Capecitabine as Salvage Treatment for Lymphoepithelioma-Like Carcinoma of Lung

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Abstract: Lymphoepithelioma-like carcinoma (LELC) of lung has previously demonstrated good clinical response to 5-fluorouracil containing chemotherapy regimen, similar to the observation in undifferentiated nasopharyngeal carcinoma. Capecitabine, which is converted into active 5-fluorouracil within tumor cells, has been found effective in colorectal, breast, and recently nasopharyngeal carcinomas. We report our experience in five patients with advanced or metastatic LELC of lung who were treated with single agent capecitabine as salvage chemotherapy. The finding of disease control in three of five patients, especially with exceptionally durable stable disease (14.8 months) in one patient, suggests the potential clinical activity of capecitabine in LELC of lung. Future studies on capecitabine-containing chemotherapy regimens in LELC of lung are warranted.

Key Words: Lymphoepithelioma-like carcinoma, 5-Fluorouracil, Capecitabine.

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Lymphoepithelioma-like carcinoma (LELC) of lung has been a well-recognized special entity of non-small cell lung cancer (NSCLC), with etiological link to Epstein-Barr virus and histologically close resemblance to undifferentiated nasopharyngeal carcinoma (NPC). The largest reports were mainly ethnically Orientals from Southern China, Taiwan, and Hong Kong.[1] Because of its uncommon occurrence, there have been no large-scale randomized controlled trials on the optimal treatment options for advanced LELC of lung. Most of the previous reports on options of chemotherapy treatment were largely anecdotal. Nevertheless, there has been promising response to 5-fluorouracil (5-FU) and cisplatin combination chemotherapy as first-line treatment in advanced LELC of lung, mimicking the clinical response in NPC.[2,3] The use of systemic chemotherapy in the salvage treatment of advanced disease has not been well reported. Capecitabine, basically functioning as a prodrug of 5-FU, has been considered as a reasonable alternative treatment in malignancies that are particularly responsive to 5-FU, like colon cancer and NPC. Therefore, we conducted this retrospective study to review our preliminary experience with the use of capecitabine in treatment of advanced LELC of lung.

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PATIENTS AND METHODS

Case Identification

This is a retrospective case series of patients with pathologically confirmed advanced unresectable LELC of lung who had received capecitabine (Xeloda, Roche Pharmaceuticals) as salvage chemotherapy in the Department of Medicine at Queen Mary Hospital, a University-affiliated teaching hospital in Hong Kong, since 2002. The eligible cases were identified from our prospective clinical database of all newly diagnosed lung cancers in Queen Mary Hospital, as previously approved by our Institutional Review Board. The diagnostic workup of primary LELC of lung has been described previously.[1,2,4] The classification of tumor staging was based on tumor node metastasis staging system.[5]

Chemotherapy for LELC of Lung

Our institutional treatment protocol for primary LELC of lung has been reported previously.[1,2] The first-line chemotherapy for advanced or metastatic primary LELC of lung involved a combination of 5-FU (1000 mg/m^2, days 1–4), leucovorin, and cisplatin (100 mg/m^2, day 1) (FLP) at 4-weekly interval for 4 to 6 cycles. On disease progression after first-line chemotherapy, other chemotherapy regimens (containing paclitaxel, docetaxel, or gemcitabine) that were commonly used in NSCLC would be considered.[6] Capecitabine, being converted to 5-FU within tumor tissues, was considered as an alternative salvage treatment especially with the recent preliminary experience in NPC.[7] The standard regimen of capecitabine was 1250mg/m^2 orally twice daily for 2 weeks followed by a 1-week rest period in 3-weekly cycles, which would be stopped on disease progression or intolerable adverse reactions.

