Toxicity of 5-Fluorouracil

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Fluorouracil (5-FU) is a relatively unique drug in oncology because administration in different doses and schedules results in dramatically different patterns of qualitative toxicity. In the 41 years 5-FU has been

Introduction
Fluorouracil (5-FU) is a remarkable drug that has been available for 41 years and has become the mainstay of chemotherapy for gastrointestinal cancer.[1-7] It is one of a minority of drugs in clinical medicine for which the qualitative spectrum of toxicity changes dramatically when the drug is used in different doses and schedules (Table 1). These different methods of administration have been demonstrated to produce significantly different toxicity patterns, particularly when bolus schedules are compared to infusional schedules.[8] For example, bolus single-agent 5-FU given weekly—which was, in the past, the standard schedule and route of administration for this drug in gastrointestinal cancer—is associated with myelosuppression as its major toxicity, with mucositis and diarrhea being minor toxicities. The major toxic event caused by 5-FU administered by 96-hour high-dose infusion is mucositis. Low-dose (250 to 300 mg/m²/d) continuous infusion of 5-FU is associated with little myelosuppression but results in an unusual toxicity: palmar-plantar dysesthesia, more commonly known as hand-foot syndrome. Finally, the commonly used 5-FU/calcium folinate regimens, depending on the doses and schedules, may produce the combination of mucositis, diarrhea, and myelosuppression or, in weekly high-dose regimens, diarrhea as the only significant toxicity. Toxicity of 5-fluourouracil may also vary with the characteristics of the patient. For example, in a large adjuvant colon cancer study, it has been demonstrated that older patients (> 70 years) are more likely to experience mucositis and myelosuppression from 5-FU/calcium folinate regimens (Table 2).[9] It is also possible that the relatively rare neurotoxicity is more common in older patients receiving 5-FU. Gender is another risk factor for 5-FU toxicity. Female patients have a statistically higher incidence of all 5-FU toxicities (Table 3).[9] The latter finding may be associated with some degree of decreased 5-FU catabolism in women. Fluorouracil toxicity may be exacerbated by drugs that inhibit the major enzyme responsible for 5-FU metabolism—dihydropyrimidine dehydrogenase—such as the irreversible inactivator 776C85[10] and the nucleic acid uracil.[11] Uracil acts as a competitive inhibitor of dihydropyrimidine dehydrogenase and does not irreversibly inactivate the enzyme. Strategies to treat or prevent 5-FU–related toxicities include general supportive measures and specific strategies, such as prevention of mucositis by the use of oral ice chips, and treatment of severe 5-FU–related diarrhea with the somatostatin analog octreotide (Sandostatin).


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