Editorial

Gemcitabine-capecitabine: a therapeutic option in previously treated advanced primary pulmonary lymphoepithelioma-like carcinoma

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First reported in 1987, primary pulmonary lymphoepithelioma-like carcinoma (PLELC) is a rare histological subtype of non-small cell lung cancer (NSCLC) accounting for less than 1% of all cases, and even fewer in Western countries. It has been mostly reported in non-smokers and middle-age women (1). Due to the high prevalence in the Asian region, cases have mainly been described in Hong Kong, Taiwan, and Guangdong (1-5). Clinico-pathological features of PLELC are distinct from those of other NSCLC subtypes. Previous investigations showed this subtype is associated with better prognosis than other NSCLC such as squamous cell carcinoma, adenocarcinoma and large cell carcinoma of the lung, event at advanced stages (6,7). A specificity of PLELC is the strong association with Epstein-Barr virus (EBV) infection, and its histological characteristics are similar to those undifferentiated nasopharyngeal carcinomas. Importantly, it is important to differentiate it from advanced nasopharyngeal carcinoma. Lymphoepithelial-like carcinoma, which in the fourth World Health Organization (WHO) classification was under "other and unclassified carcinomas", was renamed in the 2021 WHO classification as lymphoepithelial carcinoma. It belongs to a type of squamous cell carcinoma, with diffuse positive staining for a combination of cytokeratin 5/6, p40, p63 (8).

PLELC was describe to be sensitive to chemotherapy, and platinum-based regimens have been the first choice for advanced PLELC since decades. Indeed, platinum-based chemotherapy was demonstrated to be an independent predictor for overall survival (OS) in advanced PLELC (4). In lack of specific studies assessing efficacy of systemic treatment, treatment strategies followed the NSCLC guidelines. The most widespread used therapeutic strategies in literature included platinum doublet with paclitaxel/docetaxel, pemetrexed or gemcitabine (before the recent advent of immunotherapy). Interestingly, although consensus has never been reached on the optimal chemotherapy regime, gemcitabine-based regimens appear to be of particular interest. A retrospective study studied 127 patients with unresectable PLELC treated frontline with gemcitabine plus platinum, taxanes plus platinum or pemetrexed plus platinum (2). Median progression-free survival (PFS) and OS were 7.7 months [95% confidence interval (CI): 6.6–8.8] and 36.7 months (95% CI: 30.9–42.5), respectively. Gemcitabine plus platinum demonstrated the highest response rate and the longest

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PFS. Another retrospective study enrolling 33 advanced PLELC patients demonstrated longer PFS with platinum-gemcitabine regimen (10 months) than with platinum-pemetrexed regimen (5 months; P=0.001) (3). Moreover, in metastatic or recurrent nasopharyngeal carcinoma, a phase III clinical trial demonstrated a better efficacy with cisplatin-gemcitabine than with cisplatin-fluouracine [median PFS, 7.0 *vs.* 5.6 months; objective response rate (ORR), 64% *vs.* 42%; median OS, 29.1 *vs.* 21.9 months] (9). Given the similarities between nasopharyngeal carcinoma and PLELC, this is another argument to support gemcitabine-based regimens in PLELC.

Data are even scarcer in second line treatment and beyond. PLELC patients failing upfront chemotherapy (relapse/refractory) faced few therapeutic options given no approved standard of care. A large retrospective cohort included 69 patients with a PLELC, 52 of them had a stage III unresectable or stage IV disease (4). Response to upfront line of chemotherapy was 61.8%, with a disease control rate of 80.6%. In 2nd line, ORR was 20% and disease control rate was 60%. The median PFS of upfront and 2nd line treatment was 10.1 months (95% CI: 8.2–12.0) and 7.1 months (95% CI: 0.1–14.1), respectively. Median OS was 22.7 months (95% CI: 11.5–33.9). Another study found, for 19 PLELC patients who received second-line treatment, a 1-year PFS rate of 25% and a median PFS duration of 5.9 months (3).

The study published in this journal by Zou *et al.* assessed the efficacy of a combination of gemcitabine and capecitabine in recurrent PLELC patients (10). Previous studies showed that gemcitabine and capecitabine combination was active, especially in pancreatic tumors, biliary tract carcinomas or thymic tumours (11-13). Capecitabine is an oral precursor of 5-fluorouracile (5-FU). Capecitabine is more tolerable, and efficiency is similar compared with intravenous FU/leucovorin. Moreover, the convenience of oral administration makes it an attractive treatment option in diverse solid tumors. Dose-limiting toxicities for gemcitabine include hepatic transaminase increases, myelosuppression, and flu-like symptoms, whereas toxicities for capecitabine are mainly gastro-intestinal events and hand-foot syndrome. Thus, gemcitabine and capecitabine have nonoverlapping toxicity and a well-tolerated safety profile. So far, efficacy results from this combination were not described in PLELC patients. Authors reported in this issue results of a retrospective, monocentric Chinese cohort study from the Sun Yat-sen University Cancer Center, involving patients previously treated for a PLELC between 2013 and 2021 (10). A total of 16 patients receiving a combination of gemcitabine and capecitabine after at least one prior systemic therapy were included. Patients received intravenous gemcitabine (1,000 mg/m^2 on days 1 and 8) and oral capecitabine (1,000 mg/m^2 twice daily on days 1–14) every 3 weeks. Capecitabine could be continued after 4 to 6 cycles of combination therapy. Consistent with the literature, half of patients were women, most of them were never-smokers (10/16). Median age was quite young, 45.5 years (range, 35.0–65.0 years). As expected, platinum-based therapy was the first-line treatment in all patients, including combination with vinorelbine, pemetrexed, docetaxel, or paclitaxel.

