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Hyperammonaemic Encephalopathy During Continuous Infusion of 5-Fluorouracil in the FLOT Regimen for Respectable Gastric Cancer: Two Cases.

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1. Introduction

5-Fluorouracil (5-FU) is a pyrimidine analog and is the backbone of systemic treatment of a wide variety of solid malignancies [1]. In the recent years, the administration of continuous infusion of 5-fluorouracil is becoming more popular in the (neo)adjuvant setting in gastric, pancreatic and metastatic colorectal cancer. We report two cases who developed hyperammonaemic encephalopathy after the continuous administration of high dose continuous infusion of 5-fluorouracil. The aim of this case series is to create awareness of neurological deterioration due to hyperammonaemic encephalopathy in patients treated with 5-FU, especially with higher dose of continuous infusion. Furthermore, we discuss the underlying pathology and possible treatment consequences.

2. Case 1

A 71-year-old male was diagnosed with a resectable cT3N1M0 gastric adenocarcinoma. He had a medical history of asthma, and a right-sided hemicolectomy for a villous adenoma. Pretherapeutic DPYD genotype analysis revealed no relevant genetic polymorphism, demonstrating a normal metabolizer phenotype for dihydropyrimidine dehydrogenase (DPD) [2]. He was treated according to the Dutch guidelines with neoadjuvant chemotherapy (FLOT) consisting of docetaxel 50 mg/m2, oxaliplatin 85 mg/m2, leucovorin 200 mg/m2 and fluorouracil 2600 mg/m2 as a 24-hour continuous infusion, all on day 1 [3]. The first cycle was administered clinically. Nineteen hours after the start of fluorouracil infusion, the patient became nauseous. Four hours later however, rapid neurological deterioration followed with loss of consciousness, with a Glasgow Coma Scale (GCS) of E3M1V1, a hemiparesis of his left side, and a Babinski sign of the left foot. Blood biochemistry showed no signs of infection, electrolyte imbalances, kidney failure or other abnormalities, except for an excessive accumulation of ammonia (>290 µm/L, normal range 10-45 µm/L), see (Table 1). Computer tomography angiography (CT-A) also showed no abnormalities. The patient was diagnosed with a 5-FU-induced hyperammonaemic encephalopathy. The infusion of 5-FU was interrupted immediately and the patient was transferred to the medium care where treatment with lactulose enema was started. Within 10 hours after start of treatment, the patient fully recovered neurologically. An additional magnetic resonance imaging of the cerebrum performed 24 hours after the onset of symptoms showed no abnormalities. Neo-adjuvant treatment continued with chemoradiotherapy according to the CROSS scheme with a total irradiation dose of 41.4 Gy in 23 fractions with five weekly intravenous administrations of carboplatin and paclitaxel.4 Nineteen weeks after start of chemoradiation, the patient underwent a laparoscopic total gastrectomy and pathologic examination revealed a ypT3N1 adenocarcinoma.

Table 1: Patient characteristics and biological variables at encephalopathy suspected diagnosis

		Case 1	Case 2
Age (years)		71	63
Type of carcinoma		Gastric tubulair adenocarcinoma	Gastric adenocarcinoma
Stage of disease		cT3N2M0	cT3N2M0
Treatment regimen		FLOT	FLOT
Absolute 5-FU dosage		5150 mg	4550 mg
Total 5-FU infusion time		24 hours	24 hours
Cycle during which hyperammonic encephalopathy occurred		1st	2nd
Weight loss (before start chemotherapy)		-8.3 kg (-9.0%)	-5.5 kg (-7.2%)
Laboratory tests	***Normal values***		
Hemoglobin (mmol/L)	8.5-11.0	7.8	7.6
Leukocytes (10^9/L)	4.0-11.0	12.9	12.2
Bilirubin (mmol/L)	<17	8.5	4
gGT (U/L)	<55	18	56
ASAT (U/L)	<35	22	33
ALAT (U/L)	<45	35	37
Kreatinine (umol/L)	60-110	77	92
eGFR (CKD-EPI) (ml/min)	>90	86	77
CRP (mg/L)	<6.0	<6.0	<6.0
Ammonia concentration at time of symptoms (umol/L)	<54	>290	>290
Ammonia concentration 24 hours after onset symptoms (umol/L)	<54	21	11
Intervention		Lactulose enema Transfer to medium care	Lactulose enema Transfer to medium care

