A Case of Malignant Endocrine Tumor of the Stomach that Responded to Chemotherapy

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Abstract: A combination of cis-Dichlorodiammineplatinum (CDDP) and 5-fluorouracil (5-FU) may be used to treat gastric carcinoma and a combination of CDDP and 5'-deoxy-5-fluorouridine (5'-DFUR) is a safe and effective outpatient treatment for advanced gastric carcinoma. However, malignant endocrine tumors of the stomach such as carcinoid and endocrine cell carcinoma rarely respond to the CDDP and 5-FU combination. We treated a gastric carcinoma patient with CDDP and 5'-DFUR. Primary and metastatic lesions decreased markedly and a total gastrectomy was possible. HE staining showed that medium-sized, spindle-shaped carcinoma cells with a high N/C ratio had proliferated, to form a solid tumor. There was a massive necrotic area in the tumor, possibly the effect of chemotherapy. Grimelius staining showed argyrophilia in tumor cells, but Fontana-Masson stain was negative. Thus, this case was diagnosed as malignant endocrine cell carcinoma of the stomach.

Key words: cis-dichlorodiammineplatinum (CDDP), 5'-deoxy-5-fluorouridine (5'-DFUR), malignant endocrine tumor

Introduction

While the number of gastric carcinoma cases responding to downstaging chemotherapy with cis-dichlorodiammineplatinum (CDDP) and 5-FU analogues is increasing1-9), malignant endocrine tumors (carcinoid and endocrine cell carcinoma) rarely respond to this treatment10,11). We treated a patient, whose advanced gastric cancer was unresectable because of liver metastasis, with CDDP and 5'-deoxy-5-fluorouridine (5'-DFUR). This treatment eventually enabled resection of his primary lesion. Microscopic examination of the resected specimen was consistent with endocrine cell carcinoma.

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Case Report

The patient, a 54-year-old male, underwent upper gastrointestinal radiographs and endoscopy at another hospital because of epigastric discomfort. These examinations revealed a Borrmann type 1 tumor in the anterior wall of the upper corpus. From biopsy he was diagnosed with a poorly differentiated adenocarcinoma. Abdominal ultrasonography revealed hepatic metastatic lesions. He was admitted to Tsuboi hospital for chemotherapy. He had no signs nor symptoms of carcinoid syndrome.

Fig. 1. Upper G.I. radiograph showed Borrmann type 1 gastric carcinoma in the upper corpus (1a). Endoscopic picture of the same case (1b). Abdominal CT revealed a metastatic lesion in the liver (S4) (1c).
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Fig. 2. ×400 H.E. stain biopsy revealed middle-sized cancer cell with a high N/C ratio.

Chemotherapy Program

<table>
<thead>
<tr>
<th>CDDP 80 mg/m²</th>
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<tr>
<td>Day</td>
<td>1</td>
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<td>5'-DFUR 1200 mg/m²</td>
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Fig. 3. Chemotherapy regimen 80 mg/m² of CDDP intravenously on day 1, and 1200 mg/m² of 5'-DFUR orally on day 4-7, 11-14, 18-21, and 25-28.

The patient was 165 cm tall, weighed 51.6 kg and had a body surface area of 1.54 cm². There were no distinctly abnormal laboratory findings. An upper gastrointestinal series revealed a 5.5 cm × 4.5 cm filling defect with deep ulceration at the lesser curvature of the anterior wall of the upper corpus (Fig. 1a). An upper gastrointestinal endoscopy confirmed the presence of a Borrmann type 1 tumor (Fig. 1b). The biopsy specimen revealed the medium-sized tumor cells. The tumor cells had a high N/C ratio, and a nucleus of fine chromatin with a nucleolus. Proliferation was nodular or massive (Fig. 2), and there was poor glandular structure. While we suspected endocrine cell carcinoma, we could not confirm this because the Grimelius stain was negative in the tumor cells. So we diagnosed this case as poorly differentiated adenocarcinoma. Abdominal CT revealed hepatic metastatic lesions 2.0 cm × 1.5 cm (S8) and 5.0 cm × 4.0 cm (S4) (Fig. 1c). And therefore we elected to treat the patient without delay with CDDP and 5'-DFUR (Fig. 3). The first cycle of chemotherapy decreased the tumor to 3.6 cm × 3.0 cm (reduction rate 52%), and after the second cycle, the tumor was 3.0 cm × 3.0 cm (reduction rate 64%). After the fourth chemotherapy cycle, the primary lesion was 3.0 cm × 1.0 cm (reduction rate 79.4%), and hepatic lesions were 3.5 cm × 2.5 cm (S4, Fig. 5), and 1.0 cm × 1.0 cm (S8). Subsequently the patient was treated as an outpatient with 5'-DFUR. Since the primary tumor was near the cardiac area, we were concerned it would cause a gastrointestinal obstruction. The hepatic metastatic lesions had decreased and were not enhanced on CT examination and were therefore considered to be necrotic (Fig. 6). The patient underwent a total gastrectomy. Since the planned resection of the hepatic metastasis was not possible without injury to the patient, we administrated 250 mg of 5-FU via a catheter in the
common hepatic artery. The patient's postoperative course was uneventful and he was well until 20 months later when he died from a recurrence in the brain.

