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# 5-Fluorouracil Neurotoxicity – Diagnostic and Clinical Implications

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**SUMMARY**

The aim of the study is to present the current state of knowledge on the rare side effect of 5-fluorouracil, what is neurotoxicity. Knowledge on this subject comes from a few studies, and many of the suggested mechanisms are still hypothesized. Also imaging diagnostics (MRI) or EEG do not provide certain diagnostic guidelines. Also, causal treatment in some patients has not yet been established. According to the summary of product characteristics, before starting treatment, the concentration of dihydropyridimine dehydrogenase (DPD) should be determined, the deficiency of which may cause serious complications, including fatal ones. In clinical practice, the concentration of DPD, due to the mass use of 5-Fu, is determined only in the presence of clinical symptoms, and before a decision to continue treatment is made, because DPD evaluation is not financed by the National Health Fund. For this reason, it is difficult to present a control group, i.e. patients who have the same toxicity as patients with DPD deficiency, but who have normal levels of it. Taking into account the high popularity of the use of 5-fluorouracil in the treatment of many neoplastic diseases, and thus the possibility of encountering a clinical situation in one's practice related to the suspected neurotoxicity after the use of the drug, it seems advisable to present a synthetic presentation of the current state of knowledge. The work is summarized by guidelines and recommendations for action.

**Keywords:** Chemotherapy; 5-Fluorouracil; Encephalitis

**Abbreviations:** 5-Fu: 5-Fluorouracil; DPD: Dihydropyridimine Dehydrogenase; FUTP: Fluorouridino Triphosphate; FdUMP: 5-Fluoro-2'-Deoxyuridine Phosphate; TS: Thymidol Synthetase; TPP: Thiamine Pyrophosphate; MIL: Multifocal Inflammatory Leukoencephalopathy

## Objective of the Work

The aim of the study is to present data on a rare or rarely diagnosed symptom, which is the toxicity of 5-Fluorouracil (5-Fu) to the nervous system. 5-Fu, a fluorinated pyrimidine, as an anti-cancer antimetabolite introduced into oncological treatment in 1957 and has found wide application in chemotherapy of a number of cancers. As it is an antimetabolite, there is no substitute, which makes it necessary to use it in many multi-drug chemotherapy regimens. The range of 5-Fu toxicity includes gastrointestinal toxicity and cardio-, neuro- and myelotoxicity. The neurotoxicity of interest can be acute or chronic. Patients may experience severe neurological toxicity after 5-Fu therapy also in the absence of myelosuppression and gastrointestinal toxicity. Acute neurological syndromes, including cerebellar ataxia and upper body motor symptoms, are primarily seen in patients receiving infusions for head and neck tumours, but neurological toxicity may also occur with weekly regimens (with 24-hour infusion). (hour is more toxic than bolus) [1].

## Clinical Pharmacology of 5-Fu

The drug belongs to the group of antimetabolites - pyrimidine antagonists, which remains stable for many weeks in solutions at physiological pH. 5-Fu has a cytotoxic effect after biotransformation to two appropriate nucleotides: fluorouridino triphosphate (FUTP) and 5-fluoro-2'-deoxyuridine phosphate (FdUMP). 5-Fu anabolism proceeds through three pathways, through the conversion of the parent compound to:

1. 5-fluorouridine-5'-monophosphate (FUMP) with the participation of phosphorylase and uridine kinase
2. FUMP mediated by orotate phosphoribosyltransferase and
3. FdUMP mediated by uridine kinase and thymidine phosphorylase.

This third way is considered the least important. A particularly important mechanism is the inhibition of thymidol synthetase (TS). The combined administration of 5-Fu with leucovorin increases the effectiveness of treatment, probably by stabilizing the FdUMP-TS complex in the presence of the leucovorin metabolite, i.e., 5,10-methylenetetrahydrofolate, which results in strong inhibition of DNA synthesis, and consequently leads to cell death. From 5 to 20% of the drug is excreted from the body in an unmetabolized form. The biological half-life of the drug after rapid intravenous administration is 10 to 20 minutes, and the main route of drug excretion is the gastrointestinal tract. Long-term intravenous infusion increases total body clearance from 0.5-2 L/min (for rapid administration) to 3-6 L/min, with the lungs rather than the gastrointestinal tract becoming the major route of excretion. Among the side effects of using the drug, apart from the toxic effect on the bone marrow and intestinal epithelium, there are also symptoms of brain and cerebellar damage after administration of high doses of the drug [2].

