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Capecitabine

A Viewpoint by Richard Pazdur

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The oral fluorinated pyrimidines (OFPs) have been extensively prescribed in Japan over the past 2 decades and have been used as primary and adjuvant treatments for a variety of malignancies including advanced and localised colorectal, gastric, breast, lung, and head and neck cancers. Capecitabine represents the first OFP to achieve widespread approval by regulatory authorities outside Japan. Other OFPs have recently completed extensive clinical evaluation. These include a combination of tegafur and uracil (UFT) plus oral folinic acid, and enuracil plus oral fluorouracil.

The initial indication for capecitabine was the treatment of paclitaxel-refractory advanced breast cancer. However, the above OFPs have also completed extensive phase III evaluations as therapies for metastatic colorectal cancer. These large, randomised trials compared each OFP to intravenous fluorouracil plus folinic acid and have recently completed patient accrual. Other potential applications of OFPs are in clinical settings where protracted or continuous infusions of fluorouracil have been used (e.g. as a radiation sensitising agent, as adjuvant therapy for colorectal cancers and for the treatment of advanced gastric, pancreatic, and head and neck cancers).

Two OFPs, UFT plus folinic acid and enuracil plus fluorouracil, either inhibit (uracil in UFT) or irreversibly inactivate (enuracil) dihydropyrimidine dehydrogenase (DPD), the primary catabolic enzyme of fluorouracil. Unlike capecitabine, which is associated with hand-and-foot syndrome in more than 40% of patients, the oral agents that target DPD are not associated with this adverse event. This clinical observation has led to the speculation that toxic fluorouracil catabolites may be implicated in the pathogenesis of hand-and-foot syndrome. Inhibiting or inactivating DPD may reduce or prevent the production of these toxic by-products.

The OFPs share common features. Because they are taken orally, OFPs are a convenient dosage form for patients. When delivered in a prolonged schedule (14 or 28 days) they are associated with a marked reduction in severe or life-threatening neutropenia and oral mucositis which complicate the treatment of more than a third of patients treated with intravenous bolus schedules of fluorouracil and folinic acid. The prevention or reduction of these adverse events may provide pharmacoeconomic advantages to the OFPs. The adverse event common to all OFPs is diarrhoea.

The convenience and favourable tolerability profile of OFPs make these agents excellent candidates for use in elderly patients with poor performance status or in extensively pretreated patients. In addition, the lack of serious neutropenia associated with prolonged schedules of OFPs makes this therapeutic class an attractive one for use in combination with other cytotoxic agents.

Fluorouracil has undergone extensive clinical evaluation for more than 30 years. The recently developed OFPs may represent a preferential method of administering fluorinated pyrimidines, thus providing new life for this old friend in the next millennium. ▲