Informed consent could not be obtained because the patient died in the meantime. The health department of the Canton of Bern has granted exemption from professional confidentiality for the publication of this case report.

Fluorouracil-Induced Neurotoxicity: Risk Factors, Clinical Impact, and management strategies

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Background

5-Fluorouracil (5-FU), a fluorinated pyrimidine analogue, is a chemotherapeutic agent used for the treatment of primarily solid tumors [1]. 5-FU (or rather its active metabolites) interacts with DNA and RNA synthesis and inhibits thymidylate synthase (TS) (Fig. 1) [2-4].

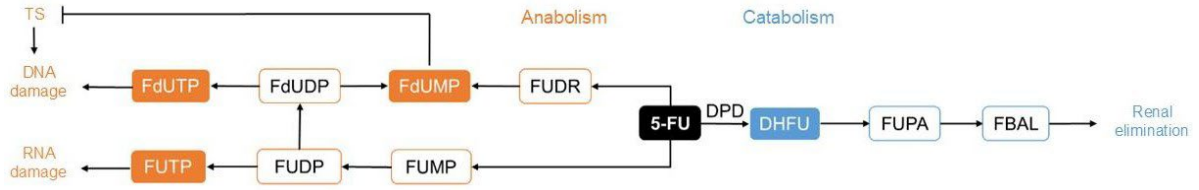

Fig. 1: Simplified metabolism of 5-Fluorouracil (5-FU) (adapted from [2-4])

5-FU (black) is converted into three main active metabolites (orange): The incorporation of fluorouridine triphosphate (FUTP) or fluorodeoxyuridine triphosphate (FdUTP) into RNA and DNA, respectively, leads to damage and ultimately cell death. Fluorodeoxyuridine monophosphate (FdUMP) inhibits thymidylate synthase (TS), causing DNA damage. 5-FU is metabolized into dihydrofluorouracil (DHFU) (blue) by dihydropyrimidine dehydrogenase (DPD), which represents the rate-limiting step of 5-FU catabolism. Up to 80% of the administered 5-FU is degraded by DPD and subsequently excreted renally as fluor-beta-alanine (FBAL) after several intermediate steps.

FUDR: Fluorouridine; FdUDP: Fluorodeoxyuridine diphosphate; FUMP: Fluorouridine monophosphate; FUDP: Fluorouridine diphosphate; FUPA: Fluor-β-ureidopropionate.

Common adverse drug reactions (ADRs) of 5-FU include bone marrow suppression, gastrointestinal toxicity and cardiotoxicity, and hand-foot syndrome [5,6]. In contrast, neurotoxicity associated with 5-FU is rare [6], with an incidence varying between 0.1–0.2% and 2–5%, depending on the source [6-8]. Neurological symptoms may include cerebellar ataxia [8,9], posterior reversible encephalopathy syndrome (PRES) [5], and, more rarely, multifocal leukoencephalopathy [10]. Additionally, seizures [11], confusion [12], disorientation [13], stroke-like symptoms [14], and even coma [13] have been reported [6]. Recently, uridine triacetate has become available as an antidote for 5-FU and capecitabine (a prodrug of 5-FU) toxicity [15]. In this report, we present a case of acute 5-FU-induced neurotoxicity requiring treatment, and discuss potential risk factors and management strategies

