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Case Report

Combination of Oxaliplatin and 5-Fluorouracil/Leucovorin for Advanced Esophageal Squamous Cell Carcinoma Refractory or Intolerant to Standard Therapies

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Keywords

Esophageal squamous cell carcinoma · FOLFOX · 5-Fluorouracil · Oxaliplatin · Cisplatin · Salvage chemotherapy

Abstract

Here, we report the four cases with metastatic esophageal squamous cell carcinoma pretreated with standard chemotherapy who then received salvage-line chemotherapy with oxaliplatin and 5-fluorouracil plus l-leucovorin (FOLFOX) at our institution. We identified four men following the mentioned regimen; their median age was 68.5 years (range, 65–76 years). All patients developed disease progression on 5-fluorouracil, cisplatin, and taxanes. Two patients achieved partial response; the other two achieved stable disease on receiving cisplatin-containing regimens as first-line therapy. The Eastern Cooperative Oncology Group performance statuses were 1 in three patients and 2 in one patient. The best response was partial response in one patient, stable disease in one, and progressive disease in two. For the two patients who achieved partial response or stable disease, the times to progression were 5.7 and 5.2 months and the overall survival times were 8.1 and 9.5 months, respectively. A grade 3 encephalopathy in one patient improved soon after chemotherapy discontinuation and supportive therapies.

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There was no treatment-related death. This is the first report suggesting the potential effectiveness of FOLFOX as salvage chemotherapy for metastatic esophageal cancer.

Introduction

Esophageal cancer is one of the most common cancers worldwide and in Japan. In contrast to Western countries, squamous cell carcinoma is the predominant histological type and accounts for approximately 90% of esophageal cancer cases in Japan. Despite recent advances in chemotherapy, palliative chemotherapy for metastatic or recurrent disease has poor outcomes. A Japanese national cancer registry revealed that the 1-year survival rate of patients treated with chemotherapy alone was 36.0% [1]. For patients with advanced esophageal squamous cell carcinoma (ESCC), regimens in combination with 5-fluorouracil (5-FU) and cisplatin have been considered as standard first-line chemotherapy with the median overall survival (OS) ranging from 7 to 10 months [2]. In the second-line setting, taxanes, including paclitaxel and docetaxel, have shown substantial efficacies [3, 4]. However, no standard regimen for later-lines of treatment for patients with metastatic ESCC has been established. Although best supportive care is a standard care for such populations, a Japanese multicenter retrospective study proposed that active salvage chemotherapy yielded an overall response rate of 11% with a survival benefit (OS, 4.2 vs. 7.8 months; hazard ratio, 0.41; 95% confidence interval, 0.31–0.54) [5]. Therefore, effective regimens for chemotherapy-refractory ESCC are still needed.

Oxaliplatin is a third-generation platinum complex that differs from cisplatin and carboplatin in its spectrum of activity and toxicity. A low-level cross-resistance between cisplatin and carboplatin has been demonstrated both in vitro and in vivo [6]. A previous study reported response rates of oxaliplatin monotherapy in patients with ovarian cancer refractory to cisplatin or carboplatin ranging from 4.3 to 29.0% [7]. Moreover, Kim et al conducted a phase II study of 5-FU/l-leucovorin plus oxaliplatin (FOLFOX) in previously platinum-treated patients with advanced gastric cancer and demonstrated a response rate of 26%, median progression-free survival (PFS) of 4.3 months, and median OS of 7.3 months [8]. Japanese retrospective studies reported that FOLFOX therapy yielded a response rate of 21.2–23.1% and a median OS of 4.2–8.9 months for gastric cancer refractory to standard therapies, including cisplatin [9]. Although oxaliplatin has been investigated for esophageal cancer mainly in the setting of definitive chemoradiotherapy [10], no studies on FOLFOX as later-line therapy have been conducted. We conducted this retrospective case series study to assess the safety and efficacy of modified FOLFOX-6 (mFOLFOX-6) in patients with ESCC refractory or intolerant to standard therapies.

Case Report

Case 1

A 67-year-old man diagnosed with metastatic ESCC 1 year and 6 months back had received 5-FU plus cisplatin as first-line treatment for 1 year, an immune checkpoint inhibitor as second-line treatment for 2 months, and paclitaxel as third-line treatment for 3 months until disease progression. The best tumor responses were stable disease (SD), progressive disease (PD), and PD after the first-line, second-line, and third-line treatments, respectively.

