

## Dehydropyrimidine Dehydrogenase Deficiency in a Cancer Patient Undergoing 5-Fluorouracil Chemotherapy

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**Abstract.** *We present a case of a Caucasian cancer patient undergoing 5-fluorouracil (5-FU)-containing chemotherapy in our department. The 49-year-old female patient suffered from adverse effects representing WHO grade 3 toxicity. Genotyping revealed that she carried the exon 14-skipping mutation which is known to result in dehydropyrimidine dehydrogenase (DPD) deficiency. DPD is the enzyme that converts 5-FU to inactive metabolites and therefore dictates the amount of 5-FU that is available to be metabolised to cytotoxic nucleotides. Consequently DPD deficiency is the cause of severe adverse and sometimes lethal reactions to 5-FU. In conclusion the identification of cancer patients at increased risk of severe toxicity prior to the administration of 5-FU would be desirable.*

### Case Presentation

A 49-year-old white female suffering from breast cancer underwent surgery and subsequent chemotherapy in our department. The chemotherapy regimen consisted of three agents: cyclophosphamide (600 mg/m<sup>2</sup>), methotrexate (40 mg/m<sup>2</sup>) and 5-fluorouracil (600 mg/m<sup>2</sup>) (CMF). The first course of CMF administered on day 1 and day 8 was tolerated well. Nine days later the routine blood count revealed leucocytes as low as 1,800. According to the Common Toxic Criteria this value represents WHO grade 3 toxicity. Although every agent of this chemotherapy singly may induce leucocytopenia, blood was obtained and genotyped for the exon 14-skipping mutation. This mutation is presently considered to be the most abundant loss-of-function allele of the dehydropyrimidine dehydrogenase (DPD) gene that results in DPD deficiency. DPD deficiency is attributed to severe side-effects of 5-fluorouracil. The result of genotyping revealed that our patient indeed carried the exon 14-skipping mutation.

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Consequently 5-fluorouracil-containing chemotherapy was cancelled. The patient recovered without specific therapy.

### Discussion

5-Fluorouracil is an analogue of pyrimidine nucleosides and is currently one of the most widely administered chemotherapeutic agents for the treatment of epithelial cancers (1). The use of 5-fluorouracil (5-FU) has been complicated by unpredictable pharmacokinetics, low response rates and seemingly random toxicity (2). The variable pharmacology is largely due to inherited differences in the expression of the metabolising enzyme dihydropyrimidine dehydrogenase (DPD). This enzyme converts fluorouracil to inactive metabolites (catabolic pathway) and therefore ultimately dictates the amount of 5-fluorouracil that is available to be metabolised to cytotoxic nucleotides (anabolic pathway) (3).

Thus, DPD deficiency is attributed to an increased risk of unusually severe adverse reactions in cancer patients receiving 5-fluorouracil chemotherapy. Patients may suffer from severe mucositis, stomatitis, diarrhea, dermatitis including desquamating dermatitis and severe prolonged myelosuppression (4,5). Neurologic toxicity, which is rare, may be induced resulting in encephalopathy and coma (6,7). Other forms of toxicity, such as myocardial ischaemia, have been difficult to attribute directly to DPD deficiency (8,2), though an increased risk of death due to a combination of toxicities has been attributed to DPD deficiency (9,10). DPD deficiency follows an autosomal recessive pattern of inheritance (11). Its prevalence is estimated to be 1-3% in the Caucasian population (2,6,11). At present it still remains unclear whether the activity of DPD might be influenced by gender (12). Nevertheless some studies have shown a female preponderance in the incidence rate of DPD deficiency with reports of up to 79% of patients suffering from the condition being women (9).

In 1985 Tuchman *et al.* were the first to describe severe toxicity, including semi-coma associated with the use of 5-FU in a 27-year-old female undergoing adjuvant therapy for breast cancer. Since the patient presented with high levels of pyrimidinuria, it was assumed that DPD could be the deficient

enzyme (13). A first report of a heterozygous carrier of the exon 14-skipping mutation that was associated with severe 5-FU-related toxicity was identified in 1996 (12). Since then severe side-effects of 5-FU linked to DPD deficiency have been demonstrated in several cancer patients (9,11,14).

Lethal toxicity of 5-FU was attributed to a complete deficiency of DPD in a 44-year-old female cancer patient who developed pancytopenia and died of infectious complications. Genotyping revealed that she was homozygous for the exon 14-skipping mutation (15). Furthermore it was shown that among 25 patients with severe 5-FU-related toxicity, 6 were found to possess the exon 14-skipping mutation, one of whom was homozygous (10). All of the 6 patients suffered from WHO grade 4 myelosuppression, leading to death in the homozygous case but also in 2 of the heterozygous cases. These data suggest that there is a high risk of 5-FU toxicity associated with DPD deficiency, even if the allelic status is heterozygous as was the case with our patient. The most dramatic example, however, is the description of severe multiorgan toxicity associated with the topical application of 5% 5-FU cream to the scalp of a 76-year-old male patient suffering from basal cell carcinoma. Such severe toxicity to topical 5-FU was shown to be the result of virtually undetectable DPD activity (16). In addition, this pharmacogenetic syndrome may be more common than anticipated, ranging from 6-38% in cancer patients (3,7,9,10).

Considering the common use of 5-FU treatment in cancer patients and the increasing percentage of patients receiving high doses of 5-FU in adjuvant therapy, it would be preferable to identify those patients at risk before the administration of 5-FU. Therefore further investigation into the genetic abnormalities that give rise to DPD deficiency and the development of sensitive diagnostic techniques to identify them is needed.

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