Chemotherapy Treatment of a Pregnant Woman with Progressive Gastric Cancer

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Abstract

We herein describe a rare case of gastric cancer that was treated with chemotherapy during pregnancy. A woman in her thirty’s at 23 weeks of gestation was admitted to the hospital with epigastralgia and left cervical lymph node swelling. She had been previously diagnosed with metastatic adenocarcinoma at another hospital. Findings from a CT scan and esophagogastroduodenoscopy revealed progressive gastric cancer, and the pathology indicated poorly differentiated adenocarcinoma. Chemotherapy was administered at 24 weeks of gestation, without the development of severe toxicity. At 32 weeks of gestation, a healthy baby girl (birth weight 1,442 g, Apgar score 7/8) was delivered by caesarean section. The child continued to show no abnormalities at 12 months after delivery.

Key words: gastric cancer during pregnancy, chemotherapy, S1, paclitaxel


Introduction

Gastric cancer during pregnancy is a rare event. Only five reports have mentioned the use of chemotherapy for the treatment of gastric cancer during pregnancy. Due to the limited information available, it is very difficult to surmise whether chemotherapy should be administered in such cases. We herein report on a case of a pregnant woman diagnosed with gastric cancer who, following treatment with chemotherapy, delivered an evidently healthy, normal child. We believe that this report will provide assistance, and serve as a reference, for other physicians who are confronted with a similar decision.

Case Report

The patient was a nulliparous woman in her thirty’s at 23 weeks of gestation who presented initially with epigastralgia and left cervical lymph node swelling. The swelling of the left cervical lymph node was diagnosed as metastatic adenocarcinoma at another hospital. Concomitantly, she was seen at our hospital after developing left back pain.

Laboratory findings indicated anemia, hypoproteinemia, and high serum levels of carcinoembryonic antigen (CEA) and carbohydrate antigen (CA) 19-9 (Table 1). A CT scan showed left cervical lymph node swelling, gastric wall thickening, left hydronephrosis accompanied by decreased left renal blood flow, bilateral adnexal swelling, pericardial effusion, ascites, and multiple metastatic bone tumors (Fig. 1). Esophagogastroduodenoscopy revealed type 4 gastric cancer located from just below the cardia to the antrum. A pathological analysis of the biopsy specimen determined that it was poorly differentiated adenocarcinoma, with no overexpression of human epidermal growth factor receptor type 2 (HER2) (Fig. 2).

Prior to choosing the course of treatment, the condition of both the patient and the fetus were considered. The patient was emaciated, and had a low performance status and pain resulting from the advanced cancer, thus indicating that she required general chemotherapy as soon as possible. While the fetus was developing normally, delivery at this stage of
gestation would endanger its life and could cause serious sequela, therefore it was considered preferable to wait until at least 28 weeks of gestation for delivery. Given this situation, it was decided to administer chemotherapy during pregnancy until it was deemed safe for delivery of the fetus. Because of the contraindication for chemotherapy during pregnancy, the potential risks and benefits were discussed with the patient; she gave her informed consent, and the institutional review board of our hospital approved the treatment. In Japan, the standard treatment regimen for gastric cancer is the combination of tegafur, gimeracil, oteracil (S1) and cisplatin (CDDP), however, prehydration in preparation for CDDP therapy can worsen hydronephrosis, ascites, and pericardial effusion. Therefore, in this case, a regimen of paclitaxel

Table 1. Laboratory Data on Admission.

