Original Article

Efficacy and safety of gemcitabine and capecitabine combination for patients with previously treated advanced primary pulmonary lymphoepithelioma-like carcinoma: a retrospective single-arm cohort study

Qi-Hua Zou[1,2#], Hui Liu[2,3#], Cai-Wen Huang[1,2,4#], Li-Ping Kang[1,2], Bo Qiu[2,3], Jian-Liang Mai[1,2], Yong-Bin Lin[2,5], Ying Liang[1,2]

[1]Department of Medical Oncology, Sun Yat-sen University Cancer Center, Guangzhou, China; [2]State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangzhou, China; [3]Department of Radiation Oncology, Sun Yat-sen University Cancer Center, Guangzhou, China; [4]Department of Medical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital & Shenzhen Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Shenzhen, China; [5]Department of Thoracic Surgery, Sun Yat-sen University Cancer Center, Guangzhou, China

Contributions: (I) Conception and design: Y Liang, YB Lin, QH Zou; (II) Administrative support: None; (III) Provision of study materials or patients: Y Liang, YB Lin, H Liu, B Qiu; (IV) Collection and assembly of data: QH Zou, CW Huang, LP Kang, JL Mai; (V) Data analysis and interpretation: QH Zou, H Liu, CW Huang, LP Kang, JL Mai; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Ying Liang, MD, PhD. Department of Medical Oncology and State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University Cancer Center, Guangzhou 510060, China. Email: liangying@sysucc.org.cn; Yong-Bin Lin, MD, PhD. Department of Thoracic Surgery and State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University Cancer Center, Guangzhou 510060, China. Email: linyb@sysucc.org.cn.

Background: Primary pulmonary lymphoepithelioma-like carcinoma (PLELC) is a rare and unique subtype of non-small cell lung cancer (NSCLC). Studies reporting on salvage treatment for pretreated PLELC are limited. Positive interactions between gemcitabine (GEM) and capecitabine (CAP) have been demonstrated in preclinical studies. In addition, the clinical benefit of the combination has been reported for other malignancies. However, the efficacy and safety of the combination for pretreated PLELC remain unclear. Therefore, we conducted this retrospective study to examine the activity and safety of gemcitabine plus capecitabine (GEM/CAP) combination for previously treated PLELC.

Methods: Patients with PLELC at Sun Yat-sen University Cancer Center who received GEM combined with CAP between May 2013 and January 2021 as the second-line therapy or beyond were retrospectively enrolled. Treatment consisted of intravenous GEM (1,000 mg/m^2 on days 1 and 8) and oral CAP (1,000 mg/m^2 twice daily on days 1–14) every 3 weeks. Evaluation of response was performed every 2 cycles in accordance with Response Evaluation Criteria in Solid Tumors version 1.1. Safety was assessed in accordance with Common Terminology Criteria for Adverse Events version 5.0. Clinical characteristics were collected from medical records. The survival data were obtained by medical records or telephone. Follow-ups were performed until February 3rd, 2021.

Results: A total of 16 patients were enrolled in this study. There were 5, 4, 4, and 3 patients treated with GEM/CAP combination as the second-, third-, fourth-, and fifth-line settings, respectively. There were 8 patients with partial response (PR) (50.00%), 6 with stable disease (SD) (37.50%), 2 with progressive disease (PD) (12.50%), and none with complete response (CR). The objective response rate and disease control rate (DCR) were 50.00% and 87.50%, respectively. The most common hematological and nonhematological adverse events (AEs) at any grade were neutropenia (31.25%) and hand-foot syndrome (43.75%). At a median follow-up of 29.3 months with 95% confidence interval (CI) of 20.3 to 38.3 months, the median progression-free survival (PFS) was 9.3 months (95% CI: 6.5–12.1 months). The median overall survival (OS) was 41.5 months (95% CI: 3.1–79.8 months).

Conclusions: This retrospective study demonstrated the potential clinical benefit of GEM in combination with CAP for pretreated PLELC. Future multicenter large-scale, prospective studies are warranted.

Keywords: Primary pulmonary lymphoepithelioma-like carcinoma (PLELC); salvage chemotherapy; gemcitabine; capecitabine

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Introduction

Primary pulmonary lymphoepithelioma-like carcinoma (PLELC) is a rare and unique pathological subtype of non-small cell lung cancer (NSCLC). In Asia, the incidence of PLELC is approximately 0.9% of NSCLC cases (1,2). Studies have reported on PLELC in Guangdong Province (3), Hong Kong (1), and Taiwan (4), but only a few cases have been described in reports from Western countries (5). PLELC tends to occur in younger, nonsmoking females (6). Most patients have early-stage or locally advanced disease at their first diagnosis, and radical resection is critical for resectable PLELC (7). PLELC was first reported in 1987 by Bégin *et al.*, who described it as an Epstein-Barr virus (EBV)-associated epithelial neoplasm (8). In 2015, the World Health Organization (WHO) categorized PLELC as a subtype of other and unclassified carcinomas of lung cancer (9). The close relationship between PLELC with EBV infection has been well documented (7). Wang *et al.* reported that 42 out of 42 patients were positive for p63 and 34 out of 34 patients were negative for thyroid transcription factor-1 (TTF-1), indicating that PLELC may be similar to squamous cell carcinoma (10). Furthermore, PLELC presents histologically under an optical microscope as an undifferentiated carcinoma with lymphocytic infiltration, similar to an undifferentiated nasopharyngeal carcinoma (NPC) (11). In terms of the genetic characteristics of PLELC, it resembles NPC rather than other lung carcinomas (3).

