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Capecitabine and Oxaliplatin (XELOX) for the Treatment of Patients with Metastatic Gastric Cancer and Severe Liver Dysfunction

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Gastric cancer patients with severe liver dysfunction secondary to hepatic metastases have limited treatment options. Most cytotoxic drugs have a narrow therapeutic index. Although both capecitabine and oxaliplatin have been well tolerated as single agents for patients with severe hepatic dysfunction, the combination of these drugs has not been investigated. We report here on a case of successful treatment of a patient suffering with severe liver dysfunction and metastatic gastric cancer; the patient was treated with a combination of capecitabine and oxaliplatin (XELOX). The initial bilirubin level of the patient was 10.9 mg/dL. After two cycles of treatment, his bilirubin level decreased to 2.1 mg/dL. He has experienced an excellent radiological response and he has received six cycles of XELOX chemotherapy. XELOX chemotherapy is feasible and it can be associated with positive outcomes for the patients suffering with metastatic gastric cancer and severe liver dysfunction.

Key Words : Gastric Cancer, Liver Failure, Capecitabine, Oxaliplatin

INTRODUCTION

Gastric cancer is the most prevalent malignant tumor and the second leading cause of cancer-related death in Korea[1]. The benefit of systemic chemotherapy for treating advanced gastric cancer in the palliative setting has long been known. When compared with the best supportive care alone, combination chemotherapy yields a significant advantage for the management of advanced gastric cancer[2, 3]. However, most of the previous clinical trials have excluded patients with impaired hepatic function. Gastric cancer patients with severe liver dysfunction secondary to hepatic metastases have limited treatment options. Administration of chemotherapy to gastric cancer patient with liver dysfunction requires careful consideration.

Capecitabine is an oral prodrug that is metabolized to 5-fluorouracil (5-FU), and it has clinical activity that mimics infused 5-FU. Capecitabine is readily absorbed from the gastrointestinal tract and it is activated through a series of enzymatic reactions that occur first in the liver and subsequently in most tissues, including the tumor tissue, to create the active drug 5-FU. A previous study demonstrated no clinically significant influence on the pharmacokinetic parameters of capecitabine or its metabolites in the setting of hepatic dysfunction[4].

Third-generation platinum oxaliplatin has been well tolerated by the patients with all levels of hepatic failure, and that liver dysfunction caused no apparent alteration in the clearance of platinum species from the plasma. There were no dose-limiting events at the maximum tested dose levels[5]. However, the safety of these combination chemotherapies for patients suffering with severe liver dysfunction has not been established.

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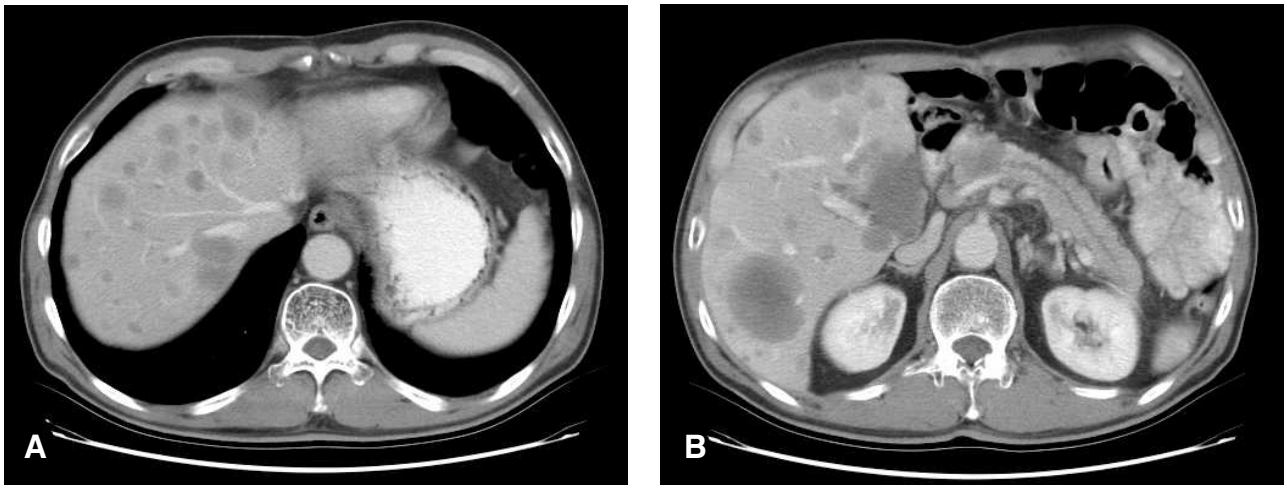

