

Therapeutic Drug Monitoring of 5-Fluorouracil: An Approach Whose Time Has Come

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Scope of the lecture:

This lecture will review the role of therapeutic drug monitoring (TDM) of the fluoropyrimidine 5-fluorouracil (5-FU) with respect to the treatment of colorectal cancer and discuss and review the consensus documents, guidelines, and recommendations for 5-FU TDM.

Learning objectives:

1. Review the key pharmacological issues that were used to assess the suitability of applying TDM for 5-FU therapy.
2. Review the conclusions relating to the potential suitability of applying TDM for 5-FU therapy.
3. Review the guidelines and recommendations on TDM for 5-FU therapy in patients with colon cancer and other human cancers.

Abstract:

5-FU has played a critical role in the systemic chemotherapy of cancer patients for over 50 years. 5-FU serves as the main backbone of combination chemotherapy for patients with colorectal cancer (CRC) in both the adjuvant and metastatic disease settings. This presentation will review the current status of 5-FU therapeutic drug monitoring (TDM) and provide the consensus documents, guidelines, and recommendations of the 5-FU TDM working group.

5-FU dosing has been typically determined by using body surface area (BSA). However, it is now well-established that BSA-based 5-FU dosing is correlated with a wide variation of 5-FU systemic exposure. Pharmacokinetic (PK) studies of 5-FU systemic exposure have shown a wide range of interpatient variation of 5-FU plasma drug levels. Over the past 30 years, increasing efforts have been placed on optimizing 5-FU dosing with the main goals of increasing antitumor efficacy while reducing drug-associated toxicity. There is growing evidence to show that 5-FU dosing based on plasma 5-FU drug level is feasible and that 5-FU TDM can improve clinical outcomes by improving efficacy of 5-FU-based combination regimens and reducing toxicities.

The clinical activity of 5-FU is modest at standard doses, and in general, dosing is limited by

the safety profile, with myelosuppression and gastrointestinal toxicity being the most commonly observed side effects. Various strategies have been developed to enhance the clinical activity of 5-FU, such as biochemical modulation, alterations in scheduling of administration, and the use of oral chemotherapy. Studies that have shown an association between plasma concentration with toxicity and clinical efficacy have shown that pharmacokinetically-guided dose adjustments can substantially improve the therapeutic index of 5-FU treatment. These studies have shown that only 20% to 30% of patients treated with a 5-FU-based regimen have 5-FU levels that are in the appropriate therapeutic range—approximately 40% to 60% of patients are under-dosed and 10% to 20% of patients are over-dosed. To date, 5-FU drug testing has not been widely used due to the lack of a simple, fast, and inexpensive method. Although 5-FU pharmacokinetic studies using cell-based and physical detection methods have been conducted since the mid-1960s, the application of 5-FU pharmacokinetic monitoring to clinical practice has become more realistic and practical since 5-FU administration via infusion schedules evolved to become the standard of care over the past 5-8 years. Recent advances in testing based on liquid chromatography-tandem mass spectroscopy and a nanoparticle antibody-based immunoassay for 5-FU may now allow for routine monitoring of 5-FU in clinical practice. We review the data on pharmacokinetically-guided dose adjustment of 5-FU and discuss the potential of this approach to advance therapeutic outcomes.

Clinical studies that were conducted during the past 20 years have demonstrated reduced toxicity and improved clinical outcomes with pharmacokinetic dose management. These pharmacokinetically-guided studies have identified an optimal target therapeutic range for 5-FU and have recommended dose adjustment algorithms to bring plasma concentrations into the optimal range. A number of retrospective and prospective clinical studies have shown that many patients who are currently being treated with 5-FU are not being given the appropriate doses to achieve optimal plasma concentration. Of note, only 20% to 30% of patients are treated in the appropriate AUC range, approximately 40% to 60% of patients are being underdosed, and 10% to 20% of patients are overdosed. Studies that have shown associations between 5-FU plasma concentration and toxicity and clinical efficacy demonstrated that pharmacokinetically-guided dose adjustments substantially improve these biological effects, which are associated with 5-FU therapy. While 5-FU monitoring has been widely used in various countries in Europe, such as France and Germany, it has not been widely in the United States.

Over the last four decades, 5-FU TDM has made significant progress, and there is now a validated algorithm of 5-FU dose adjustment based on plasma 5-FU levels to reduce toxicity and improve efficacy of 5-FU. Several methods have been developed to directly measure 5-FU drug levels in peripheral blood, including HPLC, GC-MS, and LC-MS/MS. More recently, an immunoassay has been developed that can accurately and sensitively measure 5-FU. This test has significant logistical advantages over traditional HPLC and LC-MS/MS methods. Evidence is also emerging to show that the use of 5-FU TDM results in significant cost savings with quality adjusted life-year (QALY) gain for FOLFOX chemotherapy in patients with mCRC. Finally, in this era of precision medicine, 5-FU TDM should be considered a clinically relevant and central element of personalized medicine in the everyday care of cancer patients.

This presentation will review the consensus documents and guidelines, and provide recommendations for the implementation of 5-FU TDM in clinical practice for the treatment of colorectal cancer and other human cancers.

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