Adverse effects of 5-fluorouracil: Focus on rare side effects

Sonia Amin Thomas1,2*, Zhuliet Grami1*, Sharvil Mehta1*, Kushal Patel1*

1PCOM School of Pharmacy Suwanee, GA, 30024 USA
2Wellstar North Fulton Hospital Roswell, GA, 30076 USA

*These authors contributed equally to this work
Correspondence: Sonia Amin Thomas
E-mail: soniapa@pcom.edu
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5-fluorouracil (5-FU) is an antimetabolite chemotherapy drug. 5-FU has many adverse effects like any other chemotherapy agent as it has effects not only on cancer cells, but healthy cell as well. Serious side effects which are uncommon (occurring in about 1% of patients) and will be the focus of this paper are cardiac effects, hyperammonemia or encephalopathy and neurologic effects. There are many other side effects associated with 5-FU. In this paper we will discuss the rare side effects and alternatives on what to do if they occur during treatment based on case reports.

**Keywords:** 5-FU; adverse effects; hyperammonemia; cardiotoxicity; neurological; Abbreviations: 5-FU (5-fluorouracil)

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**Introduction**

5-fluorouracil (5-FU) is an antimetabolite chemotherapy drug. It was discovered in the 1950’s by observing the rats used uracil (one of the four bases of RNA) quicker than normal tissues which showed that this would be a huge target for chemotherapy. 5-FU is used in many cancers such as colorectal, breast, gastrointestinal cancers, pancreatic, head and neck cancers and various others. It has had one of the biggest impacts on colorectal cancers as a single agent and in combination with other agents. It exerts its’ effects by inhibiting normal synthesis or DNA and RNA. 5-FU is converted to active metabolites known as FdUMP (fluorodeoxyuridine monophosphate), FdUTP (fluorodeoxyuridine triphosphate) and FUTP (fluoroouridine triphosphate) which interfere with RNA synthesis and thymidylate synthase. 5-FU also works synergistically with leucovorin and antagonistically with methotrexate[1].

5-FU has many adverse effects like any other chemotherapy agent as it has effects not only on cancer cells, but healthy cell as well. The most common side effects (occurring in greater than 30% of patients) are diarrhea, nausea, vomiting, mouth sores, poor appetite, photosensitivity, metallic taste, neutropenia and thrombocytopenia. Less common side effects (occurring in about 10-20% of patients) are skin discoloration, dermatologic effects, alopecia, nail changes and hand-foot syndrome. Serious side effects which are uncommon (occurring in about 1% of patients) and will be the focus of this paper are cardiac effects, hyperammonemia or encephalopathy and neurologic effects[2]. There are many other side effects associated with 5-FU. In this paper we will discuss the rare side effects and alternatives on what to do if
they occur during treatment based on case reports.

5-fluorouracil is a commonly used chemotherapeutic agent that has been around for many years [3]. It is used in cancer treatments ranging from breast cancer, colorectal cancer, gastric cancer, pancreatic cancer, bladder cancer, cervical cancer, esophageal cancer, etc [4]. Many cancer treatments have short term adverse effects, but there are instances where the effects are seen long after discontinuing the medication with 5-Fluorouracil in particular [5]. Many of the common known side effects of 5-Fluorouracil are diarrhea, nausea/vomiting, mouth sores, loss of appetite, sensitivity to light, taste changes, skin discoloration, low blood count, etc. [4]. A lesser known side effect of 5-Fluorouracil is the long term neurological effects it has. It causes healthy brain cells to die long after the treatment has been finished [5]. A term commonly used by cancer survivors is chemo brain. This is a condition where cancer survivors have cognitive impairment or dysfunction most commonly seen as memory problems. Examples of this would be memory lapses, slower thinking, and trouble concentrating, multi-tasking, and remembering words [6]. 5-Fluorouracil may be one of the underlying causes to these cognitive side effects, because studies have shown that around 15 percent to 20 percent of breast cancer survivors have cognitive impairment and problems years after therapy has concluded [5].

5-Fluorouracil is toxic for CNS progenitor cells and non-dividing oligodendrocytes [5, 7]. It can cause short term CNS damage as well as having long term effects due to the damage to myelinated tracts in the CNS [7]. Researchers have studied in mice that after months of exposure to 5-fluorouracil there was extensive damage to the oligodendrocytes and dividing precursor cells and after six months these cells had nearly all disappeared. Oligodendrocytes produce the myelin sheath in the central nervous system, which allows for communication and electrical synapses between nerve cells [5]. So damage to these cells could causes the cognitive dysfunction seen in patients with chemo brain.

