mFOLFOX-based Chemotherapy Can Augment Survival in Advanced Gastric Cancer with Disseminated Intravascular Coagulation
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ABSTRACT

Although gastric cancer is a frequent cancer type, disseminated intravascular coagulation is a very rare but serious complication of this disease. We report a 65-year-old man who complained of weight loss, nausea and vomiting, fatigue and dyspnea for three days. He was diagnosed as advanced gastric cancer (AGC) complicated with disseminated intravascular coagulation (DIC) which was successfully treated with mFOLFOX chemotherapy regimen. After one cycle of mFOLFOX therapy, thrombocytopenia was improved and serum LDH levels decreased. Remarkable remission was seen after 12 cycles of chemotherapy in the primary tumor and multiple metastatic bone lesions.

Keywords: Advanced gastric cancer; disseminated intravascular coagulation; mFOLFOX-based chemotherapy

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INTRODUCTION
Gastric cancer is the fifth most common cancer and the second most common cause of cancer deaths worldwide (1). Disseminated intravascular coagulation (DIC), a clinicopathological syndrome which always occurs as a consequence of an underlying disease, is a rare and serious complication of this disease, with an incidence rate of 1.6% (2, 3, 4). It may cause thrombotic complications or a fulminant course with widespread bleeding and serious organ dysfunctions.

The major causes of DIC are sepsis, serious trauma, obstetric complications and neoplasms such as gastrointestinal, pancreatic, liver, ovarian, breast, lung and prostatic carcinomas (5). The prognosis of advanced gastric cancer (AGC) with acute DIC is extremely poor and survival time is usually no more than one month despite best supportive care (6).

Here, we present a case of disseminated intravascular coagulation diagnosed as advanced gastric cancer treated with mFOLFOX-based chemotherapy. He had survived for about one year.

CASE REPORT
A 65-year-old man was admitted to the emergency room with weight loss, nausea, vomiting and fatigue for last month and dyspnea for last three days. His Eastern-Cooperative-Oncology-Group status was 3. Arterial blood pressure was 170/110 mmHg, pulse rate was 116/min, respiratory rate was 28/min and oxygen saturation was 85% in the room air. In physical examination; skin and conjunctivas were pale, liver was palpable and bilateral pretibial edema (++) was observed. Hemoglobin level was 7.7 g/dl, leukocyte number was 9,400/mm$^3$ and platelet number was 59,000/mm$^3$ in blood count. Liver function tests showed
albumin of 2.6 g/dl, total bilirubin of 1.5 mg/dl, aspartate aminotransferase of 98 IU/L, alanine aminotransferase of 34 IU/L and alkaline phosphatase of 546 IU/L. Lactate dehydrogenase level was 1,373 IU/L, Prothrombin time was 18.5 sc with 1.53 international normalized ratio, aPTT was 37.7 sc, fibrinogen level was 197 mg/dL, D-Dimer level was 6,786 ng/mL. Peripheral smear showed thrombocytopenia, fragmentations of erythrocytes and reticulocytosis. The patient was diagnosed as DIC with present findings.

Pathological examination of gastric biopsy showed signet ring cell adenocarcinoma. Tumor marker levels were CEA 115 ng/mL, CA19-9 1303 U/mL. Initial positron emission tomography-computed tomography (PET-CT) scan showed gastric cancer in the pyloric end, multiple liver, bilateral adrenal and widespread bone metastasis in the maximum intensity projection (Figure 1A). Under supportive therapy and replacement transfusions with thrombocyte and erythrocyte suspensions and fresh frozen plasmas, platelet number and hemoglobin level were decreased to 36,000/mm$^3$ and 7.8 g/dL, respectively. mFOLFOX was given which was composed of oxaliplatin 85 mg/m$^2$, leucovorin 400 mg/m$^2$ d1 followed by 400 mg/m$^2$ bolus 5-FU and a 46-hr 2,400 mg/m$^2$ 5-FU infusion which were repeated every 2 weeks for 12 cycles. After the administration of first chemotherapy, the hematologic and biochemical parameters improved and there was no evidence of DIC. At the end of 12 cycles of chemotherapy, PET-CT scan showed nearly complete remission of gastric cancer and metastatic areas. (Figure 1B). CEA and CA-19-9 levels decreased to 5 ng/mL and 78 U/mL, respectively. During chemotherapy, no serious adverse effects were observed. Following with partial response, the patient lived 14 months and died due to cancer progression.
DISCUSSION

DIC, in which coagulation system is activated and widespread intravascular coagulation appears (4), is a rare and serious complication of gastric cancer. DIC always occurs as a consequence of an underlying disease and has an uncertain course from asymptomatic disease to a fulminant course with widespread bleeding and serious organ dysfunctions (5, 7). DIC associated with gastric adenocarcinoma occurs through the exacerbation of the blood clotting process by which procoagulant materials such as mucin extracts derived from tumor cells directly stimulate coagulation factor X or damage red blood cells and platelets by direct contact with tumor cells on microvessels (8). There is the evidence of consumption and proteolytic degradation in DIC. The common laboratory abnormalities in chronic DIC in solid tumors include thrombocytopenia and circulating fibrin degradation products. Microangiopathic hemolytic anemia may occur in the absence of other DIC laboratory abnormalities, usually in association with disseminated mucin-secreting adenocarcinoma (9).

Initial presentation of DIC with gastric cancer has a poor prognosis. Supportive treatment such as replacements of platelets and erythrocytes, fresh frozen plasma transfusions has a little effect in DIC. In a study which included AGC patients who initially present with DIC, the median survival time (MST) was only 16 days with best supportive care, but significantly longer with 98 days in patients who received systemic chemotherapy. This study suggested that systemic chemotherapy is the only effective therapy for DIC caused by malignancy and that chemotherapy treatment prolongs MST (10). Similarly, when we administered supportive therapy to our patient, the hematologic and biochemical parameters got worsen.

The optimal treatment option for DIC is management of underlying disease (4). For this reason, to improve DIC in AGC, combination chemotherapy is the accurate option. Cisplatin and 5-FU are the most commonly used drugs in combination (11). But in such patients, it is a
complicated situation to perform combination chemotherapy because of DIC induced thrombocytopenia and bleeding. Even though many studies have been made to determine the best agent, it is still unclear which agent is better (12). In our clinic, we generally prefer to admit docetaxel, cisplatin, 5-FU (DCF) in AGC. Because of the general status of our patient and the instability of laboratory parameters, we preferred mFOLFOX instead of DCF. mFOLFOX therapy is an effective and tolerable regimen in AGC even in patients with impaired general status (13). In our case, we observed that administration of mFOLFOX regimen improved DIC, provided partial remission of malign mass of stomach, bilateral pleural effusion and metastasis of liver, bones and bilateral surrenal glands. Most of the studies about gastric cancer accompanied DIC included small numbers of patients (between 5 and 18) as this circumstance is rare (14). Furthermore, there have been few studies comparing prognosis between patients who receive best supportive care and palliative chemotherapy (8).

With this case, we observed that applying early and dense chemotherapy could improve DIC and augment survival in AGC accompanied DIC. However, more effective and less toxic regimens are needed to be investigated in further studies.
REFERENCES


Figure 1. (A) Initial positron emission tomography-computed tomography (PET-CT) scan showed gastric cancer in the pyloric end, multiple liver, bilateral adrenal and widespread bone metastasis in the maximum intensity projection. (B) After 12 cycles of mFOLFOX-based chemotherapy, follow up PET-CT scan showed nearly complete remission of gastric cancer and metastatic areas.