Figure 1. CT scan of the abdomen. (A and B) Multiple variable-sized metastatic nodular lesions are seen in the entire liver.

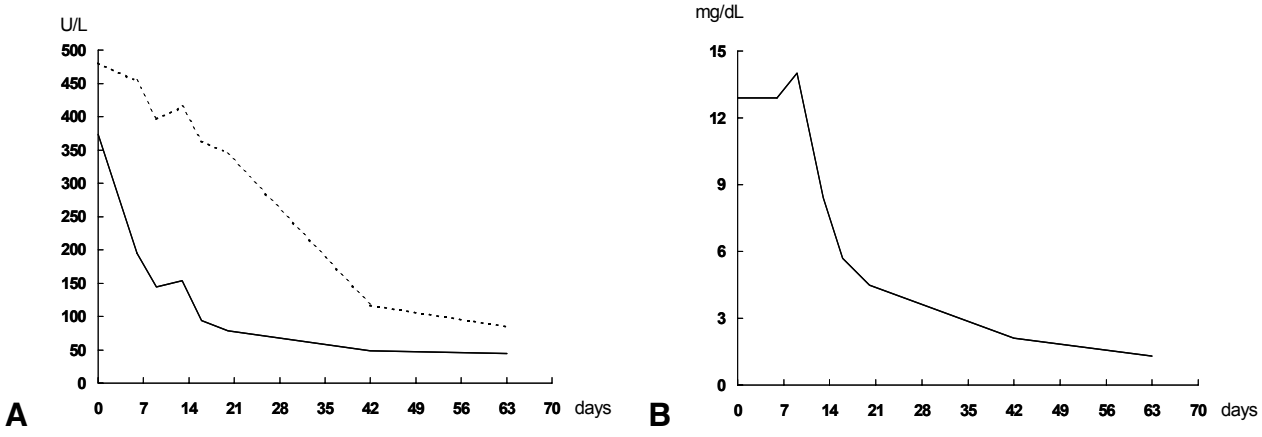

Figure 2. (A) Decreasing levels of serum alkaline phosphatase (SAP) and alanine amino transferase (ALT) (－: SAP, : ALT). (B) Decreasing level of serum total bilirubin after the 4th cycle of chemotherapy.

Table 1. Liver function tests during treatment period

Parameters	Day 1	Day 7	Day 14	Day 21	Day 42	Day 63
Bilirubin (0.2～1.2 mg/dL)	12.9	12.9	8.4	4.5	2.1	1.3
LDH (200～400 U/L)	2133	1713	2854	1035	390	375
AST (～40 U/L)	214	166	238	81	32	32
ALT (～40 U/L)	373	195	154	78	48	44
GGT (11～49 U/L)	353	261	176	88	41	41
ALP (44～128U/L)	480	454	414	345	116	85

*LDH, lactate dehydrogenase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyltransferase; ALP, alkaline phosphatase

We report here on a case of gastric cancer with advanced liver metastases and severe hepatic dysfunction that was treated with XELOX chemotherapy.