## Discussion

In the literature on the subject, we can find several clinical papers devoted to the issue of 5-Fu neurotoxicity, the vast majority of which are case studies [3]. Two main patterns of encephalopathy are recognized. The acute form is associated with hyperammonaemia and usually resolves with medical management. The delayed form is associated with multifocal inflammatory leukoencephalopathy and has been reported in patients receiving 5-FU in combination with levamisole.

## Acute Effects of High Doses of 5-Fu

Although administration of 5-FU alone is not considered a risk factor for the development of hyperammonemia, the drug may induce encephalopathies (posterior reversible, Wernicke-Korsakoff and hyperammonaemic), which usually occur after high cumulative doses of the drug, and clinically manifests as altered mental status and convulsions - the frequency of these symptoms is estimated at 0.6%. The differential diagnosis includes stroke, nonconvulsive status epilepticus, other encephalopathies (e.g., uremic, hepatic, drug-induced) as well as infections and psychogenic disorders. However, the history of recent administration of 5-FU is crucial. Acute encephalopathies are usually rare, reversible and do not require treatment, although fatalities have also been reported rarely. In the described large group of 30 cases of hyperammonemic encephalopathies from the years 1986-2018, the mortality rate due to them was 17% (although the standards of diagnosis and treatment have changed over the last 30 years); 57% of patients were admitted to the ICU and 70% achieved complete neurological recovery within 5 [2-10] days. Rechallenge with 5-FU was considered in 14 (67%) neurologically recovered patients, and relapse was observed in 57% of these. No recurrence of 5-FU-induced hyperammonaemic encephalopathy was observed as long as repeated 5-FU administration was performed with a reduced dose of 5-FU [4]. 5-FU-induced encephalopathy occurs in 5.7% of patients treated with high-dose 5-FU chemotherapy. Although some theories have been proposed, the mechanisms of 5-FU neurotoxicity are still poorly understood.

Risk factors described in the literature include azotemia, infections, dehydration and chronic constipation. Two mechanisms are known to contribute to its development. The first is dihydropyrimidine dehydrogenase (DPD) deficiency. DPD is the main enzyme that inactivates 5-FU, and patients with DPD deficiency may experience symptoms related to 5-FU accumulation. DPD deficiency is reported in 2.7% of cancer patients and is believed to be caused by a mutation in the DPD gene encoding the DPD enzymes. High concentrations of 5-FU in DPD deficiency penetrate into the cerebrospinal fluid and cause acute demyelination of neurons. The second mechanism is the catabolic type of 5-FU, which is known to be a milder type than DPD deficiency. Consistent with this mechanism, major catabolic pathways remain unaffected and transient accumulation of 5-FU catabolite causes encephalopathy by high infusion rates of 5-FU. Koenig and Patel postulate that administration of high doses of 5-FU induces fluoroacetate accumulation and directly inhibits the Krebs tricarboxylic acid cycle, which in turn impairs the adenosine triphosphate-dependent urea cycle, causing hyperammonemia. The osmotic effect of accumulated intracellular glutamine, which is the major metabolic product of ammonia metabolism in the brain, has been implicated in the pathophysiology of elevated intracranial pressure and cerebral edema exhibited in many cases of hyperammonemic encephalopathy. Hypovolemia leads to increased reabsorption of urea from the renal tubules.