Due to the low incidence of PLELC, evidence-based treatment guidelines generated from prospective clinical trials are scarce. Currently, the treatment strategy for PLELC follows the treatment guidelines for NSCLC. Chemotherapy plays an essential role in the treatment of unresectable PLELC owing to the low incidence of classic lung cancer driver gene mutations such as *EGFR* mutation and *ALK* rearrangement (10). In a panel consisting of 520 cancer-associated genes, Xie *et al.* found that the classic driver gene mutations of lung cancer were not detected, except for the mutation of *KRAS* and amplification of *ERBB2* in 2 patients (12). Platinum-based doublets combined with immune checkpoint inhibitors (ICPIs) are recommended as frontline therapy. Lin *et al.* reported the results for patients with advanced PLELC treated with platinum-based chemotherapy regimens as first-line chemotherapy (13). The objective response rate was 32.3% with median progression-free survival (PFS) and overall survival (OS) of 7.7 and 36.7 months, respectively (13). The efficacy of platinum-based doublets plus ICPIs as first-line treatment for PLELC remains unclear. Although some patients with PLELC respond to primary treatment, recurrence in those patients is common (14). There are few

Highlight box

Key findings

- A total of 16 patients with pretreated primary pulmonary lymphoepithelioma-like carcinoma (PLELC) were included in this study. The objective response rate and disease control rate were 50.00% and 87.50%, respectively. The median progression-free survival and overall survival were 9.3 and 41.5 months, respectively.

What is known and what is new?

- Reported studies about salvage treatment for pretreated PLELC are limited due to its rarity. Only a few case reports for previously treated PLELC have been documented. Positive interactions between gemcitabine and capecitabine have been reported in preclinical studies, and the clinical benefits of their combination have been reported for other malignancies.
- We explored the activity and safety of gemcitabine/capecitabine combination in pretreated PLELC, which could provide a novel treatment option for this unique cancer.

What is the implication, and what should change now?

- This study demonstrated the potential clinical benefit of gemcitabine plus capecitabine for pretreated PLELC. Further multicenter prospective studies are worthwhile.

studies of salvage systemic treatment and only a few case reports of capecitabine (CAP) and ICPIs such as nivolumab and pembrolizumab for pretreated PLELC (15-17). The exploration of second-line and beyond therapeutic strategy for PLELC will help to provide more treatment options and evidence for this unique cancer.

Gemcitabine (GEM) has been found to be an active agent in squamous cell carcinoma of the lung and also NPC (3,18). CAP essentially acts as a prodrug of 5-fluorouracil (5-FU), which is the rationale for its role as an alternative to 5-FU to treat NPC (19,20). Ho *et al.* reported that CAP had promising activity and good tolerability as salvage treatment in 5 patients (15). Among the 5 patients, there were 2 with stable disease (SD) and 1 with partial response (PR). Only 1 patient had moderately severe hand-foot syndrome, and another patient had grade 2 neutropenia (15). The combination of gemcitabine plus capecitabine (GEM/CAP) has shown a synergistic antitumor effect in preclinical studies (21). Additionally, the active efficacy and favorable toxicity profile of GEM/CAP have been reported in various studies, especially for pancreatic adenocarcinoma, biliary tract carcinoma, and thymic epithelial tumors (22-26). These findings provide support for the utility of GEM in combination with CAP. However, the effect and safety of GEM/CAP for pretreated advanced PLELC have not been reported.

Given the rationality of the GEM/CAP combination and the clinical need for effective therapeutic strategies for patients with previously treated PLELC, we conducted this retrospective study to examine the activity and safety of GEM/CAP combination in pretreated advanced PLELC. We present the following article in accordance with the STROBE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-256/rc).

Methods

Study population

In this retrospective, single-arm cohort study, patients with PLELC at Sun Yat-sen University Cancer Center between May 2013 and January 2021 were identified. Eligible patients included: (I) histologically diagnosed with PLELC; (II) progressive disease (PD) after at least 1 prior systemic therapy; (III) treated with GEM/CAP regimen as second-line therapy or beyond; (IV) having at least 1 assessable lesion; (V) Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–2; (VI) life expectancy of at least 3 months; and (VII) adequate bone marrow, liver, and kidney functions. Patients who had a history of NPC or were pregnant or lactating were excluded.

