Original Study

Real-World Effect of Maintenance and Intermittent Chemotherapy on Survival in Metastatic Colorectal Cancer

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Abstract

Improved outcomes in metastatic colorectal cancer are allowing patients to consider periods of reduced-intensity chemotherapy, however real-world use of these modifications is poorly described. In this population-based cohort, 39% of patients used either intermittent or maintenance chemotherapy during treatment and modifications were associated with improved outcomes, suggesting physicians can appropriately select patients who are safe to undergo treatment modifications.

Background: With improved survival and longer duration of treatment, clinicians managing metastatic colorectal cancer (mCRC) increasingly consider intermittent (IC) or maintenance chemotherapy (MC), but the effect of these treatment modifications on real-world outcomes is unclear. **Patients and Methods:** Using a population-based cohort of mCRC patients who received combination chemotherapy, we aimed to describe the use of IC/MC and their effect on overall survival (OS). **Results:** Among 617 patients, 120 (19%) had periods of IC, 67 (11%) had periods of MC, and 53 (9%) had periods of both. Most (85.5%) modifications occurred in the first-line setting. The receipt of IC (median OS [mOS], 37 vs. 21 months; $P < .0001$) or MC (mOS, 36 vs. 24 months; $P = .0015$) was associated with improved mOS compared with continuous combination therapy. In multivariate analysis adjusting for age, sex, and regimen used at the time of treatment modification, IC (hazard ratio [HR], 0.52; 95% confidence interval [CI], 0.42-0.65; $P < .0001$), MC (HR, 0.71; 95% CI, 0.58-0.88; $P = .002$), and the combination (HR, 0.45; 95% CI, 0.33-0.63; $P < .0001$) were all associated with improved mOS. Among patients receiving MC, individuals with (HR, 0.69; 95% CI, 0.53-0.90; $P = .005$) and without (HR, 0.74; 95% CI, 0.55-1.00; $P = .048$) re-escalation to their original cytotoxic regimen had improved mOS compared with continuous therapy. The use of IC was associated with an improved OS compared with MC (HR, 0.65; 95% CI, 0.47-0.90; $P = .009$). **Conclusion:** In patients with mCRC, IC and MC are reasonable options to maintain quality of life and do not appear to negatively affect OS in carefully selected patients.

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Introduction

The incorporation of novel agents into the treatment of metastatic colorectal cancer (mCRC) has resulted in improved outcomes, with median overall survival (mOS) exceeding 30 months in recent trials.[1] With these advances, patients are being exposed to chemotherapy for longer periods of time. As a result, strategies that maintain quality of life (QoL) are increasingly considered during treatment planning. The 2 major strategies (Figure 1) considered include complete treatment holidays with intermittent chemotherapy or periods of maintenance chemotherapy with omission of oxaliplatin/irinotecan and continuation of a fluoropyrimidine with or without a biologic.

Intermittent chemotherapy was first assessed in the United Kingdom Medical Research Council Colorectal 06 (UK MRC CR06) trial, which evaluated treatment breaks for patients with responding or stable disease after 12 weeks of 5-fluorouracil. They demonstrated similar overall survival (OS; hazard ratio [HR], 0.87;

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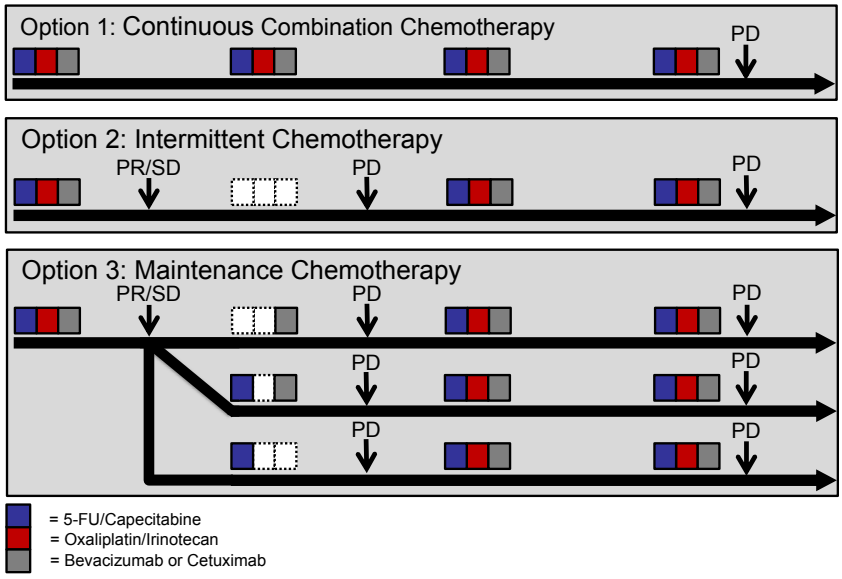
Figure 1 Overall Survival of Patients With Metastatic Colorectal Cancer Who Received Treatment De-Escalation With Either Maintenance or Intermittent Chemotherapy After Receiving Combination Chemotherapy