Infection may lead to increased tissue catabolism and may cause dehydration with or without prerenal azotemia. Chronic constipation can lead to increased production of ammonia in the colon through the action of bacterial urease and amino acid oxidase. As an aggravating factor for 5-FU-induced encephalopathy, its development can be attributed to renal dysfunction and dehydration, constipation and weight loss. In patients with renal dysfunction or patients who are dehydrated, blood levels of 5-FU catabolites such as fluoroacetate or ammonia will increase, causing encephalopathy [5]. Another theory to explain the neurological adverse effects of 5-FU therapy is that the drug causes thiamine deficiency. The active form of the vitamin is thiamine pyrophosphate (TPP). Exposure to 5-FU may increase TPP levels. This theory is supported by the fact that the symptoms of Wernicke-Korsakoff syndrome, including ataxia, nystagmus, confusion and cognitive changes, are similar to the neurotoxic effects of fluorouracil. Dehydropyrimidine dehydrogenase (DPD) is an enzyme

that breaks down 5-FU, and DPD is distributed in the liver, gastrointestinal mucosa, and peripheral lymphocytes. More than 80% of the administered 5-FU is catabolized by DPD. Thus, a deficiency of this enzyme can cause life-threatening or fatal toxicity in patients treated with fluoropuridine-based chemotherapy. The incidence of DPD deficiency in cancer patients is estimated at 2.7%, and this disease may be accompanied by severe fluorouracil toxicity [6]. In addition, inhibition of ATP production is believed to be the cause of lactic acidosis, often seen with 5-fluorouracil toxicity [7].

## Acute Effects of Low Doses of 5-Fu

Encephalopathy due to low doses of 5-fluorouracil is very rare and not well documented in the literature. Few cases have been reported, and in most patients the neurologic symptoms were transient, usually resolving after discontinuation of the drug, and recovery was often complete within a few weeks. Neurological toxicity manifested by somnolence, confusion, convulsions, cerebellar ataxia and rarely encephalopathy was uncommon. Treatment included hydration and supportive care. Leucovorin, which is commonly combined with 5-FU in regimens, enhanced the anticancer effect and, at the same time, the toxicity [8].

## Chronic Consequences of 5-Fu Use

Neurological toxicity includes peripheral neuropathy and encephalopathy. Clinically, it manifests as cerebellar disorders and multifocal inflammatory leukoencephalopathy (MIL), in which the addition of levamisole to 5-Fu was a risk factor. These diseases do not have an established causal treatment [9]. 5-FU encephalopathy is less frequent and less well defined, with clinical features more typical of diffuse metabolic encephalopathy. It often occurs with concomitant metabolic abnormalities. Drug interactions with levamisole and possibly other chemotherapeutic agents may play an important, though undetermined, role in the pathogenesis of this syndrome. MIL is a cerebral demyelinating syndrome that develops after chemotherapy with 5-fluorouracil (5-FU) and levamisole, although a case of a patient who developed MIL after administration of 5-FU alone has been described. This patient was diagnosed with a partial deficiency in dihydropyrimidine dehydrogenase, an enzyme necessary for the catabolism of 5-FU, suggesting that MIL appears to present a distinct clinical and radiographic syndrome with 5-FU alone and that patients with dihydropyrimidine dehydrogenase deficiency are at increased risk for this condition. and other toxic effects of 5-FU [10].

## Conclusion

1) Clinical criteria for the diagnosis of 5-fluorourail-associated encephalopathy are as follows:

a) Development of an encephalopathy during or shortly after 5-FU administration;

b) Absence of other metabolic factors that may affect consciousness and mental functioning, such as hypoglycemia, organ failure, electrolyte imbalances, sepsis, and central nervous system involvement by cancer;

c) The absence of any side effects resulting from the concomitant use of other drugs [11].

2) Hospital emergency department physicians, family physicians and oncologists should be aware of the potential for rare side effects of 5-FU chemotherapy and how to diagnose and treat them.

3) After excluding other causes of deterioration by MRI and EEG (stroke, central nervous system metastases), a history of recent 5-Fu use is important.

4) The neurological and psychiatric examination of a patient receiving 5-Fu should include the assessment of ammonia levels.

5) Proper identification and diagnosis of 5-Fu-associated hyperammonemic encephalopathy is critical as recovery from treatment can be rapid [12].

6) Uridine triacetate, an antidote to 5-Fu, is used to treat severe forms [13].