Clinical Parameters

Demographic data (gender, age, and smoking status), tumor characteristics (histologic evidence of LELC and TNM staging), anticancer treatments (chemotherapy regimens and their response and thoracic radiotherapy), and clinical outcomes (time to progression and survival) were retrieved by review of clinic charts and radiographs. Tumor assessment was based on RECIST criteria[8] as per institutional clinical practice, after at least two cycles of chemotherapy treatment.

RESULTS

Patient Characteristics

Since 2002, there were five patients with advanced or metastatic primary LELC of lung who received capecitabine as salvage chemotherapy in our institution (Table 1) in which they were predominantly middle aged (56 ± 8.7 years, mean ± SD), women (75%), and nonsmokers (75%). All patients had histologically confirmed LELC from lung tumor tissues, positive in-situ hybridization for Epstein-Barr virus-encoded small nuclear RNA in tumor cells, and negative nasopharyngeal biopsy to exclude NPC. Of particular note, one of the patients (case 5) had history of early-stage NPC with curative radiotherapy 2 years before his presentation in which the diagnosis of primary LELC of lung was based on radiologic pattern favoring lung primary and absence of local recurrence in nasopharynx. All patients presented with either locally advanced or metastatic diseases (IIIA in two; IIIB in two; and IV in one patient).

Chemotherapy Treatment Before Capecitabine

The median number of chemotherapy regimens used before salvage with capecitabine was 2 (range, 1–3). As per institutional protocol, all five patients had received 5-FU containing regimen (FLP) as first-line chemotherapy (median 6 cycles, range 4–6 cycles), attaining partial response in three and stable disease in two patients. Newer generation chemotherapeutic agents as for other NSCLC (paclitaxel, gemcitabine, and docetaxel) were used in second- or third-line settings (Table 1), with partial response in one patient on gemcitabine monotherapy, stable disease in one patient on paclitaxel/carboplatin and progressive disease in the rest.

Clinical Outcomes with Salvage Capecitabine

There were two patients (40%) with disease stabilization and one patient (20%) with partial response while on capecitabine as salvage treatment (Table 2). The median duration of starting capecitabine from the initiation of first-line chemotherapy was 20.9 months (range, 6.7–63.1). The number of cycles of capecitabine given ranged from 3 to 20 cycles, with one patient still receiving treatment. Treatment was stopped in four patients because of disease progression. Among the four patients with disease progression, the median time to progression was 4.1 months (range: 1.6–14.8). There was no apparent relationship between clinical response to capecitabine and previous best overall response to first-line chemotherapy (FLP). Three patients were still alive (median follow-up since start of capecitabine: 5 months; range: 5–5.5). For the two patients who died, the survival times were 2.7 and 27 months after start of capecitabine. For the patient with long duration of disease stabilization, capecitabine was started in clinical stage IIIA disease (with ipsilateral paratracheal lymphadenopathy) and her serial chest radiographs (case 2) were shown in Figure 1. Computed tomography scans of another patient (case 5) with disease control were shown in Figure 2. The capecitabine treatment was well tolerated except moderately severe degree of hand-foot syndrome in one patient requiring short-term treatment with celecoxib (case 2) and prolonged but mild (grade 2) neutropenia requiring postponement of treatment cycles in another patient (case 4). There were no febrile neutropenia or treatment-related deaths.

DISCUSSION

From our preliminary experience of salvage treatment with capecitabine in heavily pretreated patients with advanced LELC of lung, the treatment was in general well tolerated and durable disease stabilization was observed in one of five patients on such treatment, with the time to tumor progression exceptionally prolonged (14.8 months). In addition, partial tumor response was attained with capecitabine in another patient. The previous best overall tumor response to 5-FU containing chemotherapy (FLP) was not apparently predictive of subsequent response to capecitabine.

