Recent strategies to improve the outcome of fluoropyrimidine chemotherapy for patients with cancer have focused on better selection of patients likely to respond to such therapy and on protracted exposure to 5-fluorouracil (5-FU). Cellular determinants of response to fluoropyrimidines include the level of thymidylate synthase expression, the activity of dihydropyrimidine dehydrogenase (DPD), the amount of intracellular reduced folate and, for some fluoropyrimidines, the amount of intracellular thymidine phosphorylase. Expression of high levels of thymidylate synthase (TS) has been clearly associated with lack of response to fluoropyrimidine chemotherapy.[1-3] Indeed, patients with TS-overexpressing tumors might be advised to forego the toxicity of fluoropyrimidines in favor of alternative therapies that have a higher likelihood of producing an antitumor response. Another mechanism of resistance to 5-FU is overexpression of DPD in tumor cells, resulting in rapid intracellular catabolism of 5-FU.[4,5] In such cases, an emerging strategy involves administration of 5-FU with a DPD inhibitor, several of which are now available and are being tested in clinical trials.[6] Thymidine phosphorylase is an angiogenic protein that is overexpressed in many tumor cells. The novel oral fluoropyrimidine capecitabine is activated by thymidine phosphorylase and may therefore produce selective cytotoxicity in tumor cells.[7] If the fluoropyrimidine phenotype of each individual tumor could be assessed, it would greatly facilitate selection of patients most likely to benefit from 5-FU alone, in combination with a DPD inhibitor, or administered in the form of a selectively activated prodrug such as capecitabine. A number of recently completed clinical trials have suggested that protracted exposure to fluoropyrimidines might be the optimal way of administering these agents. The Southwest Oncology Group evaluated seven different strategies for administration of 5-FU in a randomized phase II trial and concluded that protracted IV infusion of 5-FU produced the most favorable toxicity profile and the longest survival and should therefore be studied further.[8] In a randomized phase III trial, the Eastern Cooperative Oncology Group and the Cancer and Leukemia Group B examined a number of 5-FU modulation strategies and concluded that none were clearly superior to weekly 24-hour infusions of high-dose 5-FU alone.[9] A recent meta-analysis demonstrated that continuous infusion of 5-FU resulted in a statistically significantly higher response rate than bolus 5-FU (22% vs 14%) as well as a slight survival advantage in patients with metastatic colorectal cancer.[10] These data all suggest that continuous IV infusion of 5-FU is at least as effective as any other means of administration of this drug and is considerably less toxic than alternative 5-FU based regimens, particularly those involving biochemical modulation with leucovorin or interferon. Even with the use of contemporary indwelling catheters and infusion pumps, protracted IV infusion of 5-FU remains a cumbersome and relatively expensive treatment strategy. An attractive alternative would be oral administration of 5-FU with the goal of achieving protracted exposure to the drug without the need for continuous intravenous infusion. Until recently, it has not been possible to administer oral 5-FU reliably because of the poor bioavailability and erratic absorption of this agent due to high levels of DPD in the gut wall and liver. A number of oral fluoropyrimidines have now been developed that overcome the problem of 5-FU bioavailability either by incorporating a DPD inhibitor into the treatment program or by chemically modifying 5-FU so that it is not a substrate for DPD during first pass metabolism. Capecitabine is the first of the oral fluoropyrimidines to be approved by the FDA for use in patients with refractory breast cancer. UFT and the combination of eniluracil and fluorouracil are still under clinical evaluation in patients with metastatic colorectal cancer and other diseases. Whether oral fluoropyrimidines will offer a therapeutic advantage over continuous IV infusion of 5-FU is unknown at this point. Similarly, whether one oral fluoropyrimidine offers an advantage over another remains speculative at present, though one could imagine situations in
which the pharmacological mechanism of one agent might be predicted to be particularly advantageous.

In an effort to address some of these questions and to consider the future of oral fluoropyrimidine chemotherapy, a meeting of experts was convened at the University of Chicago Cancer Research Center on July 11, 1998 in Chicago, Illinois. The information discussed and the issues debated at that meeting, which was cochaired by myself and Everett E. Vokes, MD, are summarized in this supplement to ONCOLOGY. The conference began with a series of presentations that summarize the clinical and biochemical pharmacology of 5-FU, the development of infusional 5-FU therapy and the importance of DPD in determining the pharmacology and clinical effects of 5-FU. These presentations were followed by a summary of the current status of regional and systemic chemotherapy for advanced colorectal cancer. The latter half of the meeting included a discussion of the role of oral fluoropyrimidine therapy in patients with cancers of the head and neck, breast, stomach, and colorectum and concluded with an overview of the clinical development of eniluracil, a potent and specific DPD inactivator.

It was clear from this meeting and from the papers that follow, that oral fluoropyrimidines are likely to play a prominent role in the management of patients with a number of types of solid tumors. At the very least, they offer an alternative, simplified strategy for achieving protracted exposure to fluoropyrimidine chemotherapy. Those agents that are selectively activated in tumor cells have the potential to provide greater antitumor efficacy or a better therapeutic index. Similarly, those agents administered with a DPD inhibitor have the potential to overcome an important mechanism of 5-FU resistance and to minimize interpatient variability in 5-FU pharmacology and toxicity. As the results of clinical trials with these agents become available, it is hoped that they will each find an important role in the management of patients with fluoropyrimidine-responsive tumors.

References:

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