## References

1. VT De Vita, S Hellman, SA Rosenberg (2001) Principles and practice of oncology, 6th. ed., Lippincott Williams & Wilkins.
2. Drzewoski J, Robak T (1991) Farmakologia kliniczna leków przeciwnowotworowych. Warszawa s p. 71-77; Denisso T, Kowalski DM (2006) Przegląd leków stosowanych w onkologii. Krzakowski M red Onkologia kliniczna Warszawa tom I s pp. 241-256.
3. Chahin M, Krishnan N, Chhatrala H, Shaikh M (2020) 5-Fluorouracil-Induced Hyperammonemic Encephalopathy Challenged with Capecitabine. Case Reports in Oncological Medicine 2020: 1-4; WW Lee, JS Kim, KR Son, HM Kwon (2012) Atypical diffusion-restricted lesion in 5-Fluorouracil encephalopathy. American Journal of Neuroradiology 33(7): E102-E103; Yeon a Kim, Hyun Cheol Chung, Hye Jin Choi, Sun Young Rha, Jin Sil Seong, et al. (2006) Intermediate Dose 5-Fluorouracil-Induced Encephalopathy. Japanese J of Clin Oncol 36(1): 55-59; Pooja P Advani, Marvan G Faikh (2011) 5-FU-induced hyeprammonemic encephalopathy in a case of metastatic rectal adenocarcinoid successfully rechellanged with the fluoropirymidyne analog, capecitabine. Anticancer Research 31(1): 335-338.
4. Boilève A, Thomas L, Lillo Le A, Gaboriau L, Chouchana L, et al. (2020) 5-Fluorouracil-induced hyperammonaemic encephalopathy: A French national survey. Eur J Cancer 129: 32-40.
5. Hee Jung Yi, Kyung Sook Hong, Nara Moon, Soon Sup Chong, Ryung Ah Lee, et al. (2016) Acute hyperammonemic encephalopathy after 5-fluorouracil based chemotheraphy. Ann Surg Treat Res 90(3): 179-182.
6. Kwon Kyong, Kwon Hyuk Chan, Kim Min Chan, Kim Sung Hyun, Oh Sung Yong, et al. (2010) A case of 5-Fluorouracil induced encephalopathy. Cancer Res Treat 42(2): 118-120. Kun Huei Yehl, Ann Lii Cheng (1998) 5-Fluorouracil-related encephalopathy: At least two distinct pathogenetic mechanisms exist – reply. British Journal of Cancer 77(10): 1711-1712.
7. Welu A, Quan M, Nwankwo E, Brotherton T, Das D, et al. (2021) 5 Fluouracil hyperammonemia: A rare cause of encephalopathy. Meeting SHM Converge abstract number 727.
8. Amy L Chue, Indrjit N Fernando, Syed A Hussain, David A Yates (2009) Chemotherapy related encephalopathy in a pateient with stage IV cervical

carcinoma treated with cisplatin and 5-fluorouracil: A case report. Cases Journal 2: 8526.

9. Schlegel U (2011) Central Nervous System Toxicity of Chemotherapy. European Association of NeuroOncology Magazine 1(1): 25-29.
10. Correia RR, Vieira PL, Paiva P, Martin S, André ME (2020) Encefalopatia por 5-Fluorouracil. Sinapse 20(1): 68-70. Acharya G, Carreras Maria T Cruz, Rice TW (2017) 5-FU-induced leukoencephalopathy with reversible lesion of splenium of corpus callosum in a patient with colorectal cancer. BMJ Case Rep.
11. David A Franco, Harry S Greenberg (2001) 5-FU multifocal inflammatory leukoencephalopathy and dihydropyrimidine dehydrogenase deficiency. Neurology 56(1): 110-112.
12. Welu A, Quan M, Nwankwo E, Brotherton T, Das D, et al. (2021) 5 Fluouracil hyperammonemiaop. cit.; Meeting: SHM Converge, abstract numer 727.
13. Yano Y, Kuriyama A (2020) 5-Fu-iduced encephalopathy. Cleveland Clin J of Med 87(9): 532-533.

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