

The aim of this study was to evaluate the efficacy, safety and survival outcome. Data for response rates, progression-free survival (PFS) and overall survival (OS) were analyzed. PFS was measured from the start of GEM-P until the first objective evidence of relapse, progression or death, or was censored at last follow-up. OS was measured from the start of GEM-P until death or censored at last follow-up. PFS and OS were calculated by the Kaplan–Meier method, and comparison between groups was performed using a log-rank test. A p value of < 0.05 was considered statistically significant. PET-CT mCR was compared to those who did not (PR, SD and PD).

Results

Twenty-nine patients were identified. Median age of presentation was 53 years (range 17–72), and the condition was more common in males (M:F = 17/12 = 1.4:1). Five patients presented in stage I, two in stage II, ten in stage III and twelve in stage IV. Various subtypes were represented: AITL ($n = 10$), PTCL-nos ($n = 6$), ALCL ALK − ($n = 5$), natural killer T cell (NK/T cell) ($n = 3$), adult T cell leukemia/lymphoma (ATLL) ($n = 2$), ALCL ALK + ($n = 1$), mycosis fungoides (MF) ($n = 1$) and enteropathy T cell (EITCL) ($n = 1$) (Table 1). Baseline CT was performed in all patients, and 11 had baseline PET-CT as well. Ten newly diagnosed patients received GEM-P as first line, 9 relapsed cases as second line, 8 as third line, 1 as fifth line and 1 as sixth line. Twenty-three patients (79 %) received standard GEM-P. In 3 cases, cisplatin was substituted with carboplatin where there was pre-existing hearing impairment and 1 case with oxaliplatin where tinnitus occurred after the first cycle. In 2 cases of AITL with EBV + B cell clones, patients received R-GEM-P. One patient with ATLL was also treated with acyclovir. The median number of cycles administered was 3 (range 1–6).

Tumor response

In addition to standard on-treatment CT, post-GEM-P PET-CT was performed in 11 patients with an ORR of 73 % (95 % CI range 54–86 %). However, in first-line GEM-P patients, an ORR of 80 % was seen with 4/10 (40 %) of patients achieving CR. Tables 2 and 3 show the ORR according to the lines of treatment and histological

Table 1 Patient characteristics

Number of patients		29	
Age range (years)		24–72	
Median age at presentation (years)		53	
M:F		17: 12 (1.4:1)	
Stage at presentation	*n*		%
Stage I	5		17
Stage II	2		7
Stage III	10		35
Stage IV	12		41
Subtype			
AITL	10	(2 cutaneous)	35
PTCL-nos	6	(1 breast)	21
ALCL ALK1-	5	(1 cutaneous)	17
NK/T cell	3		10
ATLL	2		7
ALCL ALK1+	1		3
MF	1		3
EITCL	1		3

AITL angioimmunoblastic T cell lymphoma, *PTCL-nos* peripheral T cell not otherwise specified, *ALCL* large cell anaplastic lymphoma, *NK/T cell* natural killer T cell, *ATLL* adult T cell leukemia/lymphoma, *MF* mycosis fungoides, *EITCL* enteropathy-type intestinal T cell

subtypes respectively. Of the 11 patients who attained CR, 6 had complete metabolic response confirmed on PET-CT (55 %). Two out of 4 cases with positive baseline bone marrow involvement had confirmed CR on post-treatment bone marrow trephine. Two cases did not undergo repeat bone marrow trephine due to patient refusal. In addition to Tables 2 and 3, patients who relapsed 6 months or more after previous response to GEM-P achieved repeat response after rechallenge (2 CR and 1 PR).

