Safety and Efficacy of FOLFOX Followed by Cetuximab for Metastatic Colorectal Cancer With Severe Liver Dysfunction

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Abstract
Both 5-FU and oxaliplatin have been used as single agents in patients with colorectal cancer and severe liver dysfunction, but the combination of these drugs has not yet been investigated. A 67-year-old man diagnosed with colorectal cancer in 2008 presented in April 2011 to Appalachian Regional Healthcare Cancer Center with obstructive jaundice and weight loss. Imaging studies were compatible with a liver mass and dilatation of the intrahepatic bile ducts. A liver biopsy confirmed metastatic colorectal cancer. Because his total bilirubin level was 23.1 mg/dL, a percutaneous catheter was placed in May 2011. His total bilirubin level decreased to 5.9 mg/dL, but then increased to 9.4 mg/dL in June 2011. He was started on a FOLFOX regimen, with a 50% dose reduction of 5-FU bolus (200 mg/m²) and continuous infusion (1200 mg/m²) over 46 hours, and a 15% dose reduction of oxaliplatin (75 mg/m²) every 2 weeks. He tolerated this regimen very well, with normalization of his bilirubin level, a significant decrease in his tumor markers, and a partial response seen on PET/CT scan. His only significant toxicity was a grade 2 stomatitis. He received 21 cycles of FOLFOX, and was later switched to cetuximab treatment after disease progression. These findings suggest that FOLFOX might be effective in metastatic colon cancer with severe liver dysfunction, with minimal toxicity, and deserves further investigation. (J Natl Compr Canc Netw 2014;12:155–160)

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Background
Colorectal cancer (CRC) is the third most common cancer worldwide. The liver is the most frequent site of metastatic CRC (mCRC). Patients with liver metastases and liver injury usually show poor prognosis.

Standard treatment for mCRC includes infusion of 5-FU plus leucovorin and oxaliplatin (FOLFOX) or infusion of 5-FU plus leucovorin and irinotecan (FOLFIRI), alone or in combination with bevacizumab, cetuximab, or panitumumab.

Infusional 5-FU monotherapy has been used in patients with severe liver dysfunction, but the clinical outcomes have been disappointing. FOLFOX and FOLFIRI have resulted in superior responses and survival rates compared with 5-FU alone. However, the safety of these combinations in patients with severe liver dysfunction has not been established, and only a few case reports have been reported.

This report presents a case of mCRC with severe liver dysfunction that was successfully treated with FOLFOX, and subsequently with cetuximab.

Methods
A 67-year-old man diagnosed with CRC in 2008 underwent a surgical resection followed by adjuvant chemotherapy. In April 2011 he was admitted to the hospital for obstructive jaundice and weight loss. The patient’s workup showed a total bilirubin of 23.1 mg/dL (range, 0–1.0 mg/dL) with abnormal liver function tests, including an aspartate aminotransferase level of 84 U/L (range, 15–37 U/L), alanine aminotransferase level of 114 U/L (range, 30–65 U/L), a creatinine level of 1.9 mg/dL (range, 0.6–1.3 mg/dL), and a glomerular filtration rate (GFR) of 38 mL/min. Imaging studies, including magnetic resonance cholangiopancreatography and MRI of the liver, revealed a perihilar liver mass measuring 48.6 x 39.8 mm, with dilatation of the intrahepatic bile ducts (Figure 1). A liver biopsy confirmed the diagnosis of mCRC. An endoscopic retrograde cholangiopancreatography was then performed and a biliary stent was placed. However, the total bilirubin level continued to increase and a percutaneous biliary drainage catheter (PTC) was placed. His total bilirubin decreased to 5.9 mg/dL (range, <1.3 mg/dL), but then started to increase to 9.4 mg/dL. At that time, he was started on a FOLFOX regimen, with a 50% dose reduction of 5-FU bolus (200 mg/m²) and continuous infusion (1200 mg/m²) over 46 hours, and a 15% dose reduction of oxaliplatin (75 mg/m²) every 2 weeks because of mild renal insufficiency. Figure 2 summarizes the level of total bilirubin over the course of initial treatment.

The patient tolerated his treatment very well, with only grade 2 stomatitis as a significant toxicity, and his total bilirubin level normalized. His carcinoembryonic antigen (CEA) level, which is used as a tumor marker for colorectal cancer, decreased from 12.2 to 4.1 ng/mL (range, 0 to <3.0 ng/mL), and CA 19-9 levels decreased from 792 to 109 U/mL (range, 0 to <32 U/mL).