<table>
<thead>
<tr>
<th>Hematology</th>
<th>Biochemistry</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC 8,400 /µL</td>
<td>TP 5.50 g/dL</td>
</tr>
<tr>
<td>RBC 353 ×10¹¹/µL</td>
<td>Alb 2.90 g/dL</td>
</tr>
<tr>
<td>Hb 10.3 g/dL</td>
<td>Na 137 mEq/L</td>
</tr>
<tr>
<td>Plt 16.9 ×10¹¹/µL</td>
<td>K 3.6 mEq/L</td>
</tr>
<tr>
<td>Serology</td>
<td>Cl 107 mEq/L</td>
</tr>
<tr>
<td>CRP 3.8 mg/dL</td>
<td>T-Bil 0.52 mg/dL</td>
</tr>
<tr>
<td></td>
<td>D-Bil 0.08 mg/dL</td>
</tr>
<tr>
<td>Coagulation test</td>
<td>ALP 1,225 IU/L</td>
</tr>
<tr>
<td>PT 114 %</td>
<td>AST 15 IU/L</td>
</tr>
<tr>
<td>APTT 24.2 %</td>
<td>ALT 6 IU/L</td>
</tr>
<tr>
<td>Fib 535 mg</td>
<td>LDH 221 IU/L</td>
</tr>
<tr>
<td>FDP 11.5 µg/dL</td>
<td>γGTP 8 IU/L</td>
</tr>
<tr>
<td>D-dimmer 6.00 µg/dL</td>
<td>Amy 48 IU/L</td>
</tr>
<tr>
<td>Tumor marker</td>
<td>BUN 5.1 mg/dL</td>
</tr>
<tr>
<td>CEA 141.1 ng/mL</td>
<td>Cre 0.75 mg/dL</td>
</tr>
<tr>
<td>CA19-9 1,200 IU/L</td>
<td>Glucose 87 mg/dL</td>
</tr>
</tbody>
</table>

RBC: red blood cell, Plt: Platelet, CRP: C-reactive protein, PT: prothrombin time
Fib: fibrinogen, APTT: activated partial thromboplastin time, FDP: fibrin degradation product
CEA: carcinoembryonic antigen, CA19-9: carbohydrate antigen 19-9, TP: total protein
ALP: alkaline phosphatase, AST: aspartate aminotransferase, ALT: alanine aminotransferase
LDH: lactate dehydrogenase, γGTP: γ-glutamyl transpeptidase, Amy: Amylase
BUN: blood urea nitrogen, Cre: creatinine

Figure 1. CT scan findings on admission. a: left cervical lymph node swelling. b: gastric wall thickness. c: left hydronephrosis and decreased left renal blood flow. d: bilateral adnexal swelling, pericardial fluid, and ascites.
(PTX) and S1 was elected for treatment.

The patient received the first cycle of S1 (100 mg/body) and PTX (50 mg/m²) five days after the diagnosis of stage 4 gastric cancer was confirmed (at 24 weeks of gestation). S1 treatment was continued daily from day 1 to day 14, and PTX therapy was administered on day 1 and day 8. One cycle lasted for 15 days. The patient developed temporary peripheral neuropathy, and mild intrauterine growth retardation (IUGR) of the fetus was observed, but no severe physical or hematological toxicities developed. During the 2 cycles of treatment, the patient’s ascites did not decrease, however the back pain and serum levels of CEA and CA19-9 improved. Since the fetus was developing almost normally, and delivery was planned at 34 weeks of gestation. Three days prior to delivery the chemotherapy treatment was discontinued and on day 66 of hospitalization, a healthy girl weighing 1,442 grams was delivered via cesarean section. The histological examination of the placenta showed no evidence of metastasis. The infant’s Apgar score was 7/8. Although the infant required temporary artificial respiration, the infant’s development was normal, and she was discharged from the hospital with no physical or hematological abnormalities.

The patient resumed chemotherapy 11 days after delivery at which time the treatment was changed to the standard chemotherapy regimen of S1 and CDDP. The treatment cycles were repeated every 4 weeks. Three cycles after resumption of therapy, the pericardial effusion worsened resulting in the development of cardiac tamponade and drainage of pericardial fluid was performed. At this time, the chemotherapy regimen was changed to weekly PTX (every 4 weeks), however, the patient developed a refractory headache, and a diagnosis of carcinomatous meningitis was made. Although immediate whole-brain and spinal irradiation therapy was planned, the patient died 191 days after the start of treatment. The complete therapeutic course is illustrated in Fig. 3. The baby displayed no physical or hematological abnormalities at 12 months after delivery.