These adverse effects are not seen in all cancer survivors and often times are more prevalent in some cancer survivors compared to others [5]. Currently there is no definitive treatment for this condition, but there are ways to manage chemo brain [6]. The most important thing patients can do is to alert their friends and family of their condition so they can understand and help in any way possible [8]. Other ways to manage chemo brain is to keep a daily planner or calendar to track your day to day events. They can make sure to exercise the brain by doing word puzzles, reading, learning a new language, etc. It is also important to exercise the body as well, since physical exercise and activities can help in feeling better. Eating more vegetables and getting plenty of sleep and rest also helps in memory and cognitive dysfunction. Lastly keep track of all memory problems encountered, this is to make sure that the condition is not worsening and it helps on what improvements can be made to manage the condition. There are options of using Alzheimer’s medication such as donepezil or Namenda in these patients. ADHD medications such as methylphenidate may also be helpful as well [6, 8].

A cardiotoxicity that shows similar characteristics to ischemia has been associated with the administration of 5-FU in cancer patients. It may lead to dysrhythmia, ECG changes, cardiorespiratory symptoms, acute MI, cardiac shock, or even sudden death. The incidence of 5-FU cardiotoxicity is 7.6% with mortality ranging between 2.2% and 13% [9].

In a clinical trial 5-FU was given to 377 people between the ranges of 14 to 86 years old with median age of 57. The dosages of 5-FU used were <750 mg/m2/day (36%), 751-999 (16%), 1,000 (26%), 1,001 - 1,499 (4%) and 1,500 (16%). Sixty nine percent of patients experienced cardiac incidences within 72 hours of the first cycle of 5-FU. Angina occurred in 45% of patients whereas myocardial infarction was seen in 22%, arrhythmias in 23%, acute pulmonary edema in 5%, cardiac arrest and pericarditis in 1.4% and heart failure in 2%. Electrocardiographic evidence of ischemia or ST-T changes were recorded in 69% and cardiac symptoms were reproducible in 47% of patients. Based on the study, the results suggested that 5-FU cardiotoxicity is an uncommon but real occurrence that is independent of dose and may be related to a continuous infusion schedule [9].

The exact cardiotoxicity phenomenon of 5- FU is not fully understood and its mechanism still remains unclear, but one most often proposed idea is ischemia to myocardium. Ischemia could be due to a direct toxic effect on the vascular endothelium involving NO synthase, which leads to coronary vasospasms. In vitro studies by one group of researchers suggest that 5-FU causes direct vasoconstriction of vascular smooth muscle, which is mediated by the activation of protein kinase C (PKC). Another study proposes that 5-FU toxicity is a cardiomyopathic process of undetermined mechanism. Yet another assumption suggests that cardiotoxicity is due to the uncoupling of the electromechanical mechanisms that underline normal myocardial function, which could be mediated at the level of the cell membrane [9].

In several studies Capecitabine, an oral pro-drug of 5-FU, have been utilized as an alternative agent to reduce the adverse effect of 5-FU. It has been reported that Capecitabine still will induce cardiotoxicity, however to lower extent
(1.5% to 2% lower than of 5-FU), and it is not advisable to give Capecitabine to patients with history of 5- FU-induced cardiotoxicity [9].

Treatment of cardiotoxicity with 5-FU starts by ceasing the drug as soon as acute cardiotoxicity is recognized. Then nitrates or calcium channel blockers should be initiated. Some studies also recommend ACE inhibitors as prophylaxis for the prevention of 5-FU induced cardiomyopathy without effect. Regarding patients that are symptomatic, cytostatic regimens must be adjusted according to each case. It could be probable that 5-FU toxicity is reversible in the majority of cases when acute complications such as arrhythmias are resolved [9].

Experts suggest careful monitoring for cardiotoxicity during the infusion of 5-FU and a multidisciplinary monitoring should be approached to maximize clinical benefit and reduce potential harm. Continued administration with 5-FU should be reserved only for those patients who have no reasonable alternative. For those patients therapy should take place in a very careful monitored setting while applying aggressive prophylaxis. Studies show that 5-FU-induced toxicity can be reversed with responsive care in many circumstances [9].