Toxicity

Four patients encountered grade 2 tinnitus on treatment. Three occurred after the first cycle and 1 after the second cycle of GEM-P. Three patients with pre-existing hearing impairment were prescribed gemcitabine, carboplatin and methylprednisolone and tolerated treatment without exacerbation of tinnitus. Overall grade 3 or 4 anemia, neutropenia and thrombocytopenia rates were 52, 41 and 59 % respectively (Table 4). Two patients developed grade 1 peripheral neuropathy by the second cycle. Two patients encountered grade 2 raised creatinine levels. One occurred after the first cycle, where ultrasound did not reveal any obstructive features and no concomitant nephrotoxic drugs were noted. Spontaneous recovery occurred after a 1-week delay. The second patient had a history of osteoporosis and had concurrent treatment with pamidronate, aledronic acid and opioids for pain control which could have affected renal function. 11/29 (38 %) patients encountered grade 3 raised alanine aminotransferase (ALT). 7/11 cases occurred after cycle 1, 2 after cycle 2 and 2 after cycle 3. One patient had cytomegalovirus (CMV) infection during treatment, but in the other cases, no alternative cause was found, and liver function derangement was most likely gemcitabine induced.

Table 2 Response rates according to line of treatment

Response ($n = 29$)	Overall (%)	First line	Second line	Third line	Fifth–sixth line
CR	11/29 (38)	4/10 (40)	4/9 (45)	2/8 (25)	1/2 (50)
PR	10/29 (35)	4/10 (40)	2/9 (22)	3/8 (38)	1/2 (50)
SD	1/29 (3)	–	1/9 (11)	–	–
PD	7/29 (24)	2/10 (20)	2/9 (22)	3/8 (38)	–

CR complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease

Table 3 Response according to histological subtype

Subtype (*n*)	CR	PR	SD	PD
AITL (10)	5	4	–	1
PTCL-nos (6)	1	1	1	3
ALCL AKL1 − (5)	3	2	–	–
NK/T cell (3)	1	–	–	2
ATLL (2)	–	1	–	1
ALCL ALK1 + (1)	–	1	–	–
MF (1)	1	–	–	–
EITCL (1)	–	1	–	–

Survival outcome

Median duration of follow-up of patients on the study was 28 months. Median progression-free survival (PFS) for the entire cohort was 12 months (95 % CI range 2–21 months) (Fig. 1). PFS at 1 year was 48 % (95 % CI range 27–65 %)

Table 4 Toxicity profile

Hematological (%)	
G3/4 Anemia	52
G3/4 Neutropenia	41
G3/4 Thrombocytopenia	59
Non-hematological (%)	
G1 Peripheral neuropathy	7
G2 Raised creatinine	7
G2 Tinnitus	14
G3 Raised ALT	38

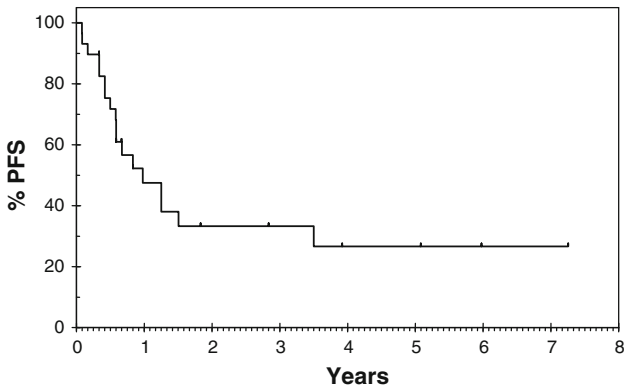

Fig. 1 Progression-free survival (PFS)

and at 2 years was 33 % (95 % CI range 16–52 %). Median overall survival (OS) is 70 months (95 % CI range 53–88 months) (Fig. 2). One-year survival was 79 % (95 % CI range 58–90 %), and 2-year survival was 63 % (95 % CI range 40–79 %). One patient with stage IVB ALCL ALK − was still alive and in remission 7 years after attaining CR with GEM-P at second line.

