Systemic Therapy for Colon Cancer

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KEYWORDS

- Irinotecan • Oxaliplatin • 5-fluorouracil
- Antiepidermal growth factor receptor antibody
- Vascular endothelial growth factor antibody • Immunotherapy • Regorafenib
- Trifluridine/tipiracil

KEY POINTS

- Determining the suitable adjuvant chemotherapy for colon cancer patients depends on the tumor stage, presence of high-risk pathologic features, microsatellite instability status, patient age, and performance status.
- Systemic treatment for colon cancer patients with metastatic disease includes chemotherapy, targeted therapy, and immunotherapy.
- Prognostic and predictive biomarkers have been developed to help better tailor treatment regimens for patients.

INTRODUCTION

Colorectal cancer is the fourth most common cancer in the United States, with an estimated 135,430 new cases in 2017. Colon cancer is the second leading cause of cancer deaths in Western countries.[1] Most colon cancer patients will be diagnosed with regional or distant metastasis, and thus will need adjuvant chemotherapy after their surgery or palliative chemotherapy for their metastatic disease. In the adjuvant setting, we have improved our ability to identify patients who will benefit the most from chemotherapy by examining patient and tumor characteristics. In the metastatic setting, there are chemotherapy drugs, biologic agents targeting the vascular endothelial growth factor (VEGF) pathway and epidermal growth factor receptor (EGFR) pathway, and immunotherapy to offer patients. Oncologists are better able to tailor systemic therapy for their patients based on predictive and prognostic biomarkers, which include: right- versus left-sided cancer and tumor biomarkers such as microsatellite instability-high (MSI-high), KRAS, NRAS, and BRAF mutations.

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LOCALLY ADVANCED COLON CANCER AND ADJUVANT CHEMOTHERAPY

The 3 chemotherapy agents utilized to treat patients with early stage colon cancer are 5-fluorouracil (5FU), capecitabine (Xeloda), and oxaliplatin (Eloxatin).

5FU is a nucleotide analogue that can inhibit thymidylate synthase (TS), an enzyme crucial for pyrimidine nucleotide synthesis. The 5FU metabolite, fluorodeoxyuridine triphosphosphate (FdUTP), also disrupts RNA synthesis. 5FU may be administered as an intravenous infusion or bolus schedule, with prolonged infusion inhibiting TS and bolus infusion leading to incorporation of FdUTP into RNA.[2] Leucovorin is administered with 5FU to enhance clinical activity.[3]

Capecitabine is the oral pro-drug for 5FU, and thus both have been shown to have equal efficacy in the adjuvant and metastatic setting.

Oxaliplatin is a platinum drug, and is an alkylating agent that inhibits DNA synthesis. It may be administered intravenously in combination with either 5FU or capecitabine.

Adjuvant therapy is given over the course of 6 months, either single-agent 5FU or capecitabine, or doublet combination of 5FU/oxaliplatin or capecitabine/oxaliplatin.

Adjuvant Therapy for Stage II Colon Cancer

When patients are diagnosed with early stage colon cancer, oncologists determine whether they should recommend adjuvant chemotherapy largely based on the risk of cancer recurrence and the amount of benefit the patients will receive with treatment. Patients with stage II colon cancer generally have good prognosis and survival (5-year overall survival is estimated to be 80%), and the added benefit in survival with adjuvant chemotherapy may not be more than 5%.[4] The QUASAR study randomized patients with stage II colon cancer to observation versus 5FU therapy, and reported a small absolute improvement in survival of 3.6% (95% confidence interval [CI] 1.0–6.0) for patients who received chemotherapy.[5] Two phase III clinical trials for patients with stage II and III colon cancer, the Multi-center International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) and the National Surgical Adjuvant Breast and Bowel Project (NSABP) C07, randomized patients to receive 5FU versus 5FU and oxaliplatin. Patients with stage II colon cancer in the MOSAIC trial had 6-year overall survival of 87% in both treatment arms, thus did not benefit from the addition of oxaliplatin to 5FU.[6] The NSABP C07 study also did not show a difference in survival in both treatment arms for patients with stage II colon cancer.[7] Based on the results from these phase III trials, patients with stage II colon cancer do not receive great benefit from either single-agent 5FU or doublet chemotherapy with 5FU/oxaliplatin over observation alone.

Microsatellite Instability High and Stage II Colon Cancer

If patients with stage II colon cancer are identified to have MSI-high tumors, they have been shown in a large retrospective study to have improved survival outcome over patients with microsatellite stable (MSS) tumors. In addition, patients with MSI-high colon cancer do not benefit from adjuvant 5FU chemotherapy.[8] Mismatch repair (MMR) proteins are responsible for correcting mistakes made by DNA polymerase during DNA synthesis. MMR protein deficiency leads to MSI, which is an accumulation of errors within short repetitive sequences of DNA, called microsatellites. MSI status is checked by either immunohistochemistry (IHC) staining for the mismatch repair proteins or by polymerase chain reaction to detect instable and shortened microsatellites. MSI-high tumors would have missing MMR protein(s) by IHC and shortened/instable microsatellites. MMR protein deficiency is caused by either germline mutation of the MMR genes (hereditary Lynch syndrome) or sporadic silencing of the MMR genes.