Variability in fluorouracil exposure during continuous intravenous infusion

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Introduction

Fluorouracil (5-FU) is an anticancer antimetabolite, which has been used for many years in the treatment of solid tumors such as colon, gastric, rectal and head and neck cancer. The individual 5-FU dose is usually calculated according to the patient’s body surface area (BSA). Several studies have shown that BSA poorly predicts drug exposure leading to under- and overdosage in many patients [1]. It is common practice to reduce the dose when symptoms of severe toxicity occur but the dose is rarely increased to enhance efficacy.

Recently, a dose adaptation strategy based on a pre-defined target exposure and regular plasma concentration measurements was successfully applied for 5-FU. After continuous intravenous infusion (c.i.v.) of 5-FU a target AUC of 20 – 24 mg×h×l–1 was associated with better tumor response and less toxicity compared to BSA-based dosing [2]. However, therapeutic drug monitoring (TDM) of 5-FU is still limited to specialized hospitals. It was the aim of this study to explore the feasibility of plasma concentration measurements for 5-FU in clinical routine.

Patients and methods

This study was approved by the Ethics Committee of the University of Bonn and conducted on the medical ward for outpatients in the Center for Integrated Oncology (CIO) of the University of Bonn and the Johanniter Hospital in Bonn, Germany from September 2010 to February 2011. Written informed consent was obtained from the patients prior to inclusion. The patients suffered from colon, gastric, rectal or head and neck cancer. The dose of 5-FU ranged from 200 mg/m²/d over 21 days to 3,000 mg/m² for 46 h. For outpatients, Baxter Folfusor® pumps were used for 24 – 46 hours c.i.v. of 5-FU in isotonic saline solution.

Blood samples of patients were obtained from a peripheral vein in the arm opposite of the infusion arm. Although 5-FU has a short half-life of 8 – 20 min [3] suggesting that steady-state is reached 1 hour after the start of the infusion, plasma concentrations after 2 – 3 h were found to be 50% lower than those measured after 21 h [4]. Based on this experience, we collected the plasma sample at least 18 h after starting, but before the end of the 5-FU infusion. Samples were collected into tubes containing EDTA, immediately put on ice and centrifuged at 3,000 rpm for 10 min at room temperature. After centrifugation of the samples, about 1 ml plasma was aspirated, stored at –80 °C and then shipped to the University Hospital of Essen for analysis.

Individual plasma concentrations were determined using the My5-FU® homogeneous immunoassay (Saladax Biomedical Inc., Bethlehem, PA, USA) [5]. A standard curve of absorbance versus 5-FU concentration was generated, and the concentration of 5-FU in patients’ samples was determined from this standard curve. AUC was calculated by multiplication of the steady-state concentration by duration of the infusion.

Toxicity was evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE) v3.0. [6].

Results and discussion

5-FU plasma concentrations in 33 samples have been analyzed. Steady-state concentrations and clearances of 5-FU varied considerably among patients (Table 1). AUC values ranged from 11.9 to 55.0 mg×h×l–1 with a mean of 25.9 and standard deviation of 10.2 mg×h×l–1 (CV 39.5%). Most
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of the patients (90.9%) exhibited an AUC value outside the target range (36.4% below, 54.5% above). Only 3 out of 33 patients exhibited an AUC within the target range indicating that BSA-based dosing generally fails to achieve the target exposure.

The results suggest that the measurement of 5-FU plasma concentrations is useful in clinical routine. Nevertheless, some critical issues and potential pitfalls have to be considered in order to exclude pre-analytical errors such as blood collection from the same arm that is used for 5-FU infusion. Therefore, it is crucial to instruct the hospital staff carefully in the sample collection and storage procedures. Moreover, it is important to verify for each individual patient that the infusion is still running during blood collection since the duration of infusion may be shorter than expected. If infusion has terminated before blood collection, the measured concentrations no longer reflect the steady-state concentration and must not be used for AUC calculation.

In order to explore the relationship between plasma concentration and toxicity, we divided the patients into 2 groups: Group A (patients with AUC below or within target range), and Group B (above target range). The observed toxicity included diarrhea (10 patients), mucositis (10), anemia (17), leucopenia (4), neutropenia (1), and thrombocytopenia (1). Despite the small number of patients there seems to be an association between high plasma exposure and the incidence of diarrhea and mucositis. Whereas 7 out of 18 patients (38.9%) in group B with AUC values above the target range exhibited diarrhea, this type of toxicity occurred only in 3 out of 15 patients (20.0%) in Group A with lower exposure. In the case of mucositis we observed the same type of distribution. For hematotoxicity, there was only a slight tendency for a higher incidence of toxicity in Group B: anemia and leucopenia occurred in 7 (46.7%) and 1 (6.7%) patients of Group A compared to 10 (55.6%) and 3 (16.7%) patients of Group B, respectively. The only cases of neutropenia (Grade 3) and thrombocytopenia (Grade 1) were observed in patients with AUC values above the target range (Group B).

Conclusions

Our results demonstrate that BSA-based dosing results in a large variability in 5-FU exposure and fails to achieve the target exposure in more than 90% of the patients. Therapeutic drug monitoring of 5-FU can be conducted in clinical routine and is urgently needed to control the systemic exposure of
5-FU. Our data suggest that dose adjustments may reduce the incidence of diarrhea and mucositis. A further study with a larger number of patients should be carried out to develop a dose adaptation algorithm based on population pharmacokinetic data.

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**References**