Diagnosis of PLELC was performed in accordance with the criteria described by the WHO classification (9). As we previously reported (7), undifferentiated carcinomas without lymphoid infiltrates and EBV-encoded RNA (EBER) staining were excluded in our study. Endoscopic examination of the nasopharynx or positron emission tomography (PET)-computed tomography (CT) scan was conducted to rule out lung metastases of NPC. All cases were restaged based on the 8th edition American Joint Committee on Cancer (AJCC) staging system [the 8th edition of the tumor-node-metastasis (TNM) classification for lung cancer] (27). Clinical and pathological characteristics, including age, gender, smoking status, ECOG PS, history of surgical operation, history of radiotherapy, prior systemic therapeutic regimens, distant metastatic sites, and status of driven gene mutation (*EGFR* mutation, *ALK* rearrangement, and *ROS1* rearrangement), were collected from retrospective chart review and medical history. For explorative purposes, plasma levels of EBV DNA determined by quantitative real-time polymerase chain reaction (RT-PCR) were monitored in 3 patients before, during, and after treatment with GEM/CAP, based on the oncologist's choice. Measurement of EBV DNA was performed along with tumor response evaluation. Patients who had smoked fewer than 100 cigarettes in their lifetime were defined as never-smokers. Patients were followed up through electronic medical records and telephone.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by Sun Yat-sen University Cancer Center Research Ethics Board (No. B2020-404-01). Written informed consent was provided before data collection.

Treatment methods

Patients were treated with intravenous infusion GEM (1,000 mg/m^2 on days 1 and 8) and oral CAP (1,000 mg/m^2 twice daily on days 1–14) every 3 weeks. CAP could be administrated as maintenance therapy after 4 to 6 cycles of GEM/CAP, based on the decision of the physician and patient. Chest and upper abdominal CT, in addition to brain magnetic resonance imaging (MRI) if brain metastasis existed, were performed every 2 cycles. Tumor response was assessed by investigators in accordance with Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST

1.1) (28). Adverse events (AEs) were retrospectively collected from the chart and medical history and classified in accordance with Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 (29).

Statistical analyses

All statistical analyses were performed by Statistical Product and Service Solutions (SPSS) software, version 25 (IBM Corp., Armonk, NY, USA) and GraphPad Prism 8 software (GraphPad Software Inc., San Diego, CA, USA). Descriptive analyses of the clinical characteristics of the patients enrolled in this study were conducted. PFS was measured from the date of the first GEM/CAP administration until either the first documented PD or death, whichever occurred earlier. OS was calculated from the date of the first GEM/CAP administration to the date of death due to any cause or censoring at the date of data cutoff (Feb 3rd, 2021). Survival functions were estimated by the Kaplan-Meier method. Univariate analysis was performed by log-rank test. Two-sided significance level was defined as $P<0.05$.

Results

Demography and disease characteristics

A total of 16 PLELC patients received GEM/CAP as salvage chemotherapy at Sun Yat-sen University Cancer Center between May 2013 and January 2021. Characteristics of the patients are shown in *Tables 1*,*2*. Eight patients (50.00%) were male. The median age was 45.5 years (range, 35.0–65.0 years). Thirteen patients (81.25%) were stage IV, and 3 patients (18.75%) had recurrence after surgical treatment or definitive radiotherapy. There were 7, 7, 4, and 0 patients with pleura, liver, bone, and brain metastases, respectively. All patients had an ECOG PS of 0–1 (0, 56.25%; 1, 43.75%). Most patients (62.50%) had no history of smoking. Platinum-based therapy was the first-line treatment in all 16 patients, including pemetrexed, docetaxel, vinorelbine, or paclitaxel combined with platinum. Five of 16 (31.25%) patients had experienced 1 prior systemic chemotherapy regimen, 4 (25.00%) had received 2 prior regimens, 3 (18.75%) had received 4 prior regimens, and the remaining (25.00%) patients had 3 prior treatment regimens. Thirteen patients were tested for *EGFR* mutation, while the other 3 patients were not tested due to lack of tumor tissues, and only 1 patient was positive with *EGFR* exon20 insertion (*Table 1*). The rearrangements of *ALK* and *ROS1* were wild type in 8 of 16 and 6 of 16 patients, respectively (*Table 1*).

Treatment

As of the last follow-up, the median therapeutic cycle of GEM/CAP was 5.5 cycles (range, 2.0–12.0 cycles). Seven patients received oral CAP as the maintenance regimen after finishing GEM/CAP treatment, with a median of 6 cycles (range, 1–35 cycles), based on the decision of the physician and patient (*Table 1*). Subsequent post progression regimens included GEM/CAP rechallenge with or without bevacizumab, afatinib, clinical trials, docetaxel with or without CAP, docetaxel with cisplatin, ICPI, nanoparticle albumin-bound paclitaxel with or without bevacizumab, nanoparticle albumin-bound paclitaxel plus platinum with nimotuzumab or ICPI, osimertinib, palliative radiotherapy, pemetrexed/platinum with or without bevacizumab, taxanes combined with platinum, tegafur, and vinorelbine plus nimotuzumab (*Figure 1*).

Three patients (No. 1, 3, and 11) who received GEM/CAP for 2, 12, and 6 cycles, respectively, had disease progression after discontinuation of treatment with GEM/CAP. One had PD after rechallenge of 2 cycles of GEM/CAP and then received GEM/CAP with bevacizumab after the second progression. The other 2 patients received rechallenge GEM/CAP with bevacizumab. Among these 3 patients, 1 had 18% tumor shrinkage with a response of SD, and the other 2 patients achieved PR.

