Clinical Experience with Chemoradiotherapy Comprising S-1 Plus Low-dose Cisplatin in a Patient with Stage IV Anal Cancer

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Abstract. We report a case of anal cancer in a 58-year-old woman who complained of narrow, bloody stools and anal pain. Physical examination revealed anal stenosis associated with a circular mass arising in the anal canal. Histological examination of biopsy specimens confirmed a diagnosis of moderately differentiated squamous cell carcinoma. Enhanced computed tomography revealed anal cancer invading the levator ani and the vagina, with lymph-node, multiple hepatic, and pulmonary metastases. The patient received two cycle of chemoradiotherapy with S-1 plus low-dose cisplatin with rest for 4 weeks, leading to complete response of the primary lesion and a partial response of the metastatic lesions. Each cycle included oral S-1 (120 mg/body; day1-21), cisplatin (10 mg/body; day1-5, 8-12) and radiotherapy (2 Gy/day; day1-5, 8-12, 15-19). Adverse effects of treatment were mild perineal skin erosion and mild appetite loss, but no hematologic toxicity. Although the patient died 16 months after first admission, chemoradiotherapy with S-1 plus low-dose cisplatin is potentially effective for the management of advanced anal cancer.

Anal cancer is an uncommon malignancy in Japan, as well as in Western countries (1, 2). Most cases of locoregional anal cancer can be successfully managed by chemoradiotherapy with 5-fluorouracil plus mitomycin (3, 4). Despite the effectiveness of chemoradiation for the primary treatment of anal cancer, only a few studies have documented patients who received a fluoropyrimidine-based regimen plus cisplatin, shown to provide some benefit in patients with metastatic anal cancer (5, 6).

Case Report

A 58-year-old woman complained of narrow, bloody stools and anal pain, persisting for 3 months. The patient was found to have anal stenosis associated with a circular mass arising in the anal canal. It was difficult to pass a narrow-diameter colonoscope through the anal canal, but biopsy confirmed a diagnosis of moderately differentiated SCC (Figure 1). The results of blood tests, including tumor marker levels, were within the normal range. Enhanced computed tomography (CT) revealed anal cancer invading the levator ani and the vagina, with lymph-node, multiple hepatic, and pulmonary metastases. The TNM classification was T4 N2 M1, stage IV (Figures 2-4, left panels).

We attempted a novel approach of using chemoradiation to treat stage IV anal cancer. The patient was given a detailed explanation of stage IV anal cancer and its prognosis, and informed consent for treatment was obtained. After the patient underwent a sigmoidostomy because of dyschezia and severe anal pain during defecation, chemoradiotherapy with S-1 plus low-dose cisplatin was started. Each cycle of treatment was
Figure 1. Colonoscopy showed a circular mass in the anal canal, and biopsy confirmed a diagnosis of moderately differentiated squamous cell carcinoma (H.E. 10×40).

Figure 2. An enhanced pelvic CT scan, showing a pelvic mass invading the levator ani and the vagina (left panel). After the completion of chemoradiotherapy, CT demonstrated a complete response of the pelvic tumor (right panel).
3 weeks. S-1 was administered orally at a daily dose of 120 mg/day (80 mg/m²/day) on days 1-21. Cisplatin was given as an intravenous infusion at a dose of 10 mg/day (6 mg/m²/day) over the course of 1 hour on days 1-5 and 8-12. For radiotherapy, 10 MV of X-ray radiation (Linac) was delivered to the midplane of the pelvis through the anterior and posterior portals from day 1 of chemotherapy. The target daily dose was 2 Gy, delivered 5 days per week, and the total dose per cycle was 30 Gy. The patient received two cycles of this chemoradiotherapy with rest for 4 weeks. Adverse effects of treatment were mild perineal skin erosion and mild appetite loss, but no hematologic toxicity. After chemoradiotherapy, the primary lesion and metastatic lesions except for one site of liver metastasis disappeared (Figures 2-4, right panels). Colonoscopy revealed no tumor, and no residual cancer was found in the biopsy specimens. After chemoradiation, the patient continued to receive chemotherapy with S-1 on alternate days plus weekly cisplatin.
In the ninth month after diagnosis, positron-emission tomography revealed that the primary lesion and metastases were well controlled, except for two sites in the liver and one in the lung (Figure 5). The liver metastases were considered resectable and were surgically resected in the tenth month.

