Lethal toxicity of uracil/tegafur in the treatment of sigmoid carcinoma

Because a hand–foot syndrome developed in a 67-year-old Caucasian male with Dukes C2 sigmoid carcinoma after the third three-weekly course of capecitabine (Roche Nederland BV, Woerden, The Netherlands) (2500 mg/m²/day for 14 days), UFT (uracil/tegafur in a 1 : 4 ratio) was initiated. On the sixth day of the first four-weekly course (300 mg/m²/day UFT and 30 mg/day leucovorin (Sandoz BV, Almere, The Netherlands) for 21 consecutive days, according to Kim et al.) [1], treatment was discontinued because of diarrhoea. On admission 3 days later, the patient had leucopenic (2.6 $\times$ 10⁹/l) fever (38.3°C) and grade III oral mucositis (WHO Common Toxicity Criteria (CTC)). Treatment consisted of fluid resuscitation and...
cefuroxim. During subsequent days his condition deteriorated with severe sepsis and multiorgan failure. The leucocyte count decreased to 0.4 \( \times \) \( 10^9/\text{l} \) and the platelet count to 64 \( \times \) \( 10^9/\text{l} \). Faecal cultures showed no pathogens. Blood cultures revealed growth of a bacillus species. An abdominal computed tomography scan showed signs of necrotising enterocolitis, and imipenem and granulocyte colony-stimulating factor were initiated. Despite recovery of the leucocyte count the patient died on the eighth day of admission. Autopsy revealed a denuded intestinal mucosa.

This case illustrates unexpected lethal toxicity on the oral 5-fluorouracil prodrug UFT. Severe intestinal and haematological toxicity of 5-FU is mostly related to deficiency of dihydropyrimidine dehydrogenase (DPD), an essential enzyme in the metabolic breakdown of 5-FU. In UFT, uracil is added to tegafur in order to bind DPD, resulting in a controlled DPD deficiency. Since capecitabine revealed no severe toxicity, apart from grade III hand-foot syndrome, it is very unlikely that DPD deficiency played a causative role in the severe UFT-related toxicity in this patient. Indeed, no polymorphisms in the \textit{DPYD} gene were noted.

Since cytochrome P450 2A6 (CYP2A6) has been reported to metabolise tegafur to yield 5-FU [2], a serum sample of the patient was screened for the polymorphisms CYP2A6*2, *3, *6, *9 and *12. The patient was heterozygous mutant for CYP2A6*9 (T-48G in the TATA box of the promoter) and wild type for the other polymorphisms. CYP2A6*9, with an allele frequency of 5% in Caucasians [3], has been reported to reduce CYP2A6 activity (enzyme activity wild type > heterozygous mutant > homozygous mutant CYP2A6*9) [3, 4]. We therefore hypothesise that in this patient the metabolism of tegafur into 5-FU was decreased compared with patients with normal CYP2A6 activity. So tegafur may be alternatively metabolised by cytosolic enzymes resulting in increased toxicity.

Akay et al. [5] published a comparable case of severe gastrointestinal and haematological UFT toxicity, but tests to determine CYP2A6 polymorphisms had not been carried out. Unfortunately, no blood concentrations were measured of tegafur or 5-FU in both patients.

This case report is an example of lethal toxicity of UFT, probably due to altered metabolism of this 5-FU prodrug because of a CYP2A6 polymorphism. Physicians should be aware of unexpected severe toxicity of UFT in patients with CYP2A6 polymorphisms.

T. M. Bosch1*, I. Meijerman2, J. H. Beijnen1,2, S. W. van Thiel3 & L. T. Vlasveld3
1Department of Pharmacy and Pharmacology, Slotervaart Hospital/The Netherlands Cancer Institute, Amsterdam, The Netherlands; 2Biomedical Analysis, Department of Pharmaceutical Sciences, Faculty of Science Utrecht University, Utrecht, The Netherlands; 3Department of Internal Medicine, Bronovo Hospital, The Hague, The Netherlands (*E-mail: tessabosch@hotmail.com)

**references**


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