Subsequently, palliative radiotherapy was initiated for painful cervical lymph node and to treat the primary lesion in the esophagus.

When m-FOLFOX6 was initiated as fourth-line treatment, the patient had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 1. A computed tomography (CT) scan revealed multiple liver, lung, and mediastinal lymph node metastases. No severe treatment-related adverse events developed except for grade 2 neutropenia and thrombocytopenia and grade 1 peripheral neuropathy and nausea. A CT scan performed after three cycles of mFOLFOX-6 revealed SD with 2% increase from the baseline CT (Fig. 1). The patient underwent 10 courses of mFOLFOX-6 in total and developed PD thereafter (increase in size of lymph nodes as well as liver and lung metastases). The time to progression was 5.7 months. Best supportive care was provided after failure of mFOLFOX-6. Eventually, the patient died 8.1 months after FOLFOX-6 initiation.

Case 2

A 76-year-old man was diagnosed with metastatic ESCC. He was administered docetaxel and cisplatin plus 5-FU (DCF) as first-line treatment for 6 months until disease progression. The best tumor response following DCF therapy was partial response (PR).

mFOLFOX-6 was initiated as second-line treatment. At mFOLFOX-6 initiation, he had an ECOG PS of 1 and CT scan revealed peritoneal metastasis. He began receiving mFOLFOX-6 and developed grade 1 nausea during the first and second cycles. Although CT at 0.9 months after three mFOLFOX-6 cycles revealed SD with 5% increase from the baseline, endoscopy revealed enlargement of primary tumor and worsening of swallowing difficulty. Accordingly, treatment with mFOLFOX-6 was discontinued. Although he received palliative radiotherapy to the primary tumor site of esophagus, his physical status worsened drastically, and he died 1.2 months after mFOLFOX-6 initiation.

Case 3

A 65-year-old man diagnosed as having locally advanced, unresectable ESCC with clinical invasion of the trachea had received definitive chemoradiotherapy with concurrent 5-FU plus cisplatin. PR was achieved, but complete response was not obtained. Therefore, he received subsequent therapies with palliative chemotherapy with 5-FU plus cisplatin for 6 months until disease progression. Subsequently, weekly paclitaxel was administered for 2 months, and the first CT revealed PD. During paclitaxel therapy, he developed seizures and hemiplegia caused by multiple brain metastases and underwent whole-brain radiotherapy. Thereafter, mFOLFOX-6 was initiated as third-line treatment. He had an ECOG PS of 2 because of hemiplegia at that time. However, no new seizures were observed following whole-brain radiotherapy. In addition to brain metastases, CT revealed multiple lung and lymph node metastases. After receiving mFOLFOX-6, he presented no treatment-related adverse events. A CT scan performed 0.8 months after two mFOLFOX-6 cycles revealed PD with 25% increase from the baseline. Thereafter, best supportive care was provided, and the patient died 2.0 months after mFOLFOX-6 initiation.

Case 4

A 70-year-old man was diagnosed with locally advanced ESCC with a primary tumor suspected of having invaded the aorta and trachea. He underwent three DCF induction therapy cycles followed by chemoradiotherapy with FP. Although the DCF therapy achieved SD, CT after the completion of chemoradiotherapy revealed new metastatic lesions in the lungs and

peritoneum. Next, the patient received weekly paclitaxel for 2 months, which resulted in disease progression. He was enrolled in a clinical trial and received an immune checkpoint inhibitor for 6 months. The immune checkpoint inhibitor achieved complete regression of lung and peritoneal metastases, but the size of the abdominal lymph node increased gradually, and a percutaneous endoscopic gastrostomy tube had to be inserted because of poor oral intake. When the patient was started on mFOLFOX-6, his ECOG PS was 1. CT did not detect lung or peritoneal metastases, and only lymph node metastasis was observed.