Discussion

The incidence of cancer during pregnancy is approximately 0.1% (1), and that of gastric cancer is lower at 0.026 to 0.1% of all pregnancies (2). Therefore, there are few reports of gastric cancer during pregnancy originating from countries other than Japan. Sakamoto et al. reviewed 137 cases reported by Japanese institutions and analyzed each patient’s clinical background characteristics, pathology, treatment, obstetric management and prognosis (3). The investigators identified the following as characteristics of gastric cancer during pregnancy: 1) the most common macroscopic feature was of the infiltrative type; 2) on pathological evaluation, the diffuse type was more common than the intestinal type; and 3) the maternal prognosis was extremely poor, with 1- and 2-year survival rates of 18.0% and 15.1%, re-

Figure 2. Findings of esophagogastroduodenoscopy on admission. a: esophago-gastric junction view from the oral side. b: view of cardia inverted from the anal side. c: same angle, closer view. d: anterograde view of cardia.
Two factors worsen the prognosis of pregnant patients: the characteristics of the pregnancy-associated gastric cancer and delayed diagnosis. On pathological examination, the aforementioned diffuse type with signet-ring cells is the most common pathological type of gastric cancer. Estrogen, which is increased during pregnancy, suppresses the growth of intestinal gastric cancer, but promotes growth of the diffuse type (4, 5). Therefore, pregnancy-associated gastric cancer progresses faster than in other time periods. Additionally, the diagnosis of gastric cancer is often delayed in pregnant women because it is difficult to distinguish between symptoms of gastric cancer and common pregnancy-induced symptoms, such as the hyperemesis and pressure resulting from the enlargement of the uterus. Furthermore, the physician and patient are often hesitant to conduct diagnostic examinations during pregnancy (2, 4-6).

Chemotherapy of unresectable gastric cancer during pregnancy is very complicated, because there are two conflicting aspects to consider. One aspect is the importance of administering chemotherapy as early as possible post diagnosis to increase the possibility of successfully treating the mother. Another aspect is the importance of continuing the pregnancy as long as possible to ensure healthy fetal development and the safety of the fetus.

Ueno et al. (2) reported that the treatment of pregnancy-associated gastric cancer depends on the stage of gastric cancer and on the stage of fetal development at the time of diagnosis. When gastric cancer is diagnosed prior to 22 weeks of gestation, the mother should be treated after termination of the pregnancy by abortion. After 28 weeks of gestation, treatment should be administered after early delivery. However, there are no clear recommendations for the management of gastric cancer-associated pregnancy from 22 to 28 weeks of gestation, as in the present case. In such cases, the condition of both the mother and fetus must be carefully considered, and an individualized management plan may be required.

According to previous reports (2, 3), the treatment of early gastric cancer during pregnancy, especially between 22 and 28 weeks of gestation, might be postponed until 28 to 30 weeks of gestation or be administered after delivery. Within the same time period, operable advanced gastric cancer might be operated on as early as possible. However, in cases of inoperable gastric cancer, the use of chemotherapy during pregnancy needs to be established.

The use of chemotherapy during the first trimester increases the risk of spontaneous abortion, fetal death, and major malformations; therefore, no chemotherapeutic agent is recommended during this time period (1, 4, 6-9, 12). However, after the second trimester, Pentheroudakis et al. reported that there was no major difference in the incidence rate of malformations or IUGR between infants from normal pregnancies and those from pregnancies in which chemotherapy was administered (8). Additionally, many reports indicate that the use of chemotherapy after the second trimester is relatively safe (1, 7-12), suggesting that while chemotherapy is not recommended, it can be practically administered.