Case Report

Medical History

A patient (age group 70–80 years old) was admitted due to progressive impairment of consciousness. Four days earlier, he had received the first intravenous dose of 5-FU-based chemotherapy (FOLFOX regimen) for metastatic esophageal cancer. From the second day of chemotherapy, he experienced a gradual decline in alertness, which led to a fall and an acetabular fracture on the day of admission. Consequently, treatment with oxycodone was initiated. After ruling out intracranial hemorrhage via CT, the patient was admitted to the internal medicine department for further diagnostics. His comorbidities included acute-on-chronic kidney disease (KDIGO G3aA1), arterial hypertension, diabetes mellitus type 2, hypothyroidism, polyneuropathy (diabetic and alcohol-related), restless legs syndrome, suspected malnutrition, and a history of thalamic infarction due to vascular encephalopathy. At the time of admission, his regular medications (daily dosage) included acetylsalicylic acid (100 mg), levothyroxine (25 µg), desloratadine (5 mg), esomeprazole (20 mg), pregabalin (50 mg), tamsulosin (0.4 mg), folic acid (5 mg), a vitamin B complex supplement (1 tablet), thiamine (300 mg), and inhaled indacaterol/glycopyrronium (110/50 µg). Additionally, he received weekly subcutaneous vitamin B12 (1000 µg) and had been administered a single dose of oxycodone/naloxone (5/2.5 mg) at an external hospital. Given the suspected drug-related contribution to his impaired consciousness, both neurology and clinical pharmacology were consulted for further evaluation.

Findings and Clinical Status

Blood pressure on admission was 129/61 mmHg, heart rate 109 bpm, oxygen saturation 92% on room air, afebrile. GCS was 9–10 (3, 2, 4–5), and pupils were markedly miotic bilaterally but reactive to light. There were no signs of meningismus or definite focal neurological deficits, Babinski sign negative bilaterally. Laboratory tests showed no evidence of electrolyte imbalance, hypoglycemia, or sepsis. Ammonia levels were within the normal range, and the COVID-19 test was negative. A trial dose of naloxone did not lead to clinical improvement. Further investigations, including brain MRI, EEG, and lumbar puncture, did not reveal a cause for the impaired consciousness.

Diagnosis

After ruling out other potential causes and given the close temporal association with recent chemotherapy, a presumptive diagnosis of 5-FU-associated neurotoxicity was made, and antidote

therapy with uridine was indicated.

Treatment and Clinical Course

In some countries, uridine triacetate is approved as Vistogard®, with a recommended dosage of 10 g orally every 6 hours for 5 days (total of 20 doses) [15,16]. However, it was found that uridine triacetate was not available anywhere in Switzerland. As an alternative, the less bioavailable uridine was administered at the same dosage. Under this treatment, the patient showed rapid clinical improvement, though with persistent amnesia for the preceding days. Retrospective testing revealed normal dihydropyrimidine dehydrogenase (DPD) activity. The patient was discharged to rehabilitation after 6 days, and after chemotherapy adjustment, no recurrence of symptoms was observed. An ADR report was submitted to Swissmedic via the regional pharmacovigilance center.

Discussion

5-FU is metabolized by the enzyme DPD (Fig. 1) [17]. The Swissmedic, the European Medicines Agency (EMA), and several professional societies, including the Swiss Society for Medical Oncology, recommend DPD phenotyping and/or genotyping (Table 1) before initiating systemic therapy with 5-FU or related drugs such as capecitabine [5,18,19]. However, despite these recommendations, routine DPD testing has not yet been widely implemented.

	Result	**Frequency**	**Interpration/ Consequences**	**Therapeutic Recommendation**
Genotyping	Partial DPD deficiency	~3–9% of Caucasians	Increased risk of 5-FU toxicity	Consider dose reduction
	Complete DPD deficiency	~0.01–0.5% of Caucasians	Risk of life-threatening or fatal toxicity	Contraindicated
Phenotyping (e.g., measurement of endogenous DPD substrate uracil in plasma)	≥16ng/ml		Indicator of partial DPD deficiency	
	≥150ng/ml		Indicator of complete DPD deficiency	

Table 1: Genotyping and Phenotyping of Dihydropyrimidine Dehydrogenase (DPD) [5, 19, 21, 22]

The combination of 5-FU with brivudine, an irreversible DPD inhibitor, is contraindicated, as fatal cases have been reported due to this interaction [5,22]. A minimum interval of 4 weeks should be maintained between brivudine and 5-fluoropyrimidine-containing drugs, and as an additional precaution, DPD activity should be assessed before treatment initiation [5].