Cases of a rare side effect with the antineoplastic drug, 5-Fluouracil (5-FU), have been reported with high dose administration. Common side effects include nausea and vomiting, mouth sores, light sensitivity, and metallic taste. At the current standard infusion dose of 2400 mg/m² over 46 hours every 2 weeks, this particular side effect is uncommon. Hyperammonemia neurotoxicity is seen at high-doses of 2600 mg/m² over 24 hours/weekly [10]. It has been reported in 5.7% of patients receiving this higher dose. The toxicity can occur anytime between 0.5 to 5 days after the administration of 5-FU [11]. Hyperammonemia encephalopathy presents in patients as acute onset of altered mental status, lactic acidosis, and respiratory alkalosis accompanying increased plasma levels of ammonia [10]. A clinical study found the ammonia level for the participants in the study ranged from 248 to 2387 µg% [12].

The administration of 5-FU, itself, isn’t a risk factor but many precipitating factors are involved. Infection, hypovolemia, constipation, and azotemia are the four known factors in developing the rare adverse effect. Sepsis can lead to multiple organ failure from insufficient perfusion to tissues resulting in improper urea excretion by the kidneys. Ammonium is converted to urea by the liver, and urea resorption is influenced by water resorption. Elevated levels occur due accumulation of the primary metabolite of 5-FU, ammonium, and resorption in the renal tubules by the kidney. Colorectal and cervical cancer can cause obstructive uropathy and cancerous peritonitis which can result in the development of azotemia, intestinal obstruction, or constipation exacerbating the development of the rare side effect of 5-FU [12]. Another postulated mechanism of constipation could be a result of bacterial urease and amino acid oxidase in the colon leading to an increase in ammonia levels [10].

The mechanism of action for resulting in hyperammonemia encephalopathy is currently not well understood. A proposed theory is that fluoroacetate, the intermediate of 5-FU metabolism, inhibits the Krebs cycle which impairs adenosine triphosphate (ATP)-dependent urea cycle. The impairment of this cycle leads to a buildup of ammonia. A major metabolite of ammonia metabolism in the brain, glutamine, produces an osmotic effect elevating the intracranial pressure and causing cerebral edema [10].

The most common clinical presentation for most patients is altered mental status and confusion. Two case reports in literature managed hyperammonemia with supportive care such as sufficient hydration and lactulose [10, 11]. A male patient with chronic kidney disease received FOLFOX plus Avastin for treatment of his colon cancer, his 5-FU dose was 2400 mg/m² continuous I.V infusion over 46 hours. On the third cycle he presented to the Emergency Room with with altered mental status. The patients elevated liver enzymes and the ammonia level was 611.1 mmol/L. He was on a ventilator and after receiving hemodialysis, adequate hydration and lactulose; after two days, his ammonia level returned back to normal [11]. That patient was re-challenged with 5-FU a week later but the dose was halved; he did not experience any further hyperammonemia episodes with the chemotherapeutic agent.

Another case report is described as a female patient with history of localized adenocarcinoid of the rectum treated for a one-year period until her disease progressed with metastases to the lung and liver. She began with the treatment regimen FOLFIRI plus Avastin for treatment of his colon cancer; his 5-FU dose was 2400 mg/m² continuous I.V infusion over 46 hours. The dose of 5-FU was administered at 2400 mg/m² over 46 hours of continuous IV infusion, and she received this therapy for eight cycles (four months. She was instituted a break from severe nausea and vomiting from the 5-FU. The patient developed altered mental status, intracranial nausea and vomiting, diarrhea, and disorientation after chemotherapy was re-initiated once computed tomography (CT) scan showed progressive disease. Her abnormal ammonia level of 203 mmol/L was the only significant laboratory finding. She was treated with hydration and lactulose and continuous monitoring of her mental status; her ammonia levels began to normalize after two days. In
continuing her chemo regimen, 5-FU was discontinued and capecitabine, the prodrug of 5-FU, was initiated instead at 1500 mg/dose twice a day for 14 days every 3 weeks in addition to Avastin \[10\]. No form of neural toxicity or rise in ammonia levels were seen thereafter.

**Conclusion**

In conclusion, even though 5-fluorouracil has been used for many years some of these adverse effects are only coming into light recently. These adverse effects are only seen in some cancer patients and have varying effects from patient to patient \[7\]. Our knowledge on the long term effects of this drug is limited but it can be said that there is harm associated with long term use of this medication in certain patients. Whether these effects worsen over time or not has yet to be seen. As of now patients must find ways to cope with these cognitive issues through supportive care.

**Conflicting interests**

The authors have declared that no conflict of interests exist.

**Author’s Contributions**

SAT contributed to background information, organization and all other sections. ZG contributed by assistance in writing the section about cardiotoxicity with 5-FU. SM contributed by assistance in writing the section about hyperammonemia with 5-FU. KP contributed by assistance in writing the section about long-term neurologic effects with 5-FU. All authors approved and read the final manuscript.

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