Repeat CT of the abdomen and pelvis after 6 months did not show any discrete mass (Figure 3). The patient received a total of 21 cycles of FOLFOX, but then his total bilirubin started to increase and he developed ascites. At that time, a CT scan of the abdomen showed splenomegalia, ascites, and cirrhotic liver, and FOLFOX was discontinued. He subsequently received 2 cycles of 5-FU, but his total bilirubin continued to increase. In July 2012 his PTC drain was changed, but his total bilirubin continued to increase, and reached 29.8 mg/dL in August 2012. His creatinine increased to 2.7 mg/dL, with a GFR of 30 mL/min. He was then started on weekly cetuximab as single agent with a loading dose of 400 mg/m², and then 250 mg/m² thereafter. He tolerated this treatment very well, with only grade 2 mucositis, and
his total bilirubin decreased to 1.9 mg/dL and creatinine level decreased to 1.5 mg/dL, as shown in Figure 4. Repeat PET/CT scan 3 months later showed stable disease, and his tumor markers were stable. He has been undergoing palliative paracentesis on a weekly basis, and the ascitic fluid was negative for malignancy on 2 different occasions. At the time of writing, he continues to receive cetuximab, with up to 19 cycles given to date.

Discussion

FOLFOX chemotherapy remains a controversial issue in patients with mCRC with severe liver dysfunction. Data suggesting clinical benefit from chemotherapy in these cases are lacking, and best supportive care without chemotherapy is often selected based on the risk of chemotherapy-induced toxicity.

The use of 5-FU, leucovorin, and oxaliplatin as single agents has been proven safe in patients with progressive liver dysfunction; however, the safety data on the combination (FOLFOX) in these patients are lacking. 5-FU pharmacokinetics and bilirubin levels have been shown to be independent of one another in patients with varying stages of hepatic impairment when 5-FU is used as a single agent. Oxaliplatin is predominantly cleared by the kidneys, and a previous study showed that reducing the dose of oxaliplatin is unnecessary in patients with impaired hepatic function, because the pharmacokinetics of oxaliplatin were independent of the degree of hepatic dysfunction. However, several studies have identified a possible connection between the use of oxaliplatin and the development of hepatotoxicity. In one retrospective analysis, 54% of the patients receiving preoperative oxaliplatin-based chemotherapy had some hepatic sinusoidal dilatation, and 48% ultimately developed perisinusoidal and veno-occlusive fibrosis. In another retrospective analysis of 97 patients, adjuvant FOLFOX was associated with splenic enlargement in 86% of patients. Another case series described the development of signs of portal hypertension, including esophageal and hemorrhoidal varices with bleeding, splenomegaly with associated thrombocytopenia, and ascites in 6 patients treated with oxaliplatin-based chemotherapy.

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**Figure 2** Timeline figure indicating the procedures and the chemotherapy (FOLFOX) in relation to total bilirubin.

**Figure 3** CT scan of the abdomen 6 months after starting FOLFOX showing no discrete mass in the liver.

**Figure 4** Timeline figure indicating the procedures and chemotherapy (cetuximab) in relation to total bilirubin.
The successful treatment of patients with mCRC and severe liver dysfunction using combination chemotherapy with FOLFOX has only been reported in case reports.\textsuperscript{10,11} Based on these data, the authors treated the patient with FOLFOX with dose modification. The dose of oxaliplatin was reduced because of his mild renal impairment. Attempts were made to increase the 5-FU dose, but the patient experienced increased toxicity with grade 3 mucositis, and therefore the continuous 5-FU infusion was kept at 1200 mg/m\textsuperscript{2} throughout the entire treatment.

Irinotecan is mainly eliminated by 2 metabolic pathways of the liver: 1) inactivation by CYP3A4 and conversion into an active metabolite, SN38, by carboxylesterase, and 2) subsequent inactivation from SN38 to SN38-G by glucuronidation.\textsuperscript{17} In a dose-escalation study of irinotecan in patients with various degrees of hepatic dysfunction, dose delivery was limited because of toxicity in patients with bilirubin levels exceeding 1.5 times the upper normal range.\textsuperscript{19} In patients with elevated bilirubin levels, dose reduction or suspension is recommended because of increased toxicity.\textsuperscript{19}

Bevacizumab, a humanized antibody against vascular endothelial growth factor A, and cetuximab, a chimeric immunoglobulin (Ig) G1 monoclonal antibody against epidermal growth factor receptor, are antibody drugs for which the metabolic pathways are not well-known.\textsuperscript{20} Antibodies such as cetuximab are thought to be metabolized by the reticuloendothelial system, without undergoing hepatic or renal metabolism. Salvage monotherapy with cetuximab is reported to be effective in CRC, with a response rate of 12.8% to 28.0%, especially in cases of wild-type KRAS.\textsuperscript{21,22} In a case series of 7 patients with mCRC and hyperbilirubinemia treated with single-agent cetuximab,\textsuperscript{23} all patients received cetuximab at 400 mg/m\textsuperscript{2}, followed by 250 mg/m\textsuperscript{2} weekly. The median number of cetuximab cycles was 4 (range, 2–14). Two patients (28.5%) experienced improvement of total bilirubin (from 2.6 to 0.8 mg/dL, and 7.9 to 3.0 mg/dL, respectively). One patient showed apparent