CASE REPORT

A 62-year-old man was admitted due to his recent jaundice and abdominal distention. He was diagnosed about 2 years ago with gastric adenocarcinoma and he underwent radical subtotal

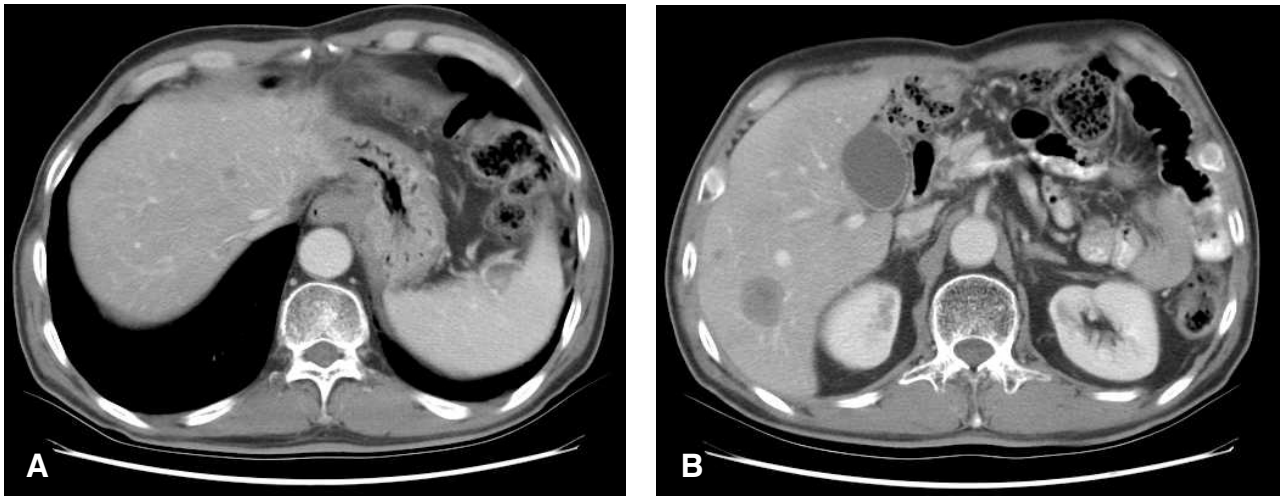

Figure 3. (3A and 3B) Markedly decreased metastatic liver nodules after the 4th cycle of chemotherapy (A and B).

gastrectomy. After surgery, he received five cycles of adjuvant chemotherapy with 5-FU and leucovorin. A physical examination showed his height to be 170 cm and the body weight was 68 kg. The condition of the chest and heart was normal. His vital signs were within normal limits. His sclera was deep icteric, but he showed neither hepatomegaly nor right upper quadrant tenderness. The neurological examination was normal. There were no specific findings on the occupational, familial and social histories. The laboratory tests on admission showed an elevated level of serum total bilirubin to 10.9 mg/dL (normal level: 0.3～1.2 mg/dL), a direct bilirubine of 8.5 mg/dL (normal level: 0～0.2 mg/dL), alanine aminotransferase of 374 U/L (normal level: 10～40 U/L), alkaline phosphatase of 480 U/L (normal level: 20～100 U/L) and lactate dehydrogenase of 2,133 U/L (normal level: 208～378 U/L). An abdominal and pelvic CT scan was performed to verify the biliary obstruction and metastatic lesions in the abdominal cavity, including the liver and biliary system. CT scan of the abdomen showed multiple metastatic nodules in the liver with no evidence of biliary tree obstruction (Figure 1). The diagnosis of the patient was confirmed to be recurrent gastric cancer with advanced liver metastases and severe hepatic dysfunction. His performance status was estimated to be ECOG 2. Given his poor liver function, the patient was treated with oxaliplatin (130 mg/m^2) on day 1 and capecitabine (1,000 mg/m^2 orally twice daily) on days 1～14 of a 21-day cycle. After the first cycle of chemotherapy, his total bilirubin dropped to 4.5 mg/dL. After two cycles of chemotherapy, his total bilirubin and alkaline phosphatase decreased to near normal levels at 2.1 mg/dL and 116 U/L, respectively. No treatment-related grade 3 or above toxicities were noted during the first 4 cycles of treatment. He continued to well tolerate chemotherapy with excellent performance and normalization of all the liver enzymes (Table 1 and Figure 2). He displayed a major radiological response on the follow-up CT scans (Figure 3); he has received 5 cycles of XELOX with ongoing clinical benefit.

