Complete response of a patient with advanced gastric cancer, showing Epstein-Barr virus infection, to preoperative chemotherapy with S-1 and cisplatin

Abstract Here we report the case of a patient with advanced gastric cancer with esophageal invasion who was treated with chemotherapy using S-1 and cisplatin (CDDP) preoperatively. The patient was a 72-year-old woman who was diagnosed with advanced gastric cancer (T3N2M0) with esophageal invasion. S-1 was orally administered at 80 mg/day (60 mg/m2 per day) on days 1–14 and CDDP was infused at 80 mg/day (60 mg/m2 per day) on day 8, followed by a 1-week rest. Marked reductions in the sizes of the primary tumor and metastatic lymph nodes around the stomach were observed after two cycles of the therapy. Adverse reactions occurring during the therapy were only grade 2 gastrointestinal disorder and grade 1 leukocytopenia. Radiological and endoscopic examinations before surgery showed that a partial response (PR) had been achieved. The patient underwent curative surgery consisting of total gastrectomy, D2 lymph node dissection, and splenectomy. Her postoperative course was uneventful, without surgical complications. No gastric cancer cells were detected in the primary lesion or lymph nodes by immunohistochemical staining with cytokeratin, confirming a histological complete response (CR). As Epstein-Barr virus-encoded small RNA (EBER) had been detected by in-situ hybridization in the gastric cancer cells of a biopsy specimen, this tumor was diagnosed as an Epstein-Barr virus (EBV)-associated gastric carcinoma (EBVaGC), which was effectively treated with S-1 and cisplatin chemotherapy.

Key words Epstein-Barr virus (EBV) · Gastric cancer · Complete response (CR) · Cisplatin (CDDP) · S-1 · Chemotherapy

Introduction

In Japan, gastric carcinoma is still one of the major causes of death. For the treatment of highly advanced and recurrent gastric cancer, adequate chemotherapy is expected. Neoadjuvant therapy for gastric cancer is still regarded as investigational. However, several small phase II studies have indicated the feasibility of neoadjuvant strategies. Currently, three large phase III trials of neoadjuvant therapy are under way.1

An agent that has been used for neoadjuvant therapy, S-1, consists of tegafur, gimeracil (5-chloro-2,4-dihydropyrimidine, as a dehydrogenase inhibitor, which inhibits 5-fluorouracil [5-FU] degradation), and ostaracil (monopotassium 1,2,3,4-tetrahydro-2,4-dioxo-1,3,5-trizine-6-carboxylate, for reducing the gastrointestinal toxicity caused by the phosphorylation of 5-FU).2,3 S-1 has shown a 46.5% response rate in patients with advanced gastric cancer in a phase II study.4 Because the antitumor effects of 5-FU are modulated by cisplatin (CDDP),5,6 5-FU/CDDP combination chemotherapy has been a standard therapy for gastric cancer. Combined chemotherapy using S-1 and CDDP has shown a 76.0% response rate in gastric cancer patients with primary lesions and a 72.2% response rate in those with abdominal lymph node metastasis in a phase I and II study.7

Here we present the case of a patient with advanced gastric cancer with esophageal invasion, who received modified preoperative adjuvant chemotherapy using S-1 and CDDP so that curative surgery could be achieved. Prominent inflammatory cell infiltration was noted in a gastric biopsy specimen, and Epstein-Barr virus (EBV) infection...
was suspected. Epstein-Barr-virus-encoded small RNA (EBER) was detected by in-situ hybridization (ISH); thus, the tumor was diagnosed as an Epstein-Barr-virus (EBV)-associated gastric carcinoma (EBVaGC). EBV has been reported to be associated with lymphoepithelioma-like carcinoma (LELC) of the stomach, similarly to nasopharyngeal cancer, which has the features of diffuse infiltrating nests of undifferentiated carcinoma cells surrounded by prominent lymphoid stroma. There is as yet no reported case of an EBVaGC patient who showed a histological complete response (CR) after combined chemotherapy with S-1 and CDDP. Here, we describe a rare case of a patient with advanced gastric carcinoma, with esophageal invasion, who was treated with S-1/CDDP combined chemotherapy and achieved a histological CR.

Case report

A 72-year-old woman was admitted to our hospital with the chief complaint of dysphagia. Physical examination revealed slight anemia (hemoglobin [Hb], 10.4 g/dl). Her serum levels of carcinoembryonic antigen (CEA) and carbohydrate antigen (CA) 19-9 were 0.6 ng/ml and 13.2 U/ml, respectively. Gastrointestinal fiberscopy (GIF) of the upper gastrointestinal tract showed type 3 advanced gastric carcinoma, which had invaded the lower part of the esophagus (Fig. 1a, b). A biopsy specimen revealed poorly differentiated adenocarcinoma with prominent inflammatory cell invasion. Abdominal computed tomography (CT) showed that the gastric wall was thickened, and metastatic lymph nodes were visible along the left gastric artery and lesser and greater curvatures (Fig. 2a). The patient was diagnosed with stage IIIB (cT3, cN2, cH0, cP0, cM0) advanced gastric carcinoma, according to the Japanese classification of gastric carcinoma. In an attempt to downstage the disease, modified preoperative chemotherapy was performed, using S-1 and CDDP, with the patient's informed consent. The chemotherapy schedule consisted of one cycle every 3 weeks. S-1 (Taiho Pharmaceutical, Tokyo, Japan) was administered orally, at 80 mg/day (60 mg/m² per day), every day on days 1–14. CDDP, purchased from Nihon Kayaku (Tokyo, Japan), was infused at 80 mg/day (60 mg/m² per day) on day 8, followed by a 1-week drug-free interval. After two cycles, endoscopy, CT, and GIF were performed to evaluate the

Fig. 1a–d. Gastrointestinal fiberscopy (GIF). a GIF before chemotherapy showed type 3 carcinoma. b Direct invasion of gastric carcinoma in esophagus before chemotherapy. c GIF after chemotherapy showed tumor regression. d The remaining esophageal tumor after chemotherapy.