

Treatment of colorectal cancer since the introduction of irinotecan

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Irinotecan-based chemotherapy regimens increasingly offer the possibility of effective palliation that crosses seamlessly into chronic survivability.

Colorectal cancer (CRC) is the third most common malignancy treated by oncologists in the United States, representing 10% of cancer diagnoses, more than 55,000 deaths, and substantial healthcare expenditures.¹⁻³ Worldwide, CRC is the third leading cause of cancer death,⁴ with more than 800,000 new cases diagnosed annually.⁴

This illness presents enormous and sobering treatment challenges. Between 25% and 60% of patients are found to have metastatic disease at the time of diagnosis,^{2,3} and of those without metastases initially, upward of 50% will progress to disseminated disease during the course of their illness.³ Once it becomes manifest, metastatic CRC (mCRC) is an implacable, potentially ferocious, and generally fatal disease. Only 1 of every 10 individuals diagnosed with mCRC can expect to survive for another 5 years.^{2,5}

Growing list of treatment options

The introduction of irinotecan (Camptosar), a topoisomerase I inhibitor, in 1996 represented the first new, effective treatment of CRC in decades. Previously, regimens based on 5-fluorouracil (5-FU) administered alone or in combination with leucovorin (LV) represented essentially the sole therapeutic choice for mCRC; the addition of irinotecan to this short list of treatment options heralded an era of expanding therapeutic possibilities for patients with unresectable disease. Irinotecan was initially approved for use

as a second-line therapy for mCRC. Results of pivotal trials by Douillard and colleagues⁶ and Saltz and colleagues⁷ led to the 2000 recommendation that an irinotecan-based regimen become the standard of care for first-line therapy of advanced disease.

In the ensuing years, the number of chemotherapy agents available for incorporation into treatment algorithms has expanded to include cytotoxic agents such as oxaliplatin (Eloxatin); targeted biologic agents such as bevacizumab (Avastin), cetuximab (Erbix), and panitumumab (Vectibix); and oral 5-FU prodrugs such as capecitabine (Xeloda). Recent guidelines published by the National Comprehensive Cancer Network list eight unique initial therapies, nine candidate algorithms for therapy after first disease progression, and numerous options for therapy after second (and later) disease progression; irinotecan is an integral part of this continuum at all intervals.⁸ Although the years before the introduction of irinotecan were characterized by a dearth of choices beyond 5-FU/LV, therapy for mCRC has recently (and optimistically) been described as approaching a state of creative chaos,⁹

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with combination regimens including irinotecan plus infusional 5-FU/LV (FOLFIRI) consistently leading to median survival approaching⁵—and surpassing¹⁰—20 months.

In its first decade of clinical use, irinotecan moved steadily forward from a second-line therapeutic agent to a key component of first-line survival strategies that is used in combination with other agents. Now, in its second decade of clinical use, as treatment regimens continue to evolve, irinotecan is transitioning to become an integral part of new strategies that combine chemotherapy agents with novel monoclonal antibodies and potential applications for neoadjuvant use in patients with initially unresectable hepatic lesions.

Invaluable perspectives on disease management

Thus, with great pleasure I introduce this supplement to *Community Oncology*, in which a distinguished group of panelists offer their invaluable perspectives on the role of irinotecan in the current management of mCRC. Using case-based discussions addressing common scenarios and dilemmas that may be encountered in actual practice settings, these educators, who are clinicians as well, draw from their own research and experience to identify and explain preferred approaches to disease management.

Leonard Saltz, MD, discusses the use of FOLFIRI for initial care in chemotherapy-naïve patients with mCRC, reemphasizing the considerable evidence supporting the use of irinotecan in this indication. Claus-Henning Köhne, MD, PhD, reviews the emerging evidence supporting a role for irinotecan in patients with initially unresectable metastatic disease; for at least some of these patients, neoadjuvant therapy with an eye toward increasing their likely candidacy

for surgery may now be an appropriate consideration. From the international academic community, Paulo Hoff, MD, FACP, explores second-line treatment strategies for patients who initially respond satisfactorily to management but suffer subsequent disease progression. Lee S. Schwartzberg, MD, FACP, addresses pertinent decision points in the selection of chemotherapy for elderly patients with CRC, a group for whom therapeutic choices traditionally have been severely limited based on what are, in many instances, misconceptions of their ability to tolerate the most commonly used treatment strategies. Finally, it is my great pleasure to use this forum to review the implications of studies suggesting that genetic testing offers a method for optimizing chemotherapy in these patients.

Metastatic CRC remains a challenging disease, with survival advantages of various regimens currently measured in months. Yet with the continual introduction of new therapies, it must be emphasized that survival has increased steadily during the previous decade; a recent report from the American Cancer Society states that the biggest fall in cancer-related deaths was seen in colon and rectal cancers.^{2,11} As patients survive longer, their exposure to newly approved and developing treatments offers hope to patients and their treating physicians. Although it remains a slow and painstaking battle to salvage every extra day, the clinical application of irinotecan-based chemotherapy regimens increasingly offers the possibility of effective palliation that crosses seamlessly into chronic survivability. The use of irinotecan in this continuum of care, as treatment regimens continue to evolve, points toward the possibility of a prolonged progression-free existence for patients with CRC.

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Conflicts of interest: Dr. Lenz is a consultant for Pfizer Inc, Genentech, sanofi-aventis Group, ImClone, Bristol-Meyers Squibb, Merck KG, ResponseGenetics, Inc., and Amgen. He has received honoraria from Pfizer Inc, Genentech, sanofi-aventis, ImClone, Bristol-Meyers Squibb, Merck KG, and Amgen; and is a stock owner of ResponseGenetics.