After the first mFOLFOX-6 cycle, the patient developed grade 2 anorexia and diarrhea; thus, dose reduction was prescribed. During the third FOLFOX therapy cycle, he developed encephalopathy due to a high level of serum ammonia (199 μg/dL). Supportive therapies such as hydration and infusion of branched-chain amino acids led to the immediate improvement of symptoms, followed by normalization of the ammonia level within one week. After that, the patient resumed chemotherapy with a further dose reduction. He achieved PR with a 35% decrease from the baseline CT on week 8 (Fig. 2). However, the size of the lymph node gradually increased, and PD was achieved 5.2 months after the initiation of FOLFOX therapy. He was still alive 9.5 months after mFOLFOX-6 initiation.

Discussion

In this case series, mFOLFOX-6 demonstrated modest antitumor activity against chemotherapy-refractory metastatic ESCC. Among four patients who received mFOLFOX-6 as salvage-line chemotherapy, one displayed PR and one displayed SD. To the best of our knowledge, this is the first report suggesting the potential effectiveness of mFOLFOX-6 as salvage chemotherapy for metastatic ESCC.

The treatment options are limited for patients with metastatic esophageal cancer progressing after standard chemotherapy. In contrast to other cancers, no targeted agents approved for esophageal cancer. Recent clinical trials have suggested that immune checkpoint inhibitors such as pembrolizumab and nivolumab provide promising therapeutic activities for heavily pretreated patients with metastatic esophageal cancer. However, it was reported that the RR was 10–30% and not all patients obtained an immunotherapy benefit [11, 12]. An attempt to identify those benefiting from immunotherapy using biomarkers has been made [13]. Thus, a significant unmet need for more effective treatments for metastatic esophageal cancer still exists.

A 2 × 2 design phase III trial (REAL2) by the Royal Marsden group completed on esophageal squamous cell and adenocarcinoma and gastric cancers evaluating the front-line use of oxaliplatin demonstrated it is an equally effective alternative to cisplatin for esophageal cancer [14]. Moreover, the PRODIGE5/ACCORD17 trial in patients with localized esophageal cancer found that chemoradiotherapy with FOLFOX was not superior to chemoradiotherapy with 5-FU plus cisplatin and the survival outcomes were similar, but the treatment-related death rate was lower in the FOLFOX group, and the researchers concluded that FOLFOX therapy was a more convenient option [10]. Our results, which showed that two of four patients gained a clinical benefit, suggest the possibility that patients with ESCC may derive benefit from oxaliplatin-based salvage chemotherapy even if pretreated with cisplatin-containing regimens, but larger studies are needed before a recommendation can be made.

In this report, one patient had grade 3 encephalopathy due to a high serum ammonia level. We previously reported that multiple prior chemotherapy regimens may be associated with

the development of hyperammonemia due to fluoropyrimidines [15]. Patients should be carefully monitored to detect hyperammonemia early, particularly when FOLFOX therapy is initiated as a later-line therapy. Conversely, we also noted that fluoropyrimidine-induced acute hyperammonemic encephalopathy can be effectively treated upon early diagnosis and with proper management. In this case series, supportive therapies led to prompt recovery and the patient in this study recovered promptly. All other adverse events in our series were grade 2 or less, suggesting that mFOLFOX-6 is feasible for patients after standard therapy failure.

We are aware of our study's limitations. First, we included only a small sample size from a single institution, and our findings should be validated in future clinical trials. However, this is the first report to show the potential effectiveness of mFOLFOX-6 in heavily pretreated patients with ESCC.

Conclusion

Our findings suggested that mFOLFOX-6 for patients with metastatic ESCC pretreated with standard therapies (including cisplatin) has potential therapeutic activity and acceptable toxicity. A prospective study is needed to further evaluate its safety and efficacy.

Statement of Ethics

We declare that written informed consent for publication was obtained from all the patients.

