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Pharmacological Monitoring of Capecitabine in a Gastric Cancer Patient with Hyperbilirubinemia

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Abstract

Objective: To examine therapeutic drug monitoring in managing hyperbilirubinemia caused by capecitabine in patients with gastric adenocarcinoma with extensive liver metastases. **Results:** The initial liver function tests showed an elevation of transaminases (aspartate amino transferase 615 UI/l, alanine aminotransferase 385.9 UI/l), hyperbilirubinemia (total bilirubin at 246.1 μmol/l), and alkaline phosphatase at 694.6 UI/l. We initiated capecitabine based combination chemotherapy, and the clinical pharmacist conducted a full-course medication monitoring of the patient's treatment including design of individualized dosing regimens and monitoring of bilirubin, infection, cancer pain, parenteral nutrition support and adverse events. After 21 days of supervision by clinical pharmacist and clinicians, the patient's bilirubin and transaminase decreased progressively, with aspartate aminotransferase, total bilirubin and alkaline phosphatase falling back to 57 UI/l, 69.8 μmol/l, 307.2 UI/l, respectively. The patient's condition improved significantly at the time of discharge, with the jaundice subsided, and the bloating relieved. **Conclusion:** Due to adverse reactions, capecitabine requires medication monitoring during use. The relationship between effectiveness and adverse effects is controversial. Adverse reactions should not be the sole criterion for the use of drugs. Clinical pharmacists can improve the safety and effectiveness of patients' medications and promote rational drug use by monitoring patients, which may be useful to help the doctors identify the high-risk patients for taking efficient treatment strategy decisions.

Keywords

Clinical Pharmacist, Capecitabine, Gastric Cancer, Hyperbilirubinemia,

Therapeutic Drug Monitoring

1. Introduction

The capecitabine-based oxaliplatin and capecitabine (XELOX) regimen can significantly improve patients' outcomes. But we can't ignore the side effects of capecitabine (Cap) [1] [2] [3]. The adverse reactions caused by chemotherapy drugs are various, and some serious adverse reactions may limit the clinical use of chemotherapy drugs. The most commonly reported toxic effects of capecitabine are diarrhea, nausea, vomiting, stomatitis and hand-foot syndrome [4]. Jaundice, the physical finding associated with hyperbilirubinemia, results when the liver is unable to properly metabolize or excrete bilirubin [5]. Capecitabine has a well-established safety profile and can be given safely to patients with advanced age, hepatic and renal dysfunctions. However, the administration of chemotherapy to gastric cancer patients with liver dysfunction requires careful consideration for liver has a very important role in the metabolism of drugs [6].

Here, we report on a patient with gastric adenocarcinoma with extensive liver metastases, whose bilirubin increased by ten times during giving capecitabine. Under the joint supervision of doctors and clinical pharmacists, the liver function of the patient decreased significantly.

2. Main Information

This case involved a 43-year-old woman who presented with five months' history of epigastralgia after weight loss which had been ongoing for a year. The weight of patient dropped from 65 kg to 53 kg which may be caused by the rapid growth of malignant tumors and stomach discomfort. The patient has no basic disease in the past and has not taken drugs. After hospitalization, the patient was treated with capecitabine (1000 mg/m^2 orally twice daily) and oxaliplatin (130 mg/m^2 intravenous infusion administered in 500 mL of 5% glucose over a period of 2 hours) of a 21-day cycle with normal liver function. The liver function tests showed an elevation of transaminases (aspartate amino transferase 615 UI/l, alanine aminotransferase 385.9 UI/l), hyperbilirubinemia (total bilirubin 246.1 μmol/l and direct bilirubin 238.2 μmol/l), and alkaline phosphatase at 694.6 UI/l, and elevation of tumor markers (carcinoembryonic antigen > 1000 ng/ml and CA199 at 180 UI/l) while after three days of using capecitabine. At the time of discharge, the patient's bilirubin and transaminase decreased progressively, with aspartate aminotransferase, total bilirubin and alkaline phosphatase falling back to 57 UI/l, 69.8 μmol/l, 307.2 UI/l, respectively (**Figure 1**).

2.1. Monitoring of Adverse Reactions of Capecitabine

Nausea, emesis and diarrhea grade 2 were noted during the 21-day cycle but these toxicities were manageable. The clinical pharmacist told the patient that

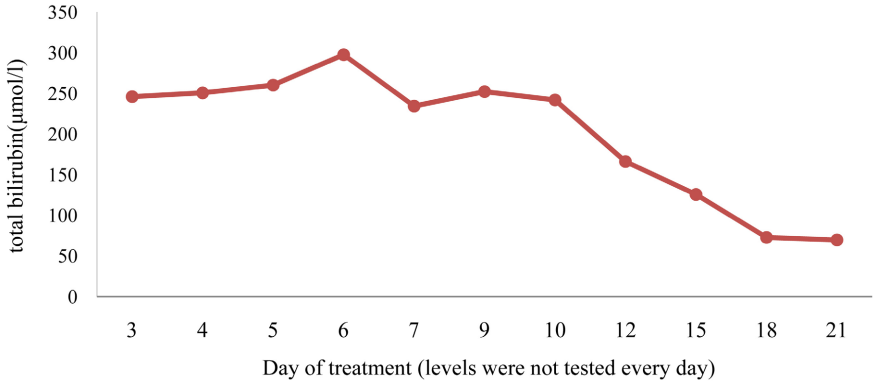

Figure 1. The concentration of total Bilirubin in the treatment of gastric cancer.

these reactions were normal adverse reactions through communication. When the patient was admitted to the hospital, the liver function was normal, but the patient's bilirubin began to rise after taking Capecitabine for 3 days. At the same time, the patient developed jaundice and bloating. A computed tomography (CT) scan of the chest, abdomen, and pelvis at that time showed that the patient had liver metastasis. However, the most worrying thing was that the patient's bilirubin had been elevated after taking capecitabine. Clinical pharmacist and physician analyzed the patient's condition and concluded that hyperbilirubinemia was associated with both liver metastasis and capecitabine. By studying the drugs used by patients before, capecitabine was still recommended as first-line therapy. Eventually, the clinical pharmacist suggested to adjust the capecitabine dose to reduce it to 75%. On the fourth day, the dose of capecitabine was reduced (1000 mg/m^2 orally twice daily). During chemotherapy, reduced glutathione and polyene phosphatidylcholine were used to protect liver function [7] due to an increase in the accumulation of bilirubin. Surprisingly, the total bilirubin level of the patient gradually decreased after 7 days, and the patient's jaundice also improved significantly. She has received 21-day cycle of capecitabine with ongoing clinical benefit and good tolerance of treatment.

2.2. Drug Adjustment of Cancer Pain

Clinical pharmacists monitored the patient's pain by numerical rating scale (NRS) while paying close attention to the patient's mental state. After 5 days, the patient developed delirium and irritability. Morphine was withheld to check for opiate delirium as a possible cause of changes in the patient's altered mental status (AMS). Subsequently, the clinical pharmacist adjusted the dose of morphine (20 mg two times daily, which was later decreased to 10 mg two times daily). After one day, the patient's delirium improved, and the pain was also controlled below 3 points.

2.3. Monitoring of Nutritional Support

It is important to note that amino and organic acid test results were obtained and were not consistent with urea cycle defect [8]. During chemotherapy, the

patient had been vomiting, and ate less with progressive weight loss, so the clinical pharmacist recommended that the patient should be treated with combination of enteral nutrition and parenteral nutrition. The specific scheme at the beginning is shown in Table 1. The pharmacist adjusted the intestinal nutrient solution in time to reduce the intake of parenteral nutrient solution on the fifth day (Table 2).

