VIA MEDICA

CLINICAL VIGNETTE

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Complications associated with accelerated 5-fluorouracil (5-Fu) infusion

Keywords: 5-Fu, 5-fluorouracil, toxicity

Introduction

Antimetabolite 5-fluorouracil (5-Fu) has been used in oncology since over 70 years. It still maintains its position as a basic cytostatic in the treatment of cancer. 5-Fu is analog of tymidine inhibiting DNA and RNA synthesis (Fig. 1). This drug was administered intravenously with bolus injections in the 60's and the 70's of the XX century. Results of prospective clinical trial of Seifert's et al. [1] showed a comparison of systemic prolonged infusion of 5-Fu *versus* intravenous bolus injection daily for 5 days. A higher response rate and lack of myelotoxicity were advantages of prolonged 5-Fu infusion [1]. New era of 5-Fu infusions begun in the 80's of the XX century when devices for central venous access and infusion pumps were introduced into clinical practice. Lokich et al. [2] started to develop concepts of prolonged infusion of 5-Fu to increase exposition of neoplastic cells in order to reach maximal efficacy.

Possibility of modifying 5-Fu metabolism by dihydropyrimidine dehydrogenase (DPD) has been proven [2]. Dihydropyrimidine dehydrogenase is an enzyme that plays an important role in catabolizing 5-Fu in the liver. It's deficiency (e.g. due to a mutation in the DPD gene) contributes to the occurrence of severe adverse events [3, 4]. High activity of DPD inside neoplastic cells diminishes significantly cytotoxic effect of 5-Fu [3].

Meta-analysis of randomized trials comparing the administration of 5-Fu by continuous intravenous infusion and bolus administration of 5-Fu showed that prolonged infusion of 5-Fu increased dose intensity up to 5 folds compared to bolus injection with a relatively low incidence of complications and with higher response rate and longer overall survival [5].

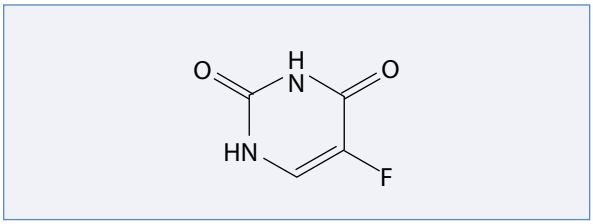

Figure 1. 5-fluorouracil (5-Fu) chemical formula

Long infusions are connected with lower percentage of marrow myelosuppression but they can induce gastrointestinal side effects sometimes dose-limiting such as mucositis, diarrhea, nausea, vomiting, decrease appetite and skin toxicity. 5-Fu given with bolus injection causes myelotoxicity sometimes limiting the dose of anti-cancer drug. There is a greater risk of toxicity in patients over 70 years old and in women.

Case presentation

A 72-year old female with rectum adenocarcinoma diagnosed in August 2022 in stage IV (metastases in

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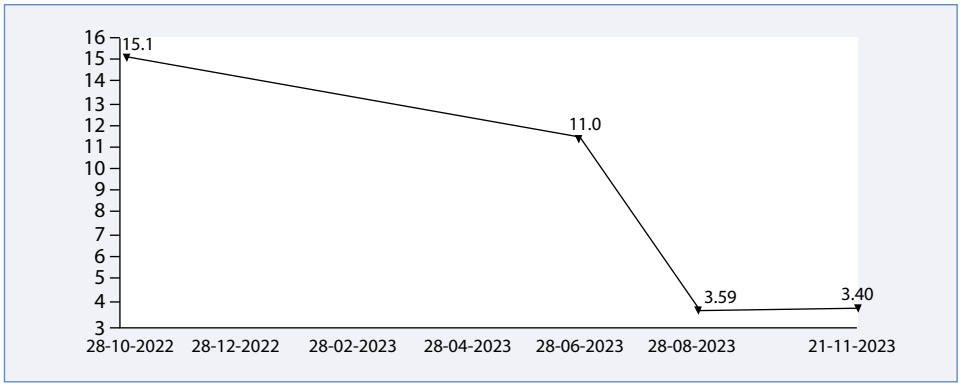

Figure 2. Carcino-embryoic antigen (CEA) test results chart

aortal lymph nodes). The patient was qualified for chemotherapy FOLFOX6 regimen due to the detection of a *KRAS* mutation in a molecular test. On the basis of biochemical investigation before starting the anti-cancer therapy the only abnormality was secondary anemia. As a result of device error (probably piezoelectric system failure) patient received the whole dose of 5-Fu in 2 hours instead of 46 hours as 5th cycle in February 2023. Granulocyte colony stimulating factors (G-CSFs) were given and oral care was recommended. Patient in good general condition was discharged from the hospital. The patient was admitted to the hospital seven days later (without earlier contact with oncologist) due to symptoms of mucositis G4 according to common toxicity criteria for adverse events (CTCAE) and diarrhea. Neutropenia (0.3 × 10^3/uL), anemia (Hb-9.3 g/dL), increased infection parameters [C reactive protein (CRP) = 144.00 mg/L, procalcitonin BRAHMS = 0.14 ng/mL], electrolyte disturbances: hypocalcemia (Ca 1.92 mmol/L), hypophosphatemia (P-0.51 mmol/L) have been revealed. A central vascular access was inserted. We implemented hiperosmolar diet, topical preparations (Nystatin) and an intravenous antifungal drug (Fluconazole). Due to increase of CRP and procalcitonin positive empirical antibiotic therapy (meropenem with vancomycin) was initiated, electrolyte disturbances were replenished parenterally. The use of G-CSF was continued. Results of bacteriological blood and stools culture were negative. Results of bacteriological culture from oral cavity raised yeast-like fungi.

After normalization of blood cell count and electrolyte disorders, remission of diarrhea the patient was discharged home in good general condition.

Due to hospitalization there was an interruption in therapy. Follow-up computed tomography (CT) scan was performed in August and in November 2023. The carcino-embryoic antigen (CEA) marker level remained normal (Fig. 2). The patient was scheduled for the next follow-up examinations but she did not come.

Discussion

The development of advanced software techniques allowed for more accurate infusions and significantly relieved the health system. Yet, there's no device without imperfections. With every development there's need to qualify medical staff to minimize mistakes.

It is important to educate patients about side effects symptoms so that they can assess when there is a need to urgently report to the center responsible for treatment in the event of serious complications. There is a need to define procedures in case of 5Fu overdose in every oncological department.

Article Information and Declarations

Ethics statement

Article have been conducted according to the principles stated in the Declaration of Helsinki. All authors have read and agreed to the published version of the manuscript.

Author contributions

All authors were responsible for designing the study, collecting data, and writing the article.

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Conflict of interest

Authors declare no conflict of interest.

Supplementary material

None.

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