Evaluation of response

All 16 patients who had at least 2 cycles of chemotherapy were evaluable for the best response. There were 8 (50.00%) patients with PR, 6 (37.50%) with SD, 2 (12.50%) with PD, and no complete response (CR) in accordance with RECIST 1.1. Images of 2 patients are shown in *Figure 2*. The best overall response rate (ORR) was 50.00%, and the disease control rate (DCR) was 87.50% (*Table 3*).

The association between changes of concentration of EBV DNA with response

The concentration of plasma EBV DNA before, during, and after treatment with GEM/CAP were collected in 3 patients (No. 11, 13, and 16) to explore the relationship between changes in EBV DNA level with response to GEM/CAP

Table 1 Baseline characteristics of patients (n=16)

Variable	Data
Age (years)	
Median	45.5
Range	35.0–65.0
Gender, n (%)	
Male	8 (50.00)
Female	8 (50.00)
ECOG PS, n (%)	
0	9 (56.25)
1	7 (43.75)
History of smoking, n (%)	
Yes	6 (37.50)
No	10 (62.50)
Pleura metastases, n (%)	
Yes	7 (43.75)
No	9 (56.25)
Liver metastases, n (%)	
Yes	7 (43.75)
No	9 (56.25)
Bone metastases, n (%)	
Yes	4 (25.00)
No	12 (75.00)
Brain metastases, n (%)	
Yes	0
No	16 (100.00)
EGFR mutation, n (%)	
Positive	1 (6.25)
Negative	12 (75.00)
Untested	3 (18.75)
ALK rearrangement, n (%)	
Positive	0
Negative	8 (50.00)
Untested	8 (50.00)
ROS1 rearrangement, n (%)	
Positive	0
Negative	6 (37.50)
Untested	10 (62.50)
No. of prior chemotherapy, n (%)	
1	5 (31.25)
2	4 (25.00)
3	4 (25.00)
4	3 (18.75)
Cycles of GEM/CAP combination	
Median	5.5
Range	2.0–12.0
Cycles of CAP maintenance	
Median	6
Range	1–35

ECOG, Eastern Cooperative Oncology Group; PS, performance status; No., number; GEM, gemcitabine; CAP, capecitabine.

treatment (*Figure 3*). EBV DNA concentration decreased significantly after GEM/CAP treatment in the 3 patients, and even descended to zero in 2 of them. The concentration of EBV DNA in 1 of these 2 patients remained zero without tumor progression until the time of data cutoff (Feb 3rd, 2021), with PFS of 29.3 months. All 3 patients achieved PR. The level of EBV DNA then elevated significantly in 2 of the 3 patients when further tumor progression occurred, with PFS of 6.4 and 11 months, respectively.

Safety

All 16 patients were evaluable for toxicity. In general, treatment was well tolerated. The majority of therapy-related AEs were grade 1–2. The most common hematological and nonhematological adverse reactions at any grade were neutropenia and hand-foot syndrome (31.25% and 43.75%, respectively). Only 2 patients had grade 3–4 AEs. One patient had grade 3 hand-foot syndrome, and the other had grade 4 febrile neutropenia and recovered after treatment. There were no chemotherapy-related deaths (*Table 4*).

Survival analysis

At the time of data cutoff (Feb 3rd, 2021), the survival data of the 16 patients were evaluated. Seven patients were still

Table 2 Individual patient, treatment, and outcome characteristics

Pt No.	Sex	Age (years)	Prior chemotherapy regimen	Disease extension	Line of GEM/CAP therapy	No. of cycles	Best response	CAP maintenance	PFS (months)	OS (months)
1	M	46	PEM/DDP/BEV, TAX/BEV	Pleura; abdominal, cervical, thoracic, supraclavicular LNs	3	2	PD	No	4.0	17.3
2	M	65	DOC/NDP, GEM/NDP, TAX/NDP	Liver; lung; pleura; abdominal, thoracic, supraclavicular LNs	4	6	SD	Yes	8.8	9.2^{+}
3	M	62	PEM/DDP, DOC/BEV, icotinib	Liver; lung; pleura; bone; thoracic, supraclavicular LNs	4	12	PR	No	16.7	41.5
4	F	51	VIN/DDP, TAX/DDP	Thoracic LNs	3	4	SD	No	11.5	33.4^{+}
5	F	52	PEM/DDP, TAX/CBP	Pleura; lung; supraclavicular, thoracic LNs	3	8	PR	No	9.3	17.9
6	M	39	PEM/DDP, DOC/BEV	Thoracic LNs	3	4	SD	No	4.6^{+}	73.5^{+}
7	F	51	TAX/DDP, DOC/GEM, clinical trial	Pleura; lung; supraclavicular, thoracic LNs	4	4	SD	No	6.9	27.7^{+}
8	F	45	TAX/DDP, TAX/DDP, PEM/CBP/BEV	Liver; lung; pleura; bone; abdominal, thoracic, supraclavicular LNs	4	9	PR	No	8.8	26.6^{+}
9	F	48	TAX/NDP	Lung; abdominal, thoracic, supraclavicular LNs	2	4	PR	Yes	18.3	52.9^{+}
10	M	43	TAX/DDP, PEM, DOC/GEM, TAX/CAP	Thoracic LNs	5	5	SD	No	21.5	33.9^{+}
11	F	38	TAX/NDP	Liver; bone; abdominal, thoracic, supraclavicular LNs	2	6	PR	Yes	6.4	19.6
12	M	43	TAX/NDP, GEM/DDP, tegafur, etoposide	Liver; thoracic, supraclavicular LNs	5	4	PR	Yes	6.6	16.0
13	M	56	TAX/DDP	Abdominal, thoracic LNs	2	6	PR	Yes	29.3^{+}	29.3^{+}
14	M	37	PEM/DDP/BEV, TAX/CBP/BEV, DOC/BEV, PEM/CBP/BEV	Liver; lung; pleura; thoracic LNs	5	3	PD	No	2.0	4.1
15	F	35	PEM/NDP	Thoracic LNs	2	6	SD	Yes	20.7^{+}	20.7^{+}
16	F	45	TAX/CBP	Liver; spleen; bone; abdominal, thoracic, supraclavicular LNs	2	6	PR	Yes	11.0	21.6^{+}