5-FU: 5-fluorouracil, FLOT: docetaxel 50 mg/m2, oxaliplatin 85 mg/m2, leucovorin 200 mg/m2 and fluorouracil 2600 mg/m2, gGT: Gamma-glutamyltransferase, ASAT: Aspartate transaminase, ALAT: alanine aminotransferase, eGFR: Estimated Glomerular Filtration Rate (eGFR), CRP: C-reactive protein

3. Case 2

A few months later, a second patient with a 5-FU-induced hyperammonaemic encephalopathy was diagnosed. This was a 63-year old male patient with a resectable cT3N2M0 gastric adenocarcinoma, who presented without any further relevant medical history. Also in this patient, genotype analysis revealed a normal DPD metabolizer phenotype. Neo-adjuvant chemotherapy with FLOT was started on the outpatient clinic. The first cycle was clinically well-tolerated besides a mild vertigo (CTC grade 1) and neutropenia (grade 3), therefore the second cycle had to be postponed with one week. Fifteen hours after the start of the 2nd cycle the patient developed some nausea. The patient fully completed the cycle. Notably, 24 hours after end of the infusion with 5-FU, the patient was found unconscious at home. The patient was immediately hospitalized. At admission, neurological examination revealed a GCS of E2M4V2 with convulsions and involuntary eye-movements. CT-cerebrum showed no signs of acute ischemia or cerebral vascular bleeding. Laboratory tests were normal except for an ammonia blood concentration of >290 µm/L. Similar to case 1, treatment with lactulose enema was started. The patient neurologically completely recovered within 24 hours after start of treatment. Further neoadjuvant chemotherapy was cancelled and after a few weeks a subtotal gastrectomy was performed. The pathologic examination showed a R0-resection (ypT2N1). It was decided to restart FLOT as adjuvant chemotherapy. The dose of 5-FU was reduced by 50% and from the second cycle oral lactulose was given from day 0 till 2 because of an elevated ammonia blood concentration (85 µm/L) 24 hours after the first adjuvant cycle of FLOT. No relapse of hyperammonaemic encephalopathy was observed.

4. Discussion

We describe two gastric cancer patients who developed a 5-FU-induced hyperammonaemic encephalopathy following treatment with high dose 5-FU continuous infusion according to the FLOT regimen. Hyperammonaemic encephalopathy is a known metabolic complication of 5-FU, characterized by elevated blood levels of ammonia, decreasing level of consciousness, lethargy, vomiting and focal neurological deficits. Treatment involves cessation of the underlying cause of hyperammonaemia, and administration of lactulose enema.

Hyperammonaemic encephalopathy is a rare side effect of 5-FU

with a low incidence of 0.6-0.7%, however, with a high reported mortality of 17% [5-8]. It is characterized by an acute deterioration in mental status, with markedly elevated plasma ammonia levels, and no known history of liver cirrhosis. Unfortunately, the pathophysiology is only partly understood. Two mechanisms of accumulation of ammonia have been acknowledged, as visualized in (Figure 1). The first elicited mechanism of accumulation of ammonia is via the DPD pathway. 5,6-dihydro-5-fluorouracil (5-FUH2) is the primary DPD-mediated metabolite of 5-FU. 5-FUH2 is further catabolized into ammonia (NH3) and α-fluoro-β-alanine (FBAL).9 FBAL can be converted into fluoro-acetate, which directly inhibits the Krebs cycle. By inhibiting the Krebs cycle, less adenosine triphosphate, oxaloacetate and aspartate are produced, which are essential substrates for the urea cycle, and therefore for the degradation of NH3. One could speculate that not a low, but specifically a high DPD enzyme activity results in high and more rapidly achieved concentrations of 5-FUH2. This in turn results in higher ammonia concentrations, increasing the risk for hyperammonaemic encephalopathy. In routine clinical care it is only tested for DPD deficiency, however, it is not tested for high DPD activity. The second proposed mechanism is a pre-existing inborn deficiency of the urea cycle, that specifically may come to light following high dose infusion of 5-FU [10]. The amount of NH3 that is normally produced during the 5-FU administration alone is not sufficient to cause hyperammonemia. However, a congenital (partial) metabolism disorder of the urea cycle may specifically evoke hyperammonemia. In addition, this metabolism disorder may be further aggravated by other clinical conditions known to result in a decreased degradation of ammonia, such as renal dysfunction, dehydration, constipation, infection, weight loss and sarcopenia [5, 6, 8, 11]. Of note, both our cases had significant pre-treatment weight loss (case 1: -9.0%, case 2 -7.2%), most likely partly inherent to sarcopenia, that may have attributed to the development of hyperammonemia.