Intraoperatively, metastatic tumors were found in liver segments 8 (7 cm), 4 (7 cm, 2 cm) and 3 (1.5 cm, 0.5 cm), as well as in the omentum and cecum. Extended anterior and partial hepatectomy, ileocecal resection, and resection of the omental nodules were performed. Histopathological examination of the resected specimen confirmed the lesions to be metastases from poorly differentiated SCC (Figure 6). One month after surgery, computed tomography revealed multiple metastases in the remnant liver. The recurrent lesions were refractory to chemotherapy with irinotecan, and the patient died in the 16th month after the first admission.

Discussion

The present report describes our experience with chemoradiotherapy with S-1 and low-dose cisplatin for a patient with stage IV anal cancer. This regimen was well tolerated and might be effective for anal cancer.

Although most cases of locoregional anal cancer can be successfully managed by chemoradiotherapy with 5-fluorouracil plus mitomycin (3, 4), only a few studies have shown to provide some benefit of cisplatin-based chemotherapy in patients with metastatic anal cancer (5, 6). In the present case, the Authors attempted a novel approach of chemoradiation with a combination of S-1 and low-dose cisplatin instead of a conventional regimen of infusional fluorouracil plus cisplatin. Our results showed that this regimen was well tolerated and effective against the primary
tumor, as well as the metastases from anal cancer. A previous randomized control trial demonstrated that cisplatin-based therapy failed to improve disease-free-survival as compared with mitomycin-based therapy in patients with carcinoma of the anal canal (10). However, the incidence of severe hematologic toxicity was significantly higher in the mitomycin-based group than in the cisplatin-based group. Although numerous studies have reported on treatment for locoregional anal cancer, the therapy of stage IV anal cancer has received little attention (5, 6). Our findings showed that chemoradiotherapy with S-1 and low-dose cisplatin produced a complete response of the primary lesion and a partial response of the metastatic lesions. Moreover, the patient no longer complained of anal bleeding or pain up to her death. The only adverse effects were mild perineal skin erosion and mild appetite loss, with no hematologic toxicity. The low toxicity of the S-1-based regimen is supported by the results of a recent randomized study comparing cisplatin/S-1 with cisplatin/infusional fluorouracil in advanced gastric cancer. Cisplatin/S-1 was shown to have a significantly better safety profile (11). Our findings are also supported by a recent case report by Kuga et al., documenting that chemoradiotherapy with S-1 plus low-dose cisplatin was effective for inguinal lymph node metastasis from anal canal carcinoma (12). Chemoradiation with S-1 plus low-dose cisplatin might thus be an effective treatment against both the primary tumor and metastases in patients with anal cancer.

The liver metastases refractory to chemotherapy in the present case were resected surgically since other metastatic lesions were well controlled. Unfortunately, the disease progressed rapidly after surgery. Although hepatic resection is a well-established procedure for colorectal metastatic disease, whether this procedure is indicated for patients with metastatic SCC remains controversial. Tokar et al. described

Figure 5. A positron-emission tomographic scan obtained 8 months after the completion of chemoradiotherapy, showing metastases in two sites in the liver and one in the lung.
a patient in whom repeated partial hepatectomy led to prolonged survival (13). On the other hand, Pawlik et al. reported the outcomes of 52 patients who underwent hepatic resection of metastatic SCC, including 27 patients with anal cancer. They proposed a scoring system based on three prognostic factors after surgery: i) synchronous disease, ii) hepatic metastasis size greater than 5 cm, and iii) positive surgical resection margin. These risk factors were associated with poorer overall survival in both anal and non-anal SCC (14). On the basis of their scoring system, the present case should not have undergone surgical resection.

Currently, there is no established treatment for patients with anal cancer refractory to cisplatin-based chemotherapy. Phan et al. were the first to document a patient with refractory anal canal SCC who had an excellent response to a combination of cetuximab and irinotecan (15). Lukan et al. described seven patients who received cetuximab-based treatment for metastatic anal cancer. The response to treatment was found to correlate with KRAS mutation status (16). Cetuximab is a chimeric monoclonal antibody that binds with high affinity to the extracellular domain of epithelial growth factor receptor (EGFR). SCCs such as those arising in the head and neck commonly overexpress EGFR, and the addition of cetuximab has been shown to significantly enhance survival, response rate, and disease control in patients with metastatic SCC of the head and neck (17). Molecular-targeted therapies such as cetuximab are potentially useful treatments that must be evaluated in large series of patients with metastatic anal cancer to establish their safety and efficacy.

In conclusion, our limited experience suggests that chemoradiotherapy with S-1 plus cisplatin is potentially effective for the management of advanced anal cancer. However, further studies are needed to elucidate the benefits of the present regimen for metastatic anal cancer.

References


