Since its development in 1957, fluorouracil (5-FU) has been the central component in the treatment of colorectal cancer. Over the past several decades, innumerable permutations of fluorouracil biomodulation have been studied. Indeed, rarely has a drug been so well understood in terms of its mechanisms and metabolism, and rarely has such an understanding been so extensively exploited in clinical strategies. But despite these efforts, overall progress in the management of advanced colorectal cancer has been modest.

Irinotecan and Oxaliplatin

Colorectal cancer is no longer a one-drug disease. Since 1996, irinotecan (CPT-11 [Camptosar]) has been widely available for second-line treatment, and more recent data justify its inclusion in first-line combination regimens.[1,2] Currently, oxaliplatin is widely available around the world and, presumably, will be available in the United States in the near future. These two agents expand our armamentarium for the management of this lethal disease.

How best to use them is a complicated question that is being aggressively investigated from many angles. Issues of scheduling and sequencing of these agents remain largely unresolved, and it remains to be seen whether scheduling issues will be of clinical importance with oxaliplatin and irinotecan. Notably, efforts to optimize the scheduling of fluorouracil over the past 3 to 4 decades have yielded minimal results and essentially no agreement.

Looking for the Right Combination and Schedule

In their elegant review, Khayat et al discuss the many ways in which irinotecan and oxaliplatin are being administered, both singly and combined. I would caution against any early attempts to determine the superiority of one schedule over another until adequately powered studies are performed. For example, a study cited by Khayat et al comparing the relative merits of different schedules of irinotecan has only 38 to 49 patients in each arm.[3] As such, this study is severely underpowered to make meaningful comparisons.

Several large-scale, adequately powered trials are underway, and the results are anxiously anticipated. For example, the National Cancer Institute intergroup is conducting a three-armed randomized study comparing a weekly bolus schedule of irinotecan/fluorouracil/leucovorin to an every-2-week schedule of oxaliplatin plus infusional fluorouracil/leucovorin and an every-3-week oxaliplatin-plus-irinotecan regimen. Although there may be confounding factors such as infusional vs bolus administration and weekly vs 2-weekly or 3-weekly cycles, this study could provide some important information about the use of these agents as first-line therapy that may prove helpful in guiding future decisions.

More Options, Better Care

That said, the near-term future of colorectal cancer chemotherapies will involve far more
complicated and interesting questions than simply working out the scheduling and sequencing of fluorouracil, irinotecan, and oxaliplatin. Many new agents being investigated in ongoing trials are showing encouraging evidence of antitumor activity. These agents exploit our improved understanding of tumor growth and biology.

Several of these drugs attack the angiogenic component of tumor growth, targeting vascular endothelial growth factor receptors, associated tyrosine kinases, or other components of the angiogenic process. Others target the epidermal growth factor receptor or its tyrosine kinases. Still others target specific components of cell-cycle regulation and/or signal transduction.

**Future Directions**

Where will all this lead? I think it is safe to say that the era of having one established chemotherapy regimen for all colorectal cancer patients is behind us. The availability of multiple options and choices will make management of this disease more complicated, but also more effective. The challenge will be to make the most intelligent decisions for the individual patients being treated.

To that effect, individual molecular typing of a patient’s tumor is likely to become a standard approach in selecting chemotherapies. Tumors overexpressing the gene for such fluorouracil targets as thymidylate synthase or dihydropyrimidine dehydrogenase may be selected for non-fluorouracil-containing regimens. Tumors overexpressing epidermal growth factor receptor may benefit from therapy targeting this epitope. Tumors showing evidence of particularly high vascularization and vascular proliferation may be uniquely vulnerable to antiangiogenic strategies. As science moves from the laboratory to the bedside, care of colorectal cancer will become far more individualized and effective.

It is exciting to be working in a time in which so much progress is being made. We still have a long way to go, but the prospects for the future are bright.

**References:**


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