The standard regimen for gastric cancer in Japan is the combination of S1 and CDDP, but there is no standard regimen during pregnancy. There are only five reports, including the present case, and proceedings, that mention the use of chemotherapy for gastric cancer during pregnancy, four from Japan (6, 13, 14) and one from Turkey (15). These five cases are shown in Table 2. All regimens were combination therapy, and four contained S1 and the other contained fluorouracil (5-FU). All regimens from Japan were a combi-
nation of a taxane anticancer agent and S1. The regimen from Turkey was a combination of 5-FU and folinate (LV). The difference between these regimens most likely arises from the differences in the standard treatment regimen for gastric cancer between Japan and other countries. In Japan, S1 became the key drug in gastric cancer treatment regimens following the Japan Clinical Oncology Group (JCOG) 9912 trial which demonstrated that S1 is not inferior to 5-FU (16). Additionally, the findings from two phase II studies suggested that S1 plus PTX is an effective regimen for advanced gastric cancer treatment (17, 18).

In Japan and other countries, the standard treatment regimen for gastric cancer typically contains platinum, primarily CDDP. However, in the four cases from Japan, all regimens contained taxanes, not platinum, along with S1. The pathology of all cases, except for one that was unknown, was poorly differentiated or showed signet-ring cells. Thus, the taxane was likely administered to prevent worsening of carcinomatous peritonitis, ascites, or pleural effusion that often results from the diffuse type of gastric cancer. In addition, taxanes may have been chosen for use in these four cases following reports that indicate taxanes are more effective against the diffuse type of gastric cancer compared to other anticancer agents, not only with single use, but also in combination with S1 (19-22). Owing to the limited reports of taxane use (1, 9) during pregnancy, Cardonick et al. concluded that their use during human pregnancy is not recommended, but also mentioned that this recommendation could change as more cases of exposure are published (1). For this reason, the data regarding the use of taxanes during pregnancy is herein presented; all children, except for one unreported case, did not show any abnormality at six months old. For this reason, the data regarding the use of taxanes during pregnancy is herein presented; all children, except for one unreported case, did not show any abnormality at six months old.

### Table 2. Case reports that mentioned the use of chemotherapy for gastric cancer during pregnancy.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age (y)</th>
<th>Period of treatment (gestational weeks)</th>
<th>Pathology</th>
<th>Regimen*</th>
<th>Appgar Score</th>
<th>Birth weight (g)</th>
<th>Outcome of child</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>22</td>
<td>25-28</td>
<td>Signet-ring cell</td>
<td>DTX+S1</td>
<td>8/9</td>
<td>2,112</td>
<td>no abnormality at three years old</td>
</tr>
<tr>
<td>14</td>
<td>26</td>
<td>26-37</td>
<td>Unknown</td>
<td>S1+PTX</td>
<td>unknown</td>
<td>2,493</td>
<td>no abnormality when reported</td>
</tr>
<tr>
<td>15</td>
<td>25</td>
<td>30-37</td>
<td>Poorly differentiated</td>
<td>S1+PTX</td>
<td>8/9</td>
<td>2,430</td>
<td>no abnormality when reported</td>
</tr>
<tr>
<td>13</td>
<td>26</td>
<td>29-29</td>
<td>Unknown</td>
<td>5FU+LV</td>
<td>3/5</td>
<td>930</td>
<td>unknown</td>
</tr>
<tr>
<td>Present case</td>
<td>30</td>
<td>24-32</td>
<td>Poorly differentiated</td>
<td>S1+PTX</td>
<td>7/8</td>
<td>1,442</td>
<td>no abnormality at six months old</td>
</tr>
</tbody>
</table>

*DTX: docetaxel, PTX: paclitaxel, S1: tegafur+gimeracil+oteracil
5FU: fluorouracil, LV: folinate

### References


The authors state that they have no Conflict of Interest (COI).