Abbreviation: 5-FU = fluorouracil.

95% confidence interval [CI], 0.69-1.09; $P = .23$), no difference in use of second-line chemotherapy, and fewer side effects for patients who received intermittent compared with continuous treatment.[2] Intermittent 5-fluorouracil plus irinotecan (FOLFIRI) administered on a 2-month on/2-month off schedule was also shown to result in similar progression-free survival (PFS; HR, 1.03; 95% CI, 0.81-1.29) and OS (HR, 0.88; 95% CI, 0.69-1.14) compared with continuous therapy in the Group for the Study of Gastrointestinal Cancer (GISCAD) trial, whereas the Medical Research Council COIN (MRC COIN) trial failed to meet its noninferiority criteria for intermittent 5-fluorouracil plus oxaliplatin (FOLFOX) (OS HR, 1.084; 95% CI, 0.97-1.21; PFS HR, 1.052; 95% CI, 0.95-1.17).[3,4]

The use of maintenance chemotherapy was subsequently proposed as a means of providing disease suppression during periods of less intensive therapy. When first evaluated in optimize oxaliplatin 1 (OPTIMOX1), maintenance 5-fluorouracil after a 6-cycle FOLFOX induction resulted in similar PFS (HR, 1.06; 95% CI, 0.89-1.20; $P = .47$) and OS (HR, 0.93; 95% CI, 0.72-1.11; $P = .49$) compared with continuous FOLFOX.[5] Bevacizumab has also been evaluated in the maintenance setting in the Spanish Cooperative Group for the Treatment of Digestive Tumours (MACRO TTD) as well as Swiss Group for Clinical Cancer Research 41/06 (SAKK 41/06) trials; however, neither trial showed benefit to bevacizumab maintenance.[6,7]

The optimize oxaliplatin 2 (OPTIMOX2) as well as Dutch Colorectal Cancer Group 3 (CAIRO3) attempted to evaluate whether maintenance or intermittent chemotherapy resulted in improved outcomes. OPTIMOX2 randomized patients to 6 cycles of modified 5-fluorouracil plus oxaliplatin followed by maintenance 5-fluorouracil or a complete stop to chemotherapy. Single-agent fluoropyrimidine maintenance improved duration of disease control (HR, 0.71; 95% CI, 0.51-0.99; $P = .046$) compared with intermittent chemotherapy.[8] Similarly, CAIRO3 showed that a fluoropyrimidine with bevacizumab improved time to second PFS (HR, 0.67; 95% CI, 0.56-0.81; $P < .0001$).[1,9] This strategy of a fluoropyrimidine combined with bevacizumab after induction has become one of the most widely used approaches for de-escalation and is currently highlighted by the 2016 European Society for Medical Oncology guidelines for such patients.[1]

Although maintenance therapy appears to result in improved PFS compared with intermittent chemotherapy, both strategies are important options for patients. A major concern with incorporating the evidence from the previously mentioned trials into practice is that the trials had rigid frameworks that required patients to receive a certain number of cycles before de-escalation and did not allow a mixture of intermittent and maintenance chemotherapy. With this in mind, we aimed to determine: (1) the real-world frequency of intermittent and maintenance chemotherapy; (2) whether these strategies result as detriment to survival; and