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**Table 1 Comparison of Treated Patients and Their Characteristics and Outcomes**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
<th>Patient 5</th>
<th>Patient 6</th>
<th>Patient 7</th>
<th>Present Case</th>
</tr>
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<tbody>
<tr>
<td>Age (y), gender</td>
<td>63, F</td>
<td>66, M</td>
<td>65, M</td>
<td>45, F</td>
<td>56, F</td>
<td>69, M</td>
<td>78, M</td>
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<td>ECOG performance status</td>
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<td>2</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>2</td>
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<tr>
<td>Metastatic sites</td>
<td>Liver, lung, peritoneum, ascites</td>
<td>Liver, peritoneum, ascites</td>
<td>Liver, lymph node</td>
<td>Liver, lymph node, peritoneum, ascites</td>
<td>Liver, lung, peritoneum, ascites</td>
<td>Liver, peritoneum, ascites</td>
<td>Liver</td>
</tr>
<tr>
<td>Prior chemotherapy</td>
<td>FOLFIRI, FOLFOX, HAI</td>
<td>IRIS, FOLFOX + BV, HAI</td>
<td>FOLFIRI, FOLFOX</td>
<td>HAI, FOLFOX, FOLFIRI + BV</td>
<td>FOLFOX, FOLFIRI, HAI</td>
<td>HAI + irinotecan</td>
<td>FOLFOX + BV, FOLFIRI</td>
</tr>
<tr>
<td>Total bilirubin (mg/dL)</td>
<td>2.5</td>
<td>2.3</td>
<td>2.6</td>
<td>7.9</td>
<td>13.0</td>
<td>7.4</td>
<td>9.7</td>
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<td>Alkaline phosphatase (IU/L)</td>
<td>426</td>
<td>1399</td>
<td>2130</td>
<td>1913</td>
<td>3114</td>
<td>593</td>
<td>836</td>
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<tr>
<td>KRAS status</td>
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<td>Wild</td>
<td>Wild</td>
<td>Wild</td>
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<td>Wild</td>
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<tr>
<td>Cetuximab administration (times)</td>
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<td>7</td>
<td>14</td>
<td>6</td>
<td>4</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Drop in bilirubin\textsuperscript{a}</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
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<td>Skin toxicity (grade)</td>
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<td>2</td>
<td>1</td>
<td>1</td>
<td>0</td>
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<td>Survival (mo)</td>
<td>1.3</td>
<td>3.1</td>
<td>5.9</td>
<td>2.8</td>
<td>2.6</td>
<td>1.2</td>
<td>0.5</td>
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</tbody>
</table>

Abbreviations: BV, bevacizumab; F, female; FOLFIRI, 5-FU + leucovorin + irinotecan; FOLFOX, 5-FU + leucovorin + oxaliplatin; HAI, hepatic arterial infusion; IRIS; irinotecan + S-1; M, male.

\textsuperscript{a}Drop in bilirubin represented a decrease in serum total bilirubin by 50%.

radiologic response. The median survival time was 2.5 months (range, 0.5–5.8 months). Although grade 2 skin toxicity was observed in 3 patients, no other unexpected toxicities were observed.

The previously reported cases and the present case showed significant clinical benefit, with improvement in the performance status and resolution of the jaundice, and no toxicities higher than grade 3. All previous cases had extensive liver disease, and the total bilirubin level ranged between 3.5 and 5.9 mg/dL. To the authors’ knowledge, this is the first reported case in the literature of a patient with a total bilirubin level of 9.4 mg/dL who was treated with FOLFOX and had the best outcome with 21 cycles administered. A summary of these cases, including patient characteristics and outcome, is presented in Table 1.

The present case is consistent with the previous findings that FOLFOX is efficacious in mCRC with liver dysfunction and that cetuximab, as a single agent, is effective and safe in patients with severe liver and kidney dysfunction. FOLFOX combination can be safely used in mCRC with severe liver dysfunction that is felt to be due to cancer only, without adjusting the dose of oxaliplatin, and with a 50% dose reduction of bolus and infusional 5-FU. This case, along with previously reported cases (Table 2), indicates that cetuximab may be used as a single agent without dose adjustment in patients with severe liver dysfunction, regardless of their total bilirubin level. Further studies are warranted to evaluate the maximum tolerated dose and study the pharmacokinetics of this combination.

References


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Posttest Questions
1. True or False: Infusional 5-FU monotherapy, used in patients with mCRC and severe liver dysfunction, has shown impressive clinical outcomes.
2. True or False: FOLFOX might be effective, with minimal toxicity, in patients with mCRC and severe liver dysfunction and warrants further investigation.
3. How is cetuximab thought to be metabolized?
   a. By the liver
   b. By the kidneys
   c. By the reticuloendothelial system