Combination therapy with oxaliplatin and 5-fluorouracil in a patient with severe hepatic dysfunction associated with metastatic adenocarcinoma of the large bowel

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Oxaliplatin has been shown to be valuable in the treatment of patients with colorectal cancer. Many of these patients will develop liver metastases during the course of their disease, with, in some cases, severe hepatic dysfunction. Although single agent oxaliplatin can be administered safely in patients with severely compromised liver function (as it is not metabolized by the liver), little is known of its safety in these patients when administered in the preferred combination with 5-fluorouracil (which is metabolized by the liver) and leucovorin (FOLFOX protocol). We report on a very sick patient with major liver dysfunction, a bilirubin of 11.2 mg/dl (190 μmol/dl) and an open abdominal wound, for whom palliative hospice care alone was originally proposed, who responded dramatically to the combination. His bilirubin fell to 0.6 mg/dl (10.2 μmol/dl) and his liver function tests returned to near normal levels. The combination was well tolerated and clinical improvement continued for more than 11 months before disease progression was observed. ***Anti-Cancer Drugs*** **20:845–847 © 2009 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

A significant proportion of patients with colorectal cancer have metastatic spread to the liver at some stage during the course of their disease. This is frequently accompanied by varying levels of hepatic dysfunction, as exemplified by raised levels of serum bilirubin, alkaline phosphatase, and transaminases. As many of the currently available chemotherapeutic agents are metabolized to varying degrees in the liver [1], this has the potential to limit the spectrum of therapeutically useful interventions in this patient population. Of the various parameters of liver function, total serum bilirubin is still most commonly used to decide whether or not dosage modification is indicated during exposure to a given agent.

The fluoropyrimidine 5-fluorouracil (5-FU) has proven to be effective in cancers of the large bowel. The principal mechanism for elimination of this compound is through hepatic metabolism, and initial studies in which this agent was administered as a full-dose bolus in patients with compromised liver function and jaundice, showed it to be associated with significant toxicity [2]. These findings led to recommendations that it should not be used in patients with total bilirubin levels in excess of 5 mg/dl. Subsequently, however, it has been shown that 5-FU can be safely administered by continuous intravenous infusion over periods of 24 h to patients with moderate-to-severe liver disease and bilirubin levels in excess of 5 mg%, both alone, and in combination with leucovorin therapy [3].

Oxaliplatin (Eloxatin, *trans-l*-1,2, diaminocyclohexane oxalatoplatinum), is a more recent, and valuable addition to the current armamentarium of drugs for the treatment of colorectal cancer. Its mechanism of action involves the blocking of DNA transcription and replication by covalent binding to the DNA molecule with the formation of inter-strand and intrastrand cross-links. In common with other platinum derivatives, oxaliplatin is excreted primarily through the kidneys. Its combination with 5-FU and leucovorin (FOLFOX) has been shown to confer added benefit in terms of efficacy in patients with colon cancer, but limited information exists regarding the toxicity of the combination in patients with a severe degree of liver dysfunction.

We report here on a patient with advanced colon cancer and major liver dysfunction, exposed to this regimen.

Case report

A 63-year-old male with a 3 month history of abdominal pain and recent constipation, presented to the emergency room complaining of worsening of his abdominal pain, accompanied by vomiting, over the past 3 days. On physical examination, his pulse rate was 93 bpm, blood pressure 143/88 mmHg, and temperature 36.3°C.

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His abdomen was soft and diffusely tender, with no evidence of peritoneal irritation. Loud bowel sounds were present. There were no abnormalities in his cardiovascular or respiratory systems. Plain radiograph of the abdomen showed air-fluid levels in the large bowel. Computerized tomography (CT) revealed a large mass in the distal sigmoid and proximal colon distension with air-fluid levels. There were metastases in both lobes of the liver. Liver function tests were within normal limits and his carbohydrate antigen (CA) 19-9 was 350 U/ml.

An attempt to insert a rectal stent was unsuccessful, and accompanied by microperforation. Urgent laparotomy was performed, with resection of the rectosigmoid and the formation of a colostomy. Pathological evaluation of the resected material revealed an ulcerated adenocarcinoma of the large bowel, with pericolic fat invasion; 16 of 23 positive lymph nodes and close radial margins. After the surgery, wound infection and incomplete closure of the incision prevented the early initiation of chemotherapy for his metastatic disease.

Four weeks after surgery he was admitted to the oncology department with severe jaundice. Laboratory investigations on admission showed a total bilirubin of 11.2 mg% (190 μmol/dl), alkaline phosphatase 608 IU/l, aspartate aminotransferase 149 IU/l, alanine aminotransferase 144 IU/l, and gamma glutamyl transferase 499 IU/l, creatinine 0.69 mg/dl, blood urea nitrogen 15 mg/dl. Complete blood count revealed white blood cells 10 000/mm^3 (neutrophils 79%, lymphocytes 11.7%), hemoglobin 11.3 g/dl, platelets 349 000/mm^3. Ultrasound examination showed multiple liver metastases. The common bile duct was normal (diameter 0.8 cm), but the intrahepatic bile ducts were dilated. Endoscopic retrograde cholangiopancreatography was performed, with insertion of a stent into the bile duct from the left side. Bilirubin levels and liver function tests remained unchanged.

One week later, he experienced severe shortness of breath and a chest radiograph showed significant interstitial changes. CT scan revealed an increase in the number and size of liver metastases, and marked lymphangitic spread. CA 19-9 was now 5000 U/ml.

Chemotherapy was commenced with the De Gramont protocol at 70% of the standard dose (leucovorin 280 mg/m^2 by intravenous infusion over 2 h, followed by 5-FU 280 mg/m^2 by bolus injection, and thereafter, 5-FU 1680 mg/m^2 administered by continuous infusion over a 46-h period). After 1 week, his total bilirubin and liver function tests showed no improvement and despite his severe cholestatic jaundice and incompletely healed wound, oxaliplatin 85 mg/m^2 every 2 weeks was added to his treatment programme (FOLFOX protocol). On this regimen, his shortness of breath and jaundice improved progressively over the next 4 weeks, and after 6 weeks liver function had returned to normal (total bilirubin 0.6 mg/dl, alkaline phosphatase 131 IU/l; aspartate aminotransferase 52 IU/l; alanine aminotransferase 49 IU/l, and gamma glutamyl transferase 96 IU/l). His CA 19-9 was 83.3 U/ml, creatinine 0.58 mg/dl, blood urea nitrogen 18 mg%, white blood cells 4.900/mm^3 (neutrophils 69%, lymphocytes 17%), hemoglobin 12.0 g/dl, platelets 325 000/mm^3. One month after initiation of treatment with oxaliplatin, CT scan showed significant improvement in the lymphangitic spread, liver metastases, and intrahepatic cholestasis. At this time, his abdominal wound was completely healed and 4 weeks after his first treatment with oxaliplatin, treatment with bevacizumab 5 mg/kg every 2 weeks was commenced, and the De Gramont protocol increased to the standard dose.

Further CT scans 3, 6, and 9 months later showed continued improvement, and his quality of life continued to improve. Other than mild neutropenia (nadir of neutrophil count 1100/mm^3), oxaliplatin produced no untoward effects in this patient. In particular, he did not experience any neuropathy. At 1 year, a CT scan showed stable disease in the lungs, but some progression of his liver metastases, accompanied by a worsening of his liver function tests and a CA 19-9 of 5000 U/ml. Second-line therapy with a combination of 5-FU, leucovorin, and CPT-11 (irinotecan) (FOLFIRI protocol) was not effective.

Discussion

Oxaliplatin is currently approved by the Food and Drug Administration for use in combination with 5-FU and leucovorin for the first-line treatment of patients with metastatic colonic cancer. As hepatic metastases with varying degrees of impairment of liver function are common in this patient population, the safety and efficacy of the combination in these patients is a major concern.

Two studies with single agent oxaliplatin, one assessing its toxicity profile in patients with impaired renal function [4], and one, in patients with impaired hepatic function [5], have been carried out by the National Cancer Institute Organ Dysfunction Working Group. These studies have shown that in doses ranging from 60 to 130 mg/m^2 oxaliplatin is well tolerated, and that when used as single agent therapy, dose modification is not required in patients with mild or moderate renal dysfunction, or in those with liver dysfunction. The most commonly reported side effects with oxaliplatin are mild myelosupression, moderate nausea, and vomiting, and peripheral neuropathies, which may involve the hands, feet, and perioral regions, and there was no evidence to suggest that the incidence or severity of any of these was increased in patients with renal or hepatic dysfunction.

As in routine clinical practice oxaliplatin would not be administered alone, but in combination with 5-FU and leucovorin (FOLFOX), the above studies do not provide guidelines for its dosage in combination therapy in patients whose hepatic or renal function is severely compromised. Some information has recently been made available regarding the use of this combination in three patients with metastatic colon cancer and severe liver dysfunction [6]. Bilirubin levels in these patients at the start of treatment ranged from 3.5 to 5.9 mg/dl. Treatment with the FOLFOX regimen was instituted, with exposure to oxaliplatin at a maximum dose of 85 mg/m^2. All three patients tolerated the combination well, with no treatment-related grade 3 or higher toxicities observed. After the initial improvement in disease status, disease progression was noted in two patients at 4 and 7 months from the inception of therapy, while treatment was ongoing in the third patient at 5 months.

Treatment was initiated in our patient when his general condition was extremely poor, with an open and indolent abdominal wound, and a bilirubin level substantially higher than those of the three patients described above. These features represented a major challenge. The results in this patient to date have been extremely encouraging, and provide further evidence to suggest that oxaliplatin in combination therapy (FOLFOX protocol) may be safely administered to patients with severely impaired hepatic function with no apparent increase in toxicity, and good effect.

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