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

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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.

Key Words: Dihydrouracil dehydrogenase, Fluorouracil, Stomach neoplasms
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, leukopenia (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 presented at 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 (41×10⁹/l), and after admission, the patient also manifested 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 toxicity9). More than 80% of 5-FU administered is catabolized by DPD7). Thus, the activity of DPD appears to be critically important for determining the efficacy and more specifically the toxicity of 5-FU8-11). 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.

REFERENCES