$^{+}$, alive at data cutoff. Pt, patient; No., number; GEM, gemcitabine; CAP, capecitabine; PFS, progression-free survival; OS, overall survival; M, male; PEM, pemetrexed; DDP, cisplatin; BEV, bevacizumab; TAX, paclitaxel; LNs, lymph nodes; PD, progressive disease; DOC, docetaxel; NDP, nedaplatin; SD, stable disease; PR, partial response; F, female; VIN, vinorelbine; CBP, carboplatin.

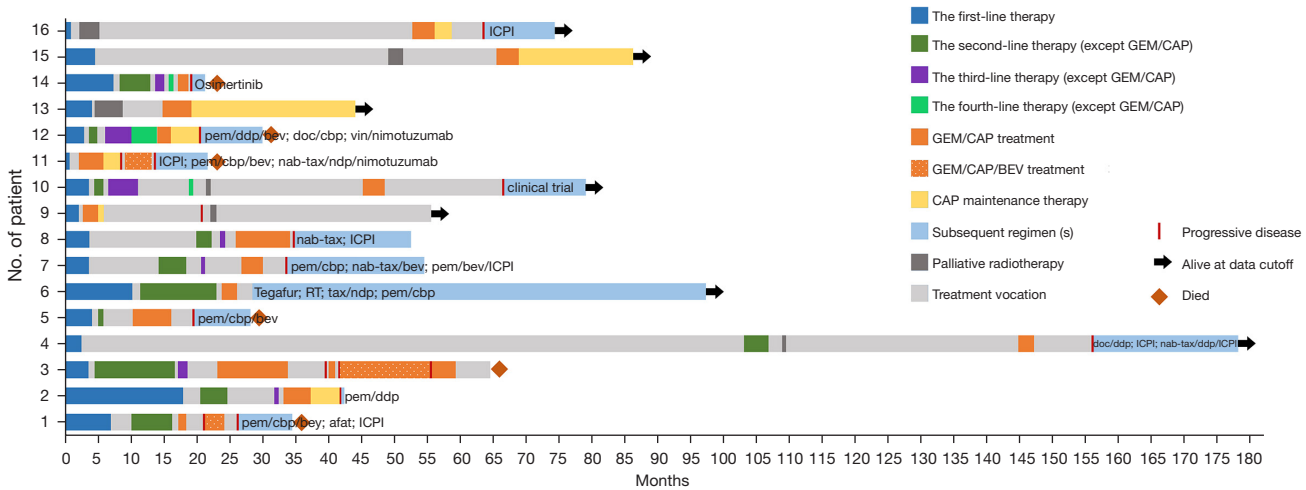

Figure 1 The swimmer plot of 16 patients with PLELC. pem, pemetrexed; cbp, carboplatin; bev, bevacizumab; afat, afatinib; ICPI, immune checkpoint inhibitor; ddp, cisplatin; doc, docetaxel; nab-tax, nanoparticle albumin-bound paclitaxel; RT, radiotherapy; tax, paclitaxel; ndp, nedaplatin; vin, vinorelbine; No., number; GEM, gemcitabine; CAP, capecitabine; PLELC, primary pulmonary lymphoepithelioma-like carcinoma.

alive, 6 patients had died, and 3 patients were lost to follow-up. At a median follow-up of 29.3 months [95% confidence interval (CI): 20.3–38.3 months], the median PFS was 9.3 months (95% CI: 6.5–12.1 months) (*Figure 4A*). The median OS was 41.5 months (95% CI: 3.1–79.8 months) (*Figure 4B*). There were no statistically significant differences in patients with or without CAP maintenance therapy for PFS (11.0 *vs.* 9.3 months, P=0.292) and OS (not reached *vs.* 41.5 months, P=0.705) by log-rank test.

Discussion

PLELC is considered a unique subtype of NSCLC and has a low incidence (7). The majority of cases of PLELC reported in the literature are from Southern China such as Guangdong Province (3,11), Hong Kong (1,15), Taiwan (4,30), and Southeast Asia (31,32). The incidence in Asia is approximately 0.9% of NSCLC cases (1,2,4), whereas data from Western countries are lacking, and the rare reporting of cases in papers suggests a much lower incidence (1). In our cohort, PLELC was mostly associated with young nonsmokers with a median age of 45.5 years (range, 35.0–65.0 years), which was consistent with other reports (7,33). Lin *et al.* reported that the median age of PLELC was 47 years, and the age was on average 10 years younger than that of other NSCLCs (33).