DISCUSSION

Advanced cancer in the setting of hepatic dysfunction poses a dilemma for physicians, as many cancer chemotherapeutic agents undergo hepatic metabolism. Most cytotoxic drugs have a narrow therapeutic index and the administration of chemotherapy to patients with liver impairment results in complicated safety issues. The treatment of patients with severe liver dysfunction secondary to metastatic gastric cancer is controversial. These patients have a limited performance status and they are at an increased risk for chemotherapy-related complications.

The benefits of systemic chemotherapy for advanced gastric cancer in the palliative setting are known. Several randomized trials have demonstrated that 5-FU-based chemotherapy is superior to the best supportive care in terms of survival and preservation of the quality of life[3, 6]. Unfortunately, most clinical trials have excluded patients with impaired hepatic function; much of what is known about individual chemotherapeutic agents in the setting of liver failure is based on small, retrospective studies. Very few agents have undergone formal phase I testing in a liver dysfunction group of patients, and empirical guidelines are frequently used in clinical practice. Furthermore, there is no standardized system for defining liver dysfunction in patients suffering with cancer. The serum total bilirubin level is the most commonly used marker to assess the need for chemotherapy dose adjustments, but this represents a

simplified strategy. Thus, there are many potential hazards that are involved in administering cancer chemotherapy to patients with impaired hepatic impairment.

The Organ Dysfunction Working Group of the National Cancer Institute performed a phase I and pharmacokinetic trial of oxaliplatin for patients who displayed a wide range of liver function abnormalities[5]. That study demonstrated that oxaliplatin was well tolerated at its recommended dose and schedule of 130 mg/m^2 every 21 days for patients with all levels of liver dysfunction, and there was no apparent alteration in the clearance of either the total or ultrafilterable platinum species from the plasma, even in patients with severe hepatic functional abnormalities. There were no dose-limiting events at the maximum dose level tested. Unfortunately, they did not report the median or range for the total bilirubin level in the severe liver dysfunction group.

Capecitabine is a novel oral fluoropyrimidine carbamate that is preferentially converted to the cytotoxic moiety 5-FU in target tumor tissue via a series of three metabolic steps. It is catabolized by dihydropyrimidine dehydrogenase, which is the initial, rate-limiting enzyme in 5-FU catabolism. A study of 14 patients with normal liver function and 13 patients with abnormalities on their liver function tests due to liver metastases demonstrated no clinically significant influence on the pharmacokinetic parameters of capecitabine or its metabolites in the setting of hepatic dysfunction (mean bilirubin: 12 mg/dL, range: 0.9～28.3 mg/dL)[4].

In another report, a woman with metastatic breast cancer and severe liver dysfunction (total bilirubin: 12 mg/dL) achieved a partial response after seven cycles of capecitabine at 2,500 mg/m^2/d in two divided doses for 2 weeks and this was followed by 1 week of rest[7].

Park and colleagues[8] have recently conducted a phase II trial of oxalipatin-capecitabine (XELOX) for patients with nonresectable advanced gastric cancer. Of the 20 evaluable patients, one achieved a complete response and 11 achieved partial responses for an overall response rate of 60%. The median progression-free survival was 7.5 month and overall survival was not reached during the study period. The combination was well tolerated with only mild toxicities reported.

Metastatic gastric cancer patients with severe liver dysfunction have a poor median survival that is estimated in weeks. We treated a patient with severe liver dysfunction secondary to metastatic gastric cancer with the XELOX regimen. The patient had extensive liver disease and a high bilirubin level (total bilirubin: 12.9 mg/dL). The patient obtained major clinical benefit as demonstrated by the improvement of his performance status and the resolution of jaundice within 3 weeks from treatment initiation. Laboratory testing demonstrated gradual improvement in the liver function as early as 3 weeks after the administration of the first cycle of XELOX chemotherapy. No increased toxicities were noted during the first four cycles of treatment. He has received the 5th cycle of XELOX with ongoing clinical benefit.

This report supports the safety of XELOX for treating patients with severe liver dysfunction secondary to liver metastasis. This regimen was associated with significant clinical benefit and it should be considered when treating patients suffering with metastatic gastric cancer together with severe liver dysfunction.

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