In our patient, renal insufficiency was present. Since up to 20% of 5-FU is excreted unchanged by the kidneys, accumulation with exacerbation of neurotoxicity could not be ruled out [23,24]. Additionally, sedative co-medications (oxycodone, pregabalin, desloratadine) may have contributed to the impaired consciousness. However, naloxone administration did not improve symptoms, and at a low dose of 50 mg, pregabalin was unlikely to be the primary cause, even in the setting of renal impairment. Desloratadine, with a long half-life (~27 h), has been associated with a 1.5- to 2.5-fold increased exposure in patients with impaired renal function, but somnolence is a rare side effect [5]. Other non-drug-related differential diagnoses, including infectious, endocrine, and neurological conditions, which could also contribute to reduced alertness, were thoroughly investigated and largely ruled out in this case.

In cases of severe toxicity, uridine triacetate can be administered as an antidote within 96 hours after 5-FU or capecitabine exposure [15]. Uridine triacetate (Vistogard®) was approved by the FDA in 2015 [15] and is available as an unlicensed drug in the EU, UK, and Australia. Delivery from the EU takes approximately 48–72 hours, with treatment costs around 80,000 CHF [25]. Uridine triacetate is a prodrug with a 4–6 times higher bioavailability than uridine (bioavailability of approximately 6–10% for doses of 8–12 g/m² [26]) [16,27,28]. Uridine triacetate is rapidly absorbed and deacetylated in the bloodstream to free uridine, which competes with FUTP incorporation into RNA [15,27]. For non-acetylated uridine, a dose of 5 g/m² body surface area (BSA) every 6 hours for 3 days (total 12 doses) was well tolerated, with a maximum tolerated single dose of 10–12 g/m² [26]. This achieved peak serum uridine concentrations of 60–80 µM (single dose of 8–12 g/m²) and 50 µM (steady-state at 5 g/m²). The recommended uridine triacetate dosage for adults is 10 g every 6 hours for 20 doses (for children, 6.2 g/m² BSA, but not exceeding 10 g per dose) [15,16,26]. This results in approximately fourfold higher serum uridine concentrations compared to non-acetylated uridine [28]. Dose-limiting ADRs include vomiting (10%), nausea (5%), and diarrhea (3%) [16,26,28].

The safety and efficacy of uridine triacetate when administered beyond 96 hours have not yet been investigated in clinical studies [15]. However, case reports have documented clinical improvement even

with delayed administration [29–31]. In approval studies, 96% of patients (n = 130) treated with uridine triacetate within 96 hours after a 5-FU/capecitabine overdose or severe/life-threatening toxicity survived until day 30 (or resumed chemotherapy if before day 30); 4% (n = 5) died [15]. Among 135 patients, four were treated after 96 hours, of whom two died. In contrast, 98% of the 131 patients treated within the 96-hour window survived. Case reports indicate that supportive care alone following 5-FU overdose resulted in a mortality rate of 84% (n = 21/25), whereas the survival rate with uridine triacetate therapy was 97% (n = 109/112) [15].

Key Notes for Clinical Practice

- Neurotoxicity is a rare ADR of 5-FU and may present with nonspecific symptoms.
- Reduced DPD activity increases the risk of 5-FU-related ADRs and should be assessed before initiating therapy.
- Uridine triacetate has been approved as an antidote in the U.S. for several years and is available as an unlicensed product in the EU and other regions. The recommended dosage is 10 g orally every 6 hours for a total of 20 doses (for children: 6.2 g/m² BSA, max. 10 g per dose). Non-acetylated uridine, when used as an alternative, has significantly lower bioavailability, resulting in lower uridine concentrations.
- When assessing a suspected ADR, factors such as temporal correlation, drug interactions, elimination disorders, and enzyme polymorphisms should be considered. Suspected ADRs should be reported to Swissmedic, with mandatory reporting required for severe adverse reactions by healthcare professionals.

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Author Contributions: TA was responsible for patient care; LH, MH, and JG were involved as consultants. LH and EL prepared the first draft. All authors critically reviewed and revised the manuscript and approved the final version for publication.

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