In addition, the frequency of driver gene mutations of PLELC is rather low compared with other types of pulmonary cancer (4,10,34,35). The use of next-generation sequencing for 27 tumor tissues of PLELC patients showed no mutations of the classic driver genes of lung cancer were detected, except for mutation of *KRAS* gene and *ERBB2* gene amplification in 2 patients (12). Therefore, chemotherapy plays an important role in patients with advanced or metastatic PLELC (4). Moreover, PLELC is similar to NPC in somatic mutation spectrum, mutation rates, and changes in signal transduction pathways (3), indicating chemotherapy drugs sensitive to NPC, such as 5-FU, GEM, paclitaxel, and platinum, may be effective in PLELC (36-39). Favorable efficacy and acceptable cytotoxicity of GEM/CAP were reported for other tumors, including pancreatic adenocarcinoma, biliary cancer, and thymic epithelial tumors (22-26). Preclinical research findings have shown a positive interaction between GEM and CAP (21). Given the need for proper and effective therapeutic regimens for patients with heavily pretreated PLELC, we conducted this retrospective study to explore the activity and toxicity of GEM/CAP for previously treated PLELC.

In our study, the combination of GEM/CAP demonstrated an ORR of 50.00% and DCR of 87.50% in heavily pretreated PLELC patients, which were much more favorable than other recommend second-line therapeutic regimens in advanced NSCLC. The ORRs of second-line

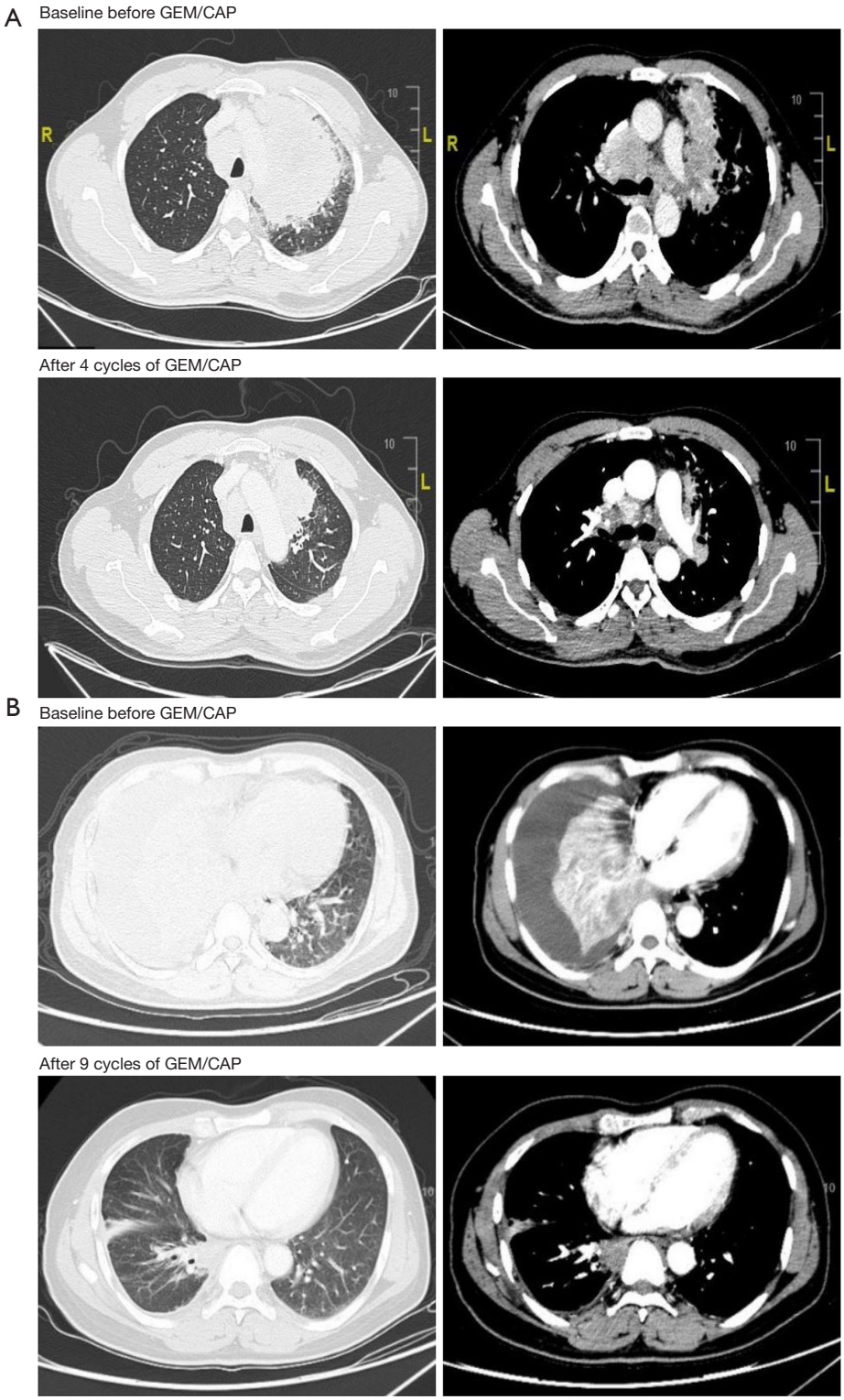

Figure 2 The CT images of 2 patients who accepted the treatment with GEM/CAP. A 43-year-old man with left PLELC achieved the best response of PR after 4 cycles of GEM/CAP (A). A 62-year-old man with right PLELC had the best response of PR after 9 cycles of GEM/CAP (B). GEM/CAP, gemcitabine plus capecitabine; CT, computed tomography; PLELC, primary pulmonary lymphoepithelioma-like carcinoma; PR, partial response.