Capecitabine, alone or in combination with other chemotherapy agents, has been approved for treatment of advanced colorectal and breast cancers. The major advantages of capecitabine include oral route of administration and preferential action on tumor cells. The latter is related to the significantly higher level of thymidine phosphorylase, an enzyme responsible for the final step in the conversion of capecitabine to 5-FU, within malignant cells.[9] Capecitabine and its intermediates are not cytotoxic but only become active after conversion to 5-FU, thus conferring a better safety profile than other fluoropyrimidines. In fact, high tumor cell thymidine phosphorylase and low stromal thymidine phosphorylase expression was associated with good tumor response to combination of capecitabine and docetaxel in a phase II trial in advanced NSCLC.[10] Therefore, the high intratumoral concentration and prolonged exposure to 5-FU may partly explain our observation of disease control with capecitabine even among those who failed prior 5-FU-containing chemotherapy.

TABLE 1. Demography and Clinical Characteristics of Five Patients with Advanced Lymphoepithelioma-Like Carcinoma of Lung Who Received Salvage Treatment with Capecitabine

Case	Gender	Age at Diagnosis (yr)	Smoking Status	Pack-Years of Smoking	TNM Staging at Diagnosis	Overall TNM Staging at Diagnosis	No. of Chemotherapy Regimens Before Capecitabine	Chemotherapy Regimens Before Capecitabine	Prior Thoracic Radiotherapy
1	Female	67	NS	0	T4N3M1	IV	2	FLP, G,	Yes
2	Female	60	NS	0	T2N2M0	IIIA	2	FLP, DC	Yes
3	Female	46	NS	0	T2N2M0	IIIA	2	FLP, GC	Yes
4	Female	58	NS	0	T4N2M0	IIIB	3	FLP, TCb, GC	Yes
5	Male	48	ES	15	T4N3M0	IIIB	1	FLP	No

TNM, tumor node metastasis; NS, nonsmoker; ES, exsmoker; FLP, 5-fluorouracil, leucovorin, cisplatin; G, gemcitabine; DC, docetaxel/cisplatin; GC, gemcitabine/cisplatin; TCb, paclitaxel/carboplatin.

TABLE 2. Treatment Outcomes of Five Patients with Advanced Lymphoepithelioma-Like Carcinoma of Lung Who Received Salvage Treatment with Capecitabine

Case	Time of Start of Capecitabine from Start of First Line Chemotherapy (mo)	Total No. of Cycles of Capecitabine Received	Best Overall Response to Capecitabine	Tumor Progression to Capecitabine Treatment	Duration of Follow-Up Since Start of Capecitabine (mo)	Time to Tumor Progression If Already Progressed (mo)	Best Overall Response to Previous Chemotherapy with FLP	Alive or Dead	Survival from Start of Capecitabine (mo)	Survival from Start of First Line Chemotherapy (mo)
1	32.5	7	SD	Yes	5.0	4.9	PR	A	5.0+	37.5+
2	20.9	20	SD	Yes	27	14.8	SD	D	27	47.9
3	14.0	3[a]	PD	Yes	2.7	1.6	PR	D	2.7	16.7
4	63.1	3	PD	Yes	5.5	3.2	PR	A	5.5+	68.6+
5	6.7	7+ (ongoing)	PR	No	5.0	NA	SD	A	5.0+	11.7+

[a] For case 3, capecitabine was continued for one more cycle on disease progression.
SD, stable disease; PD, progressive disease; PR, partial response; A, alive; D, dead; NA, not applicable.

FIGURE 1. Chest radiographs of the index patient (case 2) with durable disease stabilization to capecitabine treatment for LELC of lung: (*A*) at baseline before capecitabine treatment (right middle lobe tumor measured 4.5 × 3.5 cm); (*B*) 3 months after capecitabine treatment (right middle lobe tumor measured 4 × 3.5 cm); and (*C*) 6 months after capecitabine treatment (right middle lobe tumor measured 4.2 × 3.5 cm).