Discussion

T cell lymphoma is a rare subtype and study cohorts tend to be small. Without data from large randomised trials to suggest more effective regimens, patients continue to commonly receive CHOP-based treatment. For example, a small dedicated T cell study of 33 patients produced a CR rate of 60 % in first-line therapy [6]. Adding etoposide and gemcitabine (CHOP-EG) [5] improved the ORR to 77 % with 58 % CR but at the expense of 54 % grade 4 neutropenia and 15 % febrile neutropenia rates (Table 5). On the other hand, gemcitabine and its combination have thus far shown an ORR of between 60 and 69 % [11, 14]. In our current report, an ORR of 73 % with GEM-P exceeds previous expectations of gemcitabine-based treatment and could be an alternative to CHOP with less toxicity and more flexibility in administration. Furthermore, when used as initial therapy, a higher ORR of 80 % could be achieved. Durable responses were seen with a median PFS of 12 months, comparable to the 8 months with CHOP-EG [5]. However, although a 56 % relapse rate at 46 months using first-line CHOP-based [6] could not be matched, it has to be taken into account that two-thirds of our cohort consisted of relapsed or refractory patients. Median OS with Gem-P was 70 months with an estimated 1 year OS of 78 %. Although few trials report on OS data, results are comparable to an estimated 1-year overall survival of 69.6 % with CHOP-EG [5]. Thus, long-term remission was possible after GEM-P where 1 patient was reported to be in remission 7 years after salvage GEM-P. This report suggests GEM-P as a feasible regimen and alternative to CHOP for the treatment of newly diagnosed, refractory or recurrent T cell lymphoma.

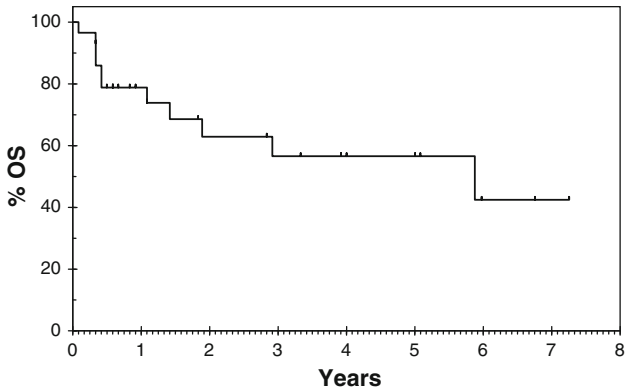

Fig. 2 Overall survival (OS)

Table 5 Response rates recorded in dedicated T cell lymphoma trials using various chemotherapy regimens

	Subtype	*n*	Regimen	CR (%)	PR (%)
Sallah [10]	Mixed T cell	10	Gemcitabine	20	40
Arkenau [11]	PTCL	16	GEM-P	19	50
Zinzani [9]	PTCL-nos	20	Gemcitabine	23	28
	MF	19			
Kim [5]*	PTCL	26	CHOP-EG	58	15
Pautier [6]*	AITL	33	CHOP-type	60	–

Relapsed/refractory trials shown except * which were first-line studies

GEM-P gemcitabine, cisplatin and methylprednisolone, *COPBLAM/IMVP-16* cyclophosphamide, vincristine, methylprednisolone, bleomycin, doxorubicin, and procarbazine, *CHOP-EG* cyclophosphamide, doxorubicin, vincristine, methylprednisolone, etoposide and gemcitabine

There has yet to be major breakthrough in the treatment of T cell lymphoma. However, a recent small phase II study involving 58 patients with ALCL treated with the antibody toxin conjugate brentuximab vedotin reported a RR of 86 % and CR rate of 57 % [14]. Anti-angiogenic therapy with bevacizumab has also been shown to potentiate the effect of chemotherapy and induce response in AITL [15] and ATLL [16]. Thus, the future approach to managing patients with T cell lymphoma is likely to involve greater stratification [17].

The challenge will therefore entail individualization of therapy, and perhaps the most efficient way to find the best treatment for this rare disease may thus not depend on recruiting large cohorts but to adopt a biomarker-driven approach in treating the separate subtypes in this heterogeneous group.