Table 3 The best response of GEM/CAP in patients with PLELC (n=16)

Best response	Number	Percentage
Complete response	0	0.00%
Partial response	8	50.00%
Stable disease	6	37.50%
Progressive disease	2	12.50%
Objective response rate	8	50.00%
Disease control rate	14	87.50%

GEM, gemcitabine; CAP, capecitabine; PLELC, primary pulmonary lymphoepithelioma-like carcinoma.

regimens were 7.10–20.00% for pretreated NSCLC in published studies (40-42). In terms of second-line therapy of advanced NPC, an ORR of 43.75%, 23.53%, and 20.50% were reported in advanced NPC treated with GEM, CAP, and toripalimab, respectively (18,43,44). Although a higher activity was demonstrated in our study, the small sample size and lack of head-to-head comparison of GEM/CAP with standard second-line therapy are limitations of our study. We hope that larger-scale clinical trials are conducted to further confirm the results of our study.

High expression of programmed cell death-ligand 1 (PD-L1) has been detected in PLELC, with 2 studies reporting a positive rate of 61.7% and 69.0%, respectively (12,45), indicating that ICPIs may potentially be feasible therapeutic agents for PLELC (30). One retrospective study showed that ORRs were 33.3% in the immunochemotherapy group and 28.6% in the immunotherapy group, with median PFS of 11.8 months in the immunochemotherapy group and 11.0 months in the immunotherapy group as front-line treatments for advanced PLELC (46). However, there are few case reports describing the response to ICPIs in patients with previously treated PLELC due to the rarity of PLELC (16,17). The comparison of the efficacy of chemotherapy with or without ICPIs in PLELC by randomized trial is worth further exploration.

In this retrospective study, the median PFS and OS were 9.3 and 41.5 months, respectively, while the reported median PFS and OS for pretreated NSCLC in published studies were 10.6 weeks to 3.5 months and 7.0 to 9.2 months, respectively (40-42). The survival data of patients treated with GEM/CAP were consistent with our previous research. Patients with PLELC had better prognosis when compared with other subtypes of NSCLC (7). The favorable clinical

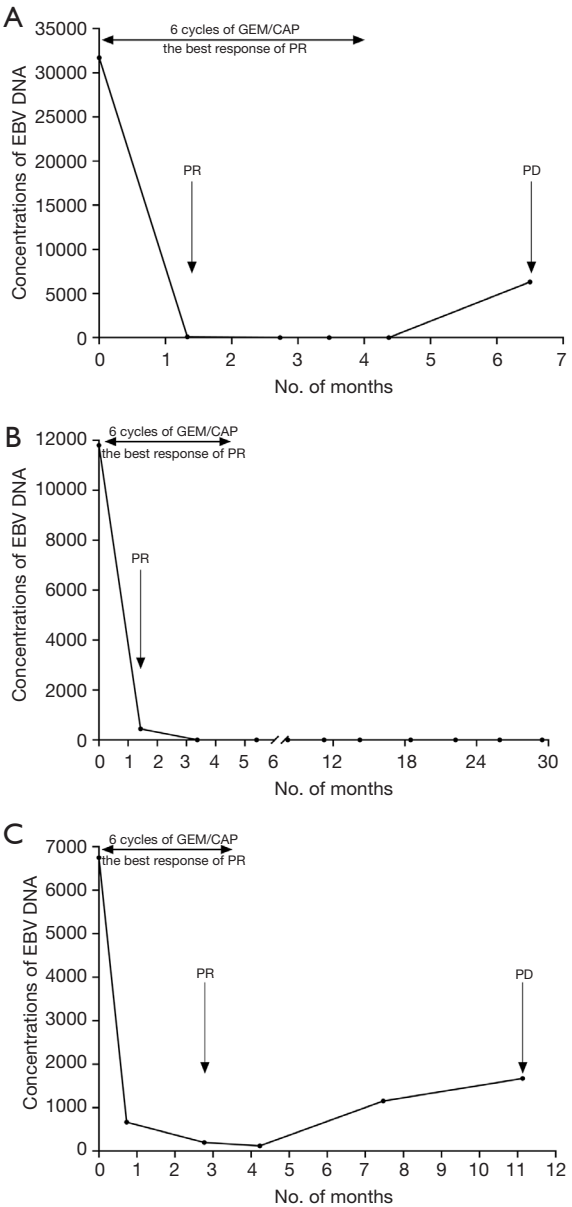

Figure 3 Plasma EBV DNA concentration profile correlating with treatment with GEM/CAP in patients 11 (A), 13 (B), and 16 (C). EBV, Epstein-Barr virus; GEM/CAP, gemcitabine plus capecitabine; No., number; PR, partial response; PD, progressive disease.

outcomes of the patients in our study may be related to the intrinsic nature of PLELC, as also reported previously (6).