Pathology

Fig. 6 shows the 40 mm × 25 mm Borrmann type 1 lesion on the anterior wall of the upper corpus. The patient was classified as P1 N1 H2 S2 OW 55 mm AW 130 mm
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Fig. 5. X-ray of hepatic metastatic lesion before and after chemotherapy.

Fig. 6. Resected primary lesion. The 40 mm × 25 mm Borrmann type 1 lesion on the anterior wall of the upper gastric body is seen.

(Hematoxylin Eosin staining showed medium-sized spindle-shaped carcinoma cells proliferating to form a solid tumor (Fig. 7a). The N/C ratio was high. There was a marked number of mitotic figures and the carcinoma invaded vessels. Pseudorosette structures were seen (Fig. 7b). There was a massive necrotic area in the tumor, possibly the effect of chemotherapy (Fig. 8). Argyrophilia was evident in tumor cells with Grimelius staining (Fig. 9), but Fontana-Masson stain was negative. The tumor cells were negative for PAS stain. On immunological staining, carcinoma cells stained with chromogranin A (Fig. 10), but not with keratin, α-
Fig. 7  Hematoxylin-Eosin stain of the primary lesion. Medium-large, spindle-shaped carcinoma cells proliferated making a solid tumor (7a, ×40). N/C ratio of the carcinoma cells was large. Mitotic changes of carcinoma cells were remarkable and they invaded vessels. Pseudorosette structures were seen (7b, ×400).

Fig. 8  HE stain of primary lesion. There was a diffuse necrotic area in the tumor. (×40)

fetoprotein, CEA, neuron-specific enolase, serotonin, glucagon, somatostacin, nor gastrin. Thus, this case was diagnosed as endocrine cell carcinoma. The pathological stage was n1, ss, ly3, v3, OW (−), aw (−), stage 4.
Discussion

Since Preusser et al. first reported EAP therapy (Etoposide, Adriamycin, and CDDP) for advanced gastric carcinoma, CDDP has become the main treatment for advanced gastric cancer in Japan. Combination chemotherapy with CDDP and 5-FU analogues has synergistic effects without severe side effects. 5'-DFUR, a prodrug of 5-FU, is efficiently converted to 5-FU by pyrimidine nucleoside phosphorylase which has higher activity in tumor than in normal tissue. Niitani et al. reported that 4 days of 5'-DFUR administration followed by 3 days withdrawal are more effective and less toxic than daily administration. A combination of 5'-DFUR (4 days administration and 10 days withdrawal) and CDDP is effective and without side effects such as diarrhea, anorexia, renal dysfunction, and leukopenia making it suitable for outpatient care. Takemoto et al. reported a case of gastric cancer in which partial response (PR) was maintained for 30 weeks with outpatient treatment for almost the entire period (4 days administration, 10 days withdrawal). Therefore a combination of 5'-DFUR and CDDP is suitable for long-term outpatient treatment.

Endocrine cell carcinoma is a special type of gastric malignancy formerly considered a
Carcinoid is now classified into essential carcinoid, which has a good prognosis, and endocrine cell carcinoma, which progresses rapidly and has a poor prognosis. There are reports of carcinoid responding to nitrogen mustard, cyclophosphamide + methotrexate, 5-FU + streptozosin. Some studies found radiotherapy ineffective for carcinoid, but others found it effective. Hayashi et al. reported a case of carcinoid with metastasis to the liver that responded to a combination of CDDP, 5-FU, doxorubicin, and cyclophosphamide. Therefore we thought endocrine cell carcinoma might respond to a combination of CDDP and 5-FU analogues. We treated this case as a common type gastric carcinoma, because in the initial biopsy the histology was poorly differentiated adenocarcinoma. The lesion decreased with chemotherapy and became resectable; histopathology was consistent with endocrine cell carcinoma. Although the patient died from a recurrence to the brain twenty months after surgery (3 years and 4 months after onset) he was treated as an outpatient throughout that period. We conclude that combination chemotherapy of CDDP and 5'-DFUR may be useful in malignant endocrine tumor of the stomach.

References


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