In a French national survey, no correlation between 5-FU dosage and ammonia levels was found, although data may suggest that patients admitted to the ICU with hyperammonic encephalopathy may have received higher doses of 5-FU than patients not admitted to the ICU.4 In another study, Liaw et al. showed that patients receiving high-dose 5-FU had higher ammonia levels than patients receiving lower-dose-5-FU.8 Taken together, all data described thus far, suggest a dose-effect relationship, or at least inter-individual variation in dose-response effect of 5-FU administration and ammonia blood concentrations. Following recovery, it is of especial importance to note that rechallenge of 5-FU in a reduced dosage is considered safe [5,6,8,12]. To prevent recurrence of hyperammonemia, Boileve et al. described a protocol consisting a free protein diet, Krebs and urea cycle intermediates and ammonium chelators [12].

Of interest, our patients were treated with the FLOT regimen, in which the dose of 5-FU of 2600 mg/m2 is administered within 24 hours. In contrast, other regularly applied treatment schedules such as the FOLFOX or FOLFIRINOX regimen, continuous 5-FU infusions of 44-46 hours are applied, resulting in relatively lower 5-FU blood concentrations. As nowadays high dose 5-FU continuous infusion such as in the FLOT regimen is becoming more frequently applied, oncologists should be aware of the potentially increased risk of hyperammonaemic encephalopathy and risk factors should be taken into account.

In conclusion, 5-FU-induced hyperammonaemic encephalopathy is a rare but serious adverse drug reaction that should be considered in neurologically deteriorating patients shortly following treatment with intravenous 5-FU. Further studies on the underlying mechanisms and clinical implications on the continuation of 5-FU based anti-cancer therapy are needed.

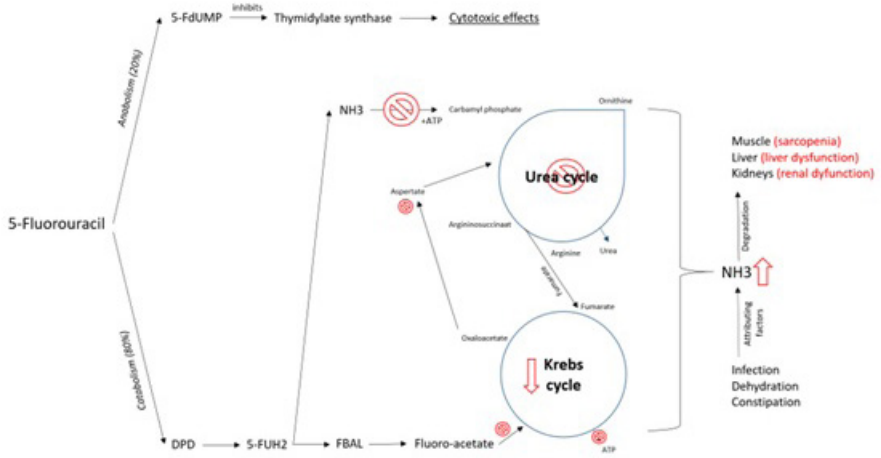

Figure 1: Pathophysiology of 5-Fluorouracil induced hyperammonic encephalopathy

Figure adapted from Boilève et al. This figures shows the two mechanisms leading to a hyperammonia after the administration of 5-FU; inhibition of the Krebs cycle in combination with a diminished urea cycle activation. In blue, aggravating factors and their working mechanisms are shown.

5-FdUMP: 5-fluorodesoxyuridine monophosphate, 5-FUH2: 5,6-dihydro-5-fluorouracil, DPD: dihydropyrimidine dehydrogenase, 5-FUH2: 5-fluorodihydrouracil, NH3: ammonium, FBAL: α-fluoro β-alanine, ATP: adenosine triphosphate

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