Conflict of interest The authors declare they have no conflict of interest pertaining to the submission of this article.

References

1. Melnyk A, Rodriguez A, Pugh WC, et al. Evaluation of the revised European–American lymphoma classification confirms the clinical relevance of immunophenotype in 560 cases of aggressive non-Hodgkin's lymphoma. Blood. 1997;89:4514–20.
2. Schmitz N, Trumper L, Ziepert M, et al. Treatment and prognosis of mature T-cell and NK-cell lymphoma: an analysis of patients with T-cell lymphoma treated in studies of the German high-grade non-Hodgkin Lymphoma Study Group. Blood. 2010;116: 3418–25.
3. Cheng AL, Chen YC, Wang CH, et al. Direct comparisons of peripheral T-cell lymphoma with diffuse B-cell lymphoma of comparable histological grades—should peripheral T-cell lymphoma be considered separately? J Clin Oncol. 1989;7:725–31.
4. Kwak LW, Wilson M, Weiss LM, et al. Similar outcome of treatment of B-cell and T-cell diffuse large-cell lymphomas: the Stanford experience. J Clin Oncol. 1991;9:1426–31.
5. Kim JG, Sohn SK, Chae YS, et al. CHOP plus etoposide and gemcitabine (CHOP-EG) as front-line chemotherapy for patients with peripheral T cell lymphomas. Cancer Chemother Pharmacol. 2006;58:35–9.
6. Pautier P, Devidas A, Delmer A, et al. Angioimmunoblastic-like T-cell non Hodgkin's lymphoma: outcome after chemotherapy in 33 patients and review of the literature. Leuk Lymphoma. 1999;32:545–52.
7. Spencer A, Reed K, Arthur C. Pilot study of an outpatient-based approach for advanced lymphoma using vinorelbine, gemcitabine and filgrastim. Intern. Med J. 2007;37:760–6.
8. Emmanouilides C, Colovos C, Pinter-Brown L, et al. Pilot study of fixed-infusion rate gemcitabine with Cisplatin and dexamethasone in patients with relapsed or refractory lymphoma. Clin Lymphoma. 2004;5:45–9.
9. Zinzani PL, Venturini F, Stefoni V, et al. Gemcitabine as single agent in pretreated T-cell lymphoma patients: evaluation of the long-term outcome. Ann Oncol. 2010;21:860–3.
10. Sallah S, Wan JY, Nguyen NP. Treatment of refractory T-cell malignancies using gemcitabine. Br J Hematol. 2001;113:185–7.
11. Arkenau HT, Chong G, Cunningham D, et al. Gemcitabine, cisplatin and methylprednisolone for the treatment of patients with peripheral T-cell lymphoma: the Royal Marsden Hospital experience. Hematologica. 2007;92:271–2.
12. Cheson BD, Horning SJ, Coiffier B, et al. Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group. J Clin Oncol. 1999;17:1244.
13. Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. J Clin Oncol. 2007;25:579–86.
14. Advani R, Shustov AR, Brice P, et al. Brentuximab vedotin (SGN-35) in patients with relapsed or refractory systemic anaplastic large cell lymphoma: a phase 2 study update [Abstract]. Blood 2011; 117: abstract 443.
15. Aguiar Bujanda D. Complete response of relapsed angioimmunoblastic T-cell lymphoma following therapy with bevacizumab. Ann Oncol. 2008;19(2):396–7.
16. Wang L, Shi WY, Yang F, et al. Bevacizumab potentiates chemotherapeutic effect on T-leukemia/lymphoma cells by direct action on tumor endothelial cells. Haematologica. 2011;96(6): 927–31.
17. Armitage JO. The aggressive peripheral T-cell lymphomas: 2012 update on diagnosis, risk stratification, and management. Am J Hematol. 2012;87(5):511–9.