Partial response was observed in 8 patients out of 16 (50%), while 6 patients had stable disease. Thus, the disease control rate was 87.50%. At a median follow-up of 29.3 months, the median PFS was 9.3 months (95% CI: 6.5–12.1 months), and the median OS was 41.5 months (95% CI: 3.1–79.8 months). Interestingly, most of patients had received ≥2 lines of prior therapies (11/16 patients), and 4 of them were pre-treated with a gemcitabine-based combination (patient 2/7/10/12). One of these patients (patient 12) had a partial response after re-challenge by gemcitabine and capecitabine, others had stable disease. Swimmer plot provided by Zou *et al.* in *Fig. 1* illustrated that disease could have slow evolution in some patients with long period of therapeutic interruption (10). Interestingly, for several patients, disease control provided by the combination of gemcitabine and capecitabine appear longer than that obtained with the previous lines (patient 11, 12 and 13 for example).

The most reported haematological and non-haematological adverse events at any grade were neutropenia and hand-foot syndrome. However, toxicities are difficult to report in retrospective studies. Safety of gemcitabine plus capecitabine was available from other cancer studies. In thymic tumors, neutropenia was the most important grade 3, and 2/30 patients had grade 3 diarrhoea in a prospective trial (12). Capecitabine was delivered at 650 mg/m^2 twice daily on days 1–14. In pancreatic cancer, gemcitabine was delivered as a 1,000 mg/m^2 intravenous administered once a week for three of every 4 weeks, and capecitabine was administered orally for 21 days followed by 7 days' rest at a daily dose of 1,660 mg/m^2. There were 5% of grade 3 diarrhoea, 38% of grade 3 neutropenia and 10% of white blood cell count decreased (13).

The past two decades have seen great progress in

developing targeted therapies in NSCLC. They are based on the genomic characterisation of the disease, and nowadays, more and more patients could benefit from these targeted therapies due to the development of next-generation sequencing. The etiologic and molecular events responsible for the occurrence of LELC were almost entirely unknown. Because of its rarity, the prevalence of oncogenic mutation in advanced patients with PLELC has not been deeply investigated until recently. Molecular characteristics of PLELC have been described from a cohort of 128 patients, selected from a large database of 41,574 lung cancers (6). Genomic alterations were identified on comparison of other histological subtypes such as lung squamous cell carcinoma, lung adenocarcinoma, and EBV-positive nasopharynx cancer. The mutation spectrum of PLELC was found to be distinct from those of other subtypes of NSCLC and EBV-positive nasopharynx cancer, as no common frequently mutated genes were observed except for TP53. The tumor-associated genes ZBTB16 (a transcriptional repressor), PPARG (belonging to nuclear receptor superfamily of PPARs), and TGFBR2 (involving in promotion of antitumor immunity) were found to be significantly downregulated with concomitant copy number variation loss (6). Some papers reported cases with epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) rearrangement, but the mutation rates in PLELC were far lower than other common types of NSCLC (5,14). Moreover, among four patients who received tyrosine kinase inhibitors after they were detected positive with EGFR/ALK mutation, all experienced disease progression a few weeks later (14). These data indicate that the main oncogenic factors for PLELC might be other than somatic driver mutations, and that tyrosine kinase inhibitors may not be suitable for this histological subtype. One patient from the current study had an uncommon EGFR exon 20 insertion. To our knowledge, response to new targeted therapies against this mutation such as mobocertinib or amivantamab have never been described in PLELC.

Last decade, the treatment landscape of NSCLC has dramatically changed due to the development of Programmed Death-(Ligand) 1 (PD-1/PD-L1) checkpoint inhibitor. Interestingly, around 70% of PLELCs are positive for PD-L1-stained tumor cells, a percentage higher than in other types of lung cancer (1,6). As the treatment modalities of PLELC mainly follows NSCLC regimens, platinum-based doublets combined with immune checkpoint inhibitors are now used as upfront therapy. Several retrospective studies are beginning to report efficacy data with immunotherapy. A Chinese study included 68 patients treated frontline with chemotherapy (n=49), immunotherapy (n=7) and chemo-immunotherapy (n=12) (15). Results showed that the median PFS was 6.9 months (range, 2.3 months–not estimable) in the chemotherapy group, 11.0 months (range, 2 months–not estimable) in the immunotherapy group, and 11.8 months (range, 6 months–not estimable) in the chemo-immunotherapy group. Another study included 133 patients treated frontline with chemotherapy (platinum-taxane or platinum-gemcitabine, n=78), or chemo-immunotherapy (n=55) (16). The median PFS was 12.8 months (95% CI: 5.2–20.4 months) in the chemo-immunotherapy group and 7.7 months (95% CI: 6.8–8.6 months) in the chemotherapy group [hazard ratio (HR) =0.48; 95% CI: 0.31–0.74; P=0.001]. The median OS was not reached in the chemo-immunotherapy group versus 35.7 months (95% CI: 26.7–44.8 months) in the chemotherapy group (HR =0.47; 95% CI: 0.20–1.07; P=0.065). Thus, immunotherapy seem to be a promising drug in this subset of patients. This question is worthy of further clinical investigation.

Collectively, this study makes a significant contribution to our limited knowledge of treatment options upon relapse in PLELC patients, showing that a combination of gemcitabine and capecitabine in previously treated patients was active and well tolerated. However, this estimate is not easily generalizable due the inclusion of only 16 patients. Further research would be needed to validate this finding. Although the best treatment remains unknown in lack of randomized clinical trial, these results can be used to help decision-making by clinicians and patients. Additionally, these results may help to establish a baseline for future studies or treatment comparisons in further research into therapeutic considerations in this disease setting.

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