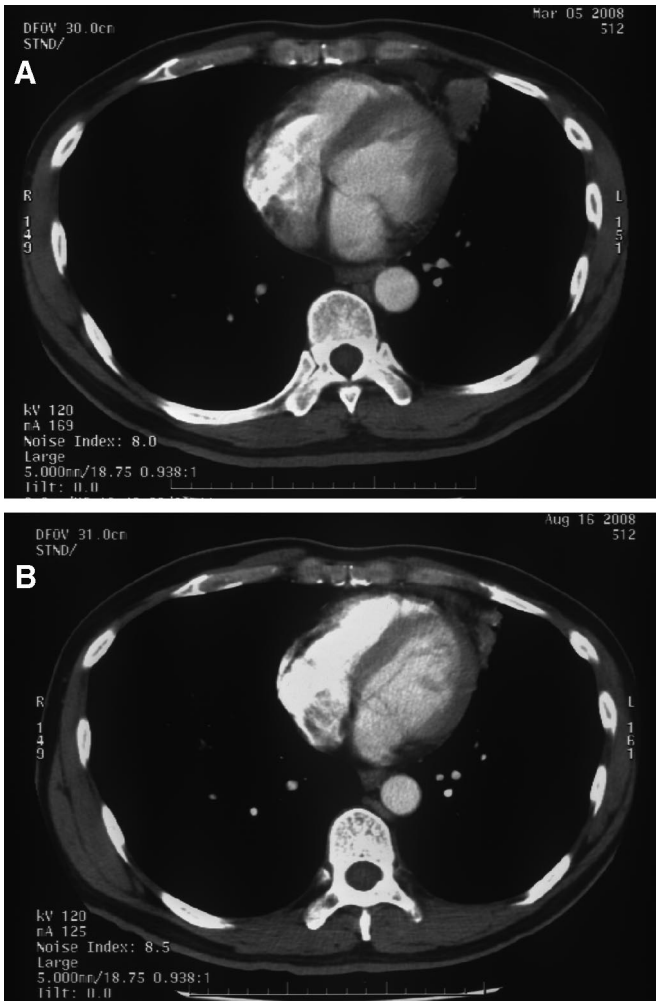

FIGURE 2. Thoracic computed tomography scans of a patient (case 5) with tumor shrinkage while on capecitabine treatment for LELC of lung: (*A*) before capecitabine treatment (lingular tumor 2.3 × 3.5cm); (*B*) around 5 months after capecitabine treatment (lingular tumor 1.7 × 2.0cm). There was 32% reduction in the total sum of longest diameters (including lingular mass, paratracheal lymph nodes, and right hilar lymph node).

Because the etiology and histologic features of primary LELC of lung are similar to NPC, the previous reports on systemic treatment for LELC of lung have mainly focused on 5-FU and cisplatin combination chemotherapy, with exceptionally good clinical response (60–70% partial response rate).[2,3] As capecitabine essentially acts through its intracellular conversion to 5-FU, it forms the rationale for its role in treatment of both malignancies. In NPC, there has been only a single phase II clinical trial of capecitabine in 17 patients with recurrent or metastatic setting, achieving an overall response rate of 23.5%, median survival 7.6 months, and estimated 1-year survival 35%.[7] In a more recent retrospective review of using capecitabine for 49 patients with recurrent or metastatic NPC, there was an overall response rate of 37%, median time-to-progression of 5 months, and median survival of 14 months.[11] For NSCLC, there have been only a few clinical trials on the use of capecitabine in combination with docetaxel[12,13] or irinotecan[14] as salvage treatment for advanced disease, suggesting favorable antitumor activity. In the first-line setting, combination of capecitabine with docetaxel has also demonstrated promising activity in advanced NSCLC.[15]

From our knowledge, the clinical experience in using capecitabine in treatment of primary LELC of lung has never been reported before, partly related to its rarity. Although this study is largely limited by its retrospective analysis, small sample size, heterogeneous patient population and prior treatment, and short duration of follow-up, the promising clinical activity and good tolerability of capecitabine in previously treated advanced LELC of lung should warrant future studies.

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