Current Practices and Challenges of Adjuvant Chemotherapy in Patients with Colorectal Cancer

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KEYWORDS

• Colorectal cancer • Adjuvant chemotherapy • Time to treatment • Wait times
• Treatment barriers

KEY POINTS

- Surgery and adjuvant chemotherapy is the standard of care for all high-risk stage II and all stage II patients with colorectal cancer.
- Research clearly indicates that the timing to the initiation of adjuvant chemotherapy is critical.
- Both clinical and systemic barriers to timely treatment exist: most notably postsurgical complications and care pathway wait times.

BACKGROUND

Colorectal cancer (CRC) is one of the most commonly diagnosed cancers globally in both men and women. Based on the most recent global cancer statistics, an estimated 1.2 million new CRC cases were diagnosed in 2008, with 608,700 patients dying of the disease.[1] The highest incidence rates are found in the developed world, where risk factors such as obesity, poor dietary choices, and physical inactivity are most prevalent.[1–3] In Canada, an estimated 23,300 new CRC cases and 9,200 deaths are estimated to have occurred in 2012.[4] CRC has consequently been the focus for many new screening and treatment initiatives to improve patient care.

Optimizing CRC care is imperative for improving overall survival (OS) and disease-free survival (DFS) rates. As with many solid tumors, the cornerstone of curative CRC treatment is surgical resection. Surgical techniques for resection vary depending on the tumor location and characteristics; however, it is recommended that all colorectal tumors are removed en bloc.[5] Because colorectal tumors often extend into

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neighboring structures, en bloc removal maximizes the curative potential of surgery, as well as aiding in the staging process.[5]

In addition to optimal surgery, governing cancer institutions' guidelines also state that patients with high-risk stage II and all patients with stage III CRC are candidates for adjuvant chemotherapy (AC) treatment.[6–9] This article explores the types of chemotherapy available for patients with CRC, the critical issue of timing of AC, and the barriers to treatment.

AC FOR COLORECTAL CANCER

Although surgery is the mainstay of CRC treatment, AC is also an important aspect of increasing DFS and OS. The role of AC is to eradicate micrometastatic tumor deposits, which can increase the chance of cancer recurrence. Recommendations regarding the role and type of AC for patients with CRC have evolved greatly in the past 20 years because of the growing number of clinical trials searching for more effective treatment.

One of the first chemotherapy regimens that showed a definitive DFS benefit in patients with CRC was 5-fluorouracil with levamisole.[10] A randomized controlled trial showed that patients with stage III colon cancer who received levamisole with 5-fluorouracil had a significant reduction (41%) in the relative risk of cancer recurrence compared with patients who did not receive any chemotherapy.[10] A later study showed similar results for patients with stage II and stage III colon cancer, but failed to show any positive effect for patients with rectal cancer.[11] This chemotherapy regimen remained the standard of care in the 1990s, until 5-fluorouracil and folinic acid (leucovorin) were found to be more beneficial.[12–14] The subsequent QUASAR (Quick and Simple and Reliable) trial determined that patients with stage II CRC also received benefits, although small, from adjuvant treatment with 5-fluorouracil and folinic acid.[15] As a result, this established the basis for offering AC to high-risk patients with stage II CRC.

In 2004, the MOSAIC (Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin [FOLFOX] in the Adjuvant Treatment of Colon Cancer) study further enhanced the treatment regimen, showing that the addition of oxaliplatin to 5-fluorouracil plus leucovorin improved DFS.[16] Although the FOLFOX regimen in the MOSAIC study has proven efficacy, administration of this chemotherapy is not ideal: each cycle is composed of a 2-hour infusion of leucovorin and oxaliplatin, followed by a bolus of 5-fluorouracil, and then a 22-hour infusion of 5-fluorouracil on 2 consecutive days every 2 weeks, for a total of 12 cycles.[16] Furthermore, the X-ACT trial found oral capecitabine (Xeloda) to be an equally effective chemotherapeutic option to 5-fluorouracil and leucovorin, although still less effective than FOLFOX.[17] Hence, common AC for high-risk patients with stage II and all stage III CRC is either FOLFOX or capecitabine, unless drug reactions or comorbidities dictate otherwise.

Chemotherapy regimens vary slightly in patients with rectal cancers compared with patients with colon cancers. Patients with rectal cancer also receive neoadjuvant chemotherapy combined with radiation therapy, because this has been found to increase local control of the tumor (thereby increasing the rate of curative surgery) and increase the number of sphincter preservations in patients with low-lying tumors.[18] However, chemotherapy is commonly continued after surgery, and treatment types are like those available for patients with colon cancer.

In recent years, targeted molecular therapies have also gained prominence as cancer treatment options in combination with chemotherapy. One such drug, bevacizumab (Avastin), is a monoclonal antibody against vascular endothelial growth factor (VEGF), and thus is an antiangiogenic agent that helps suppress tumor growth.[19,20] This targeted therapy yields the greatest benefit when used in combination with