Disclosure Statement

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Seiichiro Mitani: Eli Lilly and Co. and Ono Pharmaceutical Co., Ltd. (Personal Fees) Shigenori Kadowaki: Eli Lilly and Co., Taiho, Chugai Pharmaceutical Co., Ltd., Ono Pharmaceutical Co., Ltd., Bristol-Myers Squibb, Taiho, Merck Serono, Bayer, Eisai and Yakult Honsha (Personal Fees), Boehringer Ingelheim, Eli Lilly and Co., Ono Pharmaceutical Co., Ltd., Bristol-Myers Squibb, and Taiho (Grant) Kyoko Kato: None Toshiki Masuishi: Yakult Honsha (Personal Fees), Yakult Honsha (Grant) Kei Muro: Chugai Pharmaceutical Co., Ltd., Eli Lilly and Co., Taiho, Bayer, Takeda Pharmaceutical Co., Ono Pharmaceutical Co., Ltd., (Personal Fees) Ono Pharmaceutical Co., Ltd., Gilead Sciences, Merck Sharp and Dohme, Shionogi, Kyowa Hakko Kirin, Daiichi Sanyo, Sanofi, Phizer, Merck Serono (Grant).

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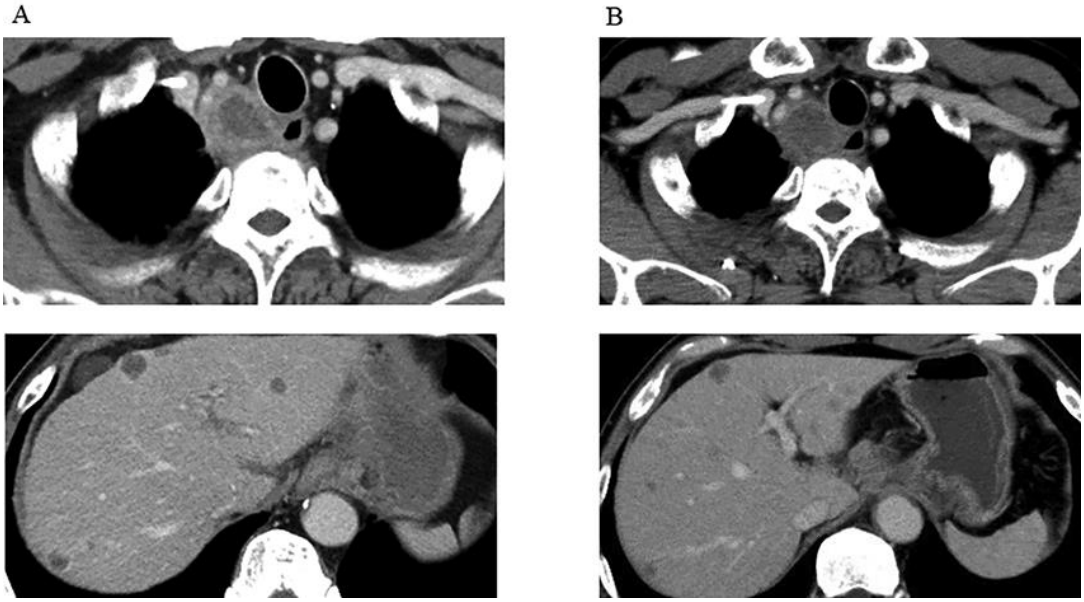

Fig. 1. Baseline computed tomography (CT) (**A**) and second follow-up CT (**B**) in case 1.

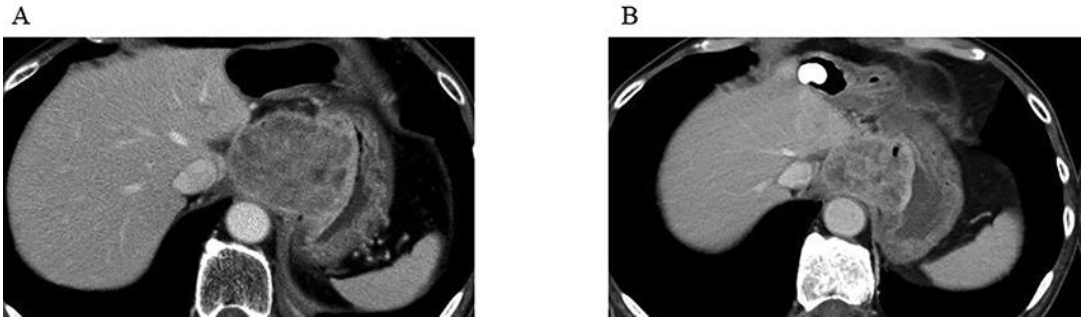

Fig. 2. Baseline computed tomography (CT) (**A**) and first follow-up CT (**B**) in case 4.