Regarding AEs, this study showed tolerable toxicity of GEM/CAP as salvage therapy in advanced PLELC. The majority of AEs were grade 1 and 2. Hand-foot syndrome and neutropenia were the most common treatment-related

Table 4 Therapy-related adverse events in patients with PLELC (n=16)

Adverse event	Any grade, n (%)	Grade 1, n (%)	Grade 2, n (%)	Grade 3, n (%)	Grade 4, n (%)
Neutropenia	5 (31.25)	2 (12.50)	2 (12.50)	0	1 (6.25)
Anemia	1 (6.25)	0	1 (6.25)	0	0
Thrombocytopenia	1 (6.25)	1 (6.25)	0	0	0
Nausea	1 (6.25)	1 (6.25)	0	0	0
Vomiting	1 (6.25)	0	1 (6.25)	0	0
Anorexia	1 (6.25)	1 (6.25)	0	0	0
Diarrhea	2 (12.50)	1 (6.25)	1 (6.25)	0	0
Constipation	3 (18.75)	2 (12.50)	1 (6.25)	0	0
Fatigue	1 (6.25)	1 (6.25)	0	0	0
Stomatitis	5 (31.25)	4 (25.00)	1 (6.25)	0	0
Alopecia	2 (12.50)	2 (12.50)	0	0	0
Hand-foot syndrome	7 (43.75)	5 (31.25)	1 (6.25)	1 (6.25)	0

PLELC, primary pulmonary lymphoepithelioma-like carcinoma.

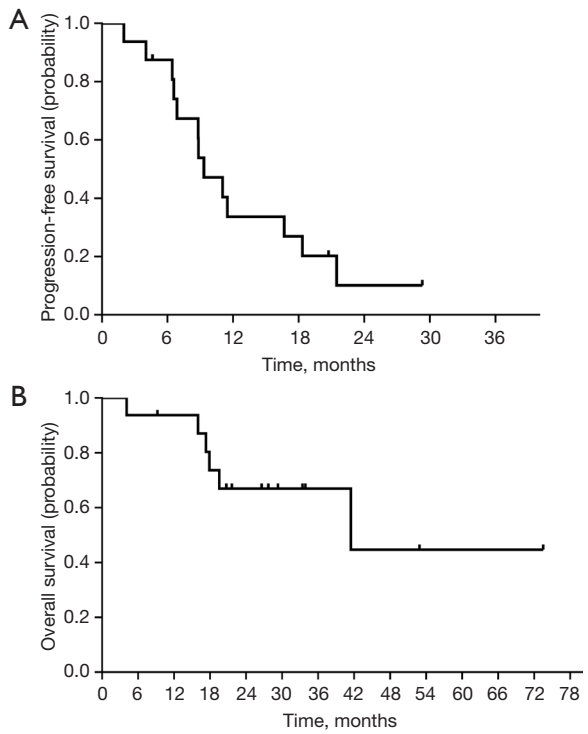

Figure 4 Survival function of PFS (A) and OS (B) in 16 patients by the Kaplan-Meier method. The median PFS was 9.3 months (95% CI: 6.5–12.1 months). The median OS was 41.5 months (95% CI: 3.1–79.8 months). PFS, progression-free survival; OS, overall survival; CI, confidence interval.

side effects, which were consistent with previous studies of GEM/CAP for other malignancies (47-49).

The role of EBV infection has previously been assessed in the tumorigenesis and development of PLELC (7,45). In our study, plasma EBV DNA levels were monitored before, during, and after treatment with GEM/CAP combination in 3 patients for explorative purposes, and we found that dynamic changes in EBV DNA level during anticancer treatment were associated with the clinical outcome. PR and prolonged PFS were observed in all 3 patients after receiving GEM/CAP treatment, with consistently declining EBV DNA levels, similar to that reported by Ngan *et al.* (50,51). Xie *et al.* showed that patients with undetectable plasma EBV DNA concentration after radical surgery had better disease-free survival and OS than those with persistently detectable EBV DNA levels after radical resection for resectable PLELC (6). Further exploration of the clinical value of routine monitoring of postbaseline dynamic changes in plasma EBV DNA level as a tumor marker is worthwhile during anticancer treatment.

In summary, this is the first study to explore the efficacy and safety of GEM/CAP regimen as salvage chemotherapy for pretreated PLELC. However, this study is limited by the nature of retrospective studies, the small sample size, and the heterogeneity of the patient population and previous treatments. Multicenter prospective clinical trials

are needed to further confirm the efficacy and safety of this regimen. In addition, evaluation of different chemotherapy regimens as well as ICPIs should be further conducted.

Conclusions

This study preliminarily showed the favorable activity and tolerable toxicity of GEM/CAP combination as second-line or beyond treatment in pretreated advanced PLELC. Further multicenter prospective studies are worthwhile.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-256/rc

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by Sun Yat-sen University Cancer Center Research Ethics Board (No. B2020-404-01). Written informed consent was provided before data collection.

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