Unpredicted Severe Toxicity after 5-Fluorouracil Treatment due to Dihydropyrimidin Dehydrogenase Deficiency

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Dihydropyrimidine dehydrogenase (DPD) is the initial and rate-limiting enzyme in the catabolism of 5-fluorouracil (5-FU). Thus, patients with a DPD deficiency are at risk of developing severe 5-FU-associated toxicity.

A 37-year-old female with gastric cancer underwent a curative operation, followed by adjuvant chemotherapy consisting of 5-FU and epirubicin. After the first cycle of chemotherapy, the patient manifested grade 2 mucositis and febrile neutropenia, and when her treatment was subsequently continued with doxifluridine she developed severe mucositis and febrile neutropenia. A PCR study revealed that her DPD mRNA level was lower than that in a control group. Thus, when considering the routine use of 5-FU for the treatment of cancer patients, an analysis of DPD activity or screening for DPD mutations is warranted in confined patients who experience unpredicted severe toxicity after initial 5-FU administration, even though DPD deficiency is a rare metabolic defect.

Key Words: Dihydrouracil dehydrogenase, Fluorouracil, Stomach neoplasms

INTRODUCTION

5-Fluorouracil (5-FU) remains one of the most frequently prescribed chemotherapeutics for the treatment of several different malignancies, including cancers of the gastrointestinal tract, breast, and head and neck. The 5-FU antitumor action mechanism depends on the anabolism of the drug to cytotoxic nucleotides, which can act at several sites. Moreover, these actions include thymidylate synthase inhibition and the incorporation of these nucleotides into RNA and DNA. Although the cytotoxic effects of 5-FU are probably mediated directly via anabolic pathways, the catabolic route also plays a significant role, as more than 80% of administered 5-FU is catabolized by dihydropyrimidine dehydrogenase (DPD), which features in the initial and rate-limiting step of the catabolic pathway. Thus, DPD performs a critical role in 5-FU pharmacokinetics by regulating the amount of 5-FU available for anabolism.

DPD activity is known to be inversely related to the plasma concentration of 5-FU in patients treated by continuous 5-FU infusion. Moreover, in patients with a DPD deficiency, even a standard or low dose of 5-FU can cause profound toxicity, including mucositis, granulocytopenia, neuropathy, and death. The cause of these potentially life-threatening toxicities appears to be a decreased catabolism, which markedly prolongs exposure to 5-FU.

Accordingly, this report presents the case of a DPD-deficient patient who developed severe toxicity after treatment with parenteral and oral 5-FU.
CASE REPORT

A 37-year-old female patient underwent curative resection for a stage II (pT3N0M0) poorly differentiated gastric adenocarcinoma, and this was followed by adjuvant chemotherapy consisting of 5-FU (600 mg/m², i.v. on days 1 and 8) and epirubicin (50 mg/m², i.v. on day 1) in 3-week cycles. However, the patient developed erythematous rashes on her hands and oral mucositis on day 5. Thus, day 8 of 5-FU administration was skipped. On day 14, the patient experienced fever, stomatitis, diarrhea, leucopenia (0.290×10⁹/l), neutropenia (0.012×10⁹/l), and thrombocytopenia (34×10⁹/l). After supportive care with a granulocyte-colony stimulating factor (G-CSF) and broad-spectrum antibiotics, her fever decreased and her general condition and blood counts recovered after 1 week. On day 35, the patient then resumed her treatment with oral doxifluridine (200 mg t.i.d., a prodrug of 5-FU), but 3 days later she developed oral mucositis, and thus further medication was cancelled. Two weeks after this initial oral doxifluridine treatment, the patient was admitted to the emergency room due to severe oral pain and diarrhea (over 500 mL per day). A physical examination revealed grade 3 oral mucositis and erythematous rashes on her hands and feet. Her CBC revealed leucopenia (1.600×10⁹/l), neutropenia (0.421×10⁹/l), and thrombocytopenia (41×10⁹/l), and after admission, the patient also manifested a fever of unidentified etiology. After 2 weeks of supportive care, the patient’s CBC and systemic symptoms improved. Real-time quantitative polymerase chain reaction (PCR) then demonstrated that her DPD mRNA level was 2.5 (control group levels 30-80, cut-off value 3.0). Twenty-nine days after initial oral doxifluridine administration, the patient was discharged, and at the last follow-up 1 year after this after, she was doing well without any evidence of disease recurrence or sequelae of 5-FU toxicity.

DISCUSSION

5-FU has a relatively narrow therapeutic index and there is a strong correlation between exposure to 5-FU and its toxicity. More than 80% of 5-FU administered is catabolized by DPD. Thus, the activity of DPD appears to be critically important for determining the efficacy and more specifically the toxicity of 5-FU.

Therefore, we present this case of a DPD-deficient patient who developed severe toxicities after exposure to parenteral and oral 5-FU. DPD deficiency was confirmed in this patient by a low mRNA level as estimated by real-time quantitative PCR. This appears to be the first report of DPD deficiency in a Korean patient.

DPD activity can be detected in a number of tissues, although the liver is the main organ responsible for the catabolism of 5-FU. Since DPD activity in a normal liver correlates well with that of peripheral blood mononuclear cells, the latter has been used as a surrogate for total body DPD activity. However, the complicated, labor-intensive DPD enzyme assay presently used to diagnose DPD deficiency is not available in most centers, which has led to attempts to develop genotyping assays that can identify DPD-deficient individuals through molecular analysis of the DPYD gene, and to measure the 5, 6-dihydrouracil/uracil ratio which reflects DPD activity and DPD mRNA levels by real-time quantitative PCR. However, in terms of genotyping assays, the size and complexity of the DPYD gene makes the genotype analysis of DPD-deficient patients difficult to investigate. Recently, a denaturing high performance liquid chromatography (DHPLC) method that examines the entire coding region of the DPYD gene (including the intron/exon splice sites and promoter region) has been introduced and used to identify patients at risk of 5-FU toxicity prior to treatment. Moreover, previous studies have shown a correlation between the antitumor effectiveness of 5-FU and DPD mRNA levels in tumors using semiquantitative reverse-transcription PCR. However, some have rejected the idea of a strong link between DPD mRNA levels and DPD activity, and have suggested instead that the activity of DPD is not only regulated at the transcriptional and translational levels, but also at the post-transcriptional level.

To date, a number of patients with DPD deficiency have been reported to suffer from severe toxicities after 5-FU treatment. Thus, based on previous experiences, it was suggested that patients with a DPD activity <70% of that observed in the normal population may be prone to develop severe 5-FU-associated side effects. In addition, the toxicity encountered in patients with severe DPD deficiency has been reported to be significantly higher than that encountered in patients with a moderate DPD deficiency. Moreover, a recent population study suggested that 31~34% of patients treated with 5-FU exhibited dose-limiting toxicity, and 40~50% of patients exhibiting grade 3 or 4 toxicity to 5-FU were shown to be partially or profoundly DPD deficient.

Consequently, when considering the routine use of 5-FU for the treatment of cancer, and even though DPD deficiency is a rare metabolic defect, we recommend performing DPD activity analysis or a screening for DPD mutations in confined patients who experience unpredicted severe toxicity after initial 5-FU administration.

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