3. Discussion

Chemotherapy has been shown to improve survival and quality of life in patients with metastatic gastric carcinoma [9]. 5-FU is a uracil analogue and antimetabolite that is metabolized mainly in the liver by dihydropyrimidine dehydrogenase (DPD). Although 5-FU is fairly safe to use in patients with liver dysfunction, regular monitoring of liver tests is advised [10]. Capecitabine, a prodrug of 5-Fluororuracil (5-FU) is activated through three enzymatic reactions. Twelves [11] have compared the use of capecitabine in patients with moderate hepatic dysfunction secondary to liver metastases to patients with normal liver function. The research has demonstrated that there are no significant differences in the pharmacokinetic parameters in the two groups, thus no need for adjustment of dose in this category of patients.

Hyperbilirubinaemia has been associated with shorter overall survival in patients with gastric cancer [12]. One possible cause of hyperbilirubinaemia in patients with gastric cancer is obstruction of the peripheral intrahepatic bile ducts

Table 1. Composition of patient parenteral nutrition solution.

Drug name	Dosage
Compound amino Acid Injection (9AA)	625 ml
50% Glucose Injection	200 ml
Medium and Long Chain Fat Emulsion Injection (C8 - 24)	200 ml
Sodium Glycerophosphate Injection	10 ml
Potassium Chloride Injection	10 ml
Magnesium Sulfate Injection	8 ml

Table 2. Adjusted parenteral nutrition solution.

Drug name	Dosage
Compound amino Acid Injection (9AA)	400 ml
50% Glucose Injection	150 ml
Medium and Long Chain Fat Emulsion Injection (C8 - 24)	150 ml
Sodium Glycerophosphate Injection	10 ml
Potassium Chloride Injection	10 ml
Magnesium Sulfate Injection	8 ml

due to tumour metastases, without major impairment of other aspects of liver function, or massive infiltration of the liver by tumour metastases resulting in non-cirrhotic liver failure [13]. Due to the possible impact of hepatic impairment on the pharmacokinetic route of nab-paclitaxel and gemcitabine that was shown in small clinical studies, these compounds should be used with caution in patients with hyperbilirubinaemia, and careful monitoring of patients and liver parameters during chemotherapy is warranted [14]. In our study, the clinical pharmacist conducted a full-course medication monitoring of the patient's treatment including design of individualized dosing regimens and monitoring of bilirubin, infection, cancer pain, parenteral nutrition support and adverse events. The clinical pharmacist discussed the treatment plan and the choice of medicine with the doctor, and adjusted the dosage in time when an adverse reaction occurred in the use of drugs. At the same time, the patient was well educated in medication. Good nutritional status and pain management improved patient compliance. After 21 days of supervision of clinical pharmacist and clinicians, the patient's bilirubin and transaminase decreased progressively, with aspartate aminotransferase, total bilirubin and alkaline phosphatase falling back to 57 UI/l, 69.8 μmol/l, 307.2 UI/l, respectively. The patient's condition improved significantly at the time of discharge, with the jaundice subsided, and the bloating relieved.

Many patients with advanced gastric cancer suffer from hyperbilirubinaemia [15]. This report suggests that capecitabine may be a safe and efficacious treatment for patients with hepatic dysfunction, but more clinical data is needed to confirm these results. Liver dysfunction resulting from liver metastases in patients with gastric carcinoma should not lead to therapeutic delay, but the indication of chemotherapy for this category of patient must be cautious because no recommendations are available and clinical data in this clinical situation are limited. Thus, it is of importance to seek for more advice and medication monitoring from clinical pharmacist to improve better survival outcome for patients with gastric cancer.

4. Conclusion

It is suggested that attention should be paid to the increase of total bilirubin in patients during chemotherapy. The increase in bilirubin may become a factor preventing the normal progress of chemotherapy. Active nutrition intervention and liver protection treatment may ensure the smooth progress of chemotherapy. The clinical pharmacist in clinic is needed for therapeutic drug monitoring when necessary. The pharmacist's expertise and knowledge helped avert adverse clinical consequences and promoted considerable cost-savings.

Authors' Contribution

All authors contributed to this project and article equally. Gao Ling collected the data; Gu Yanting provided technical help and fruitful discussion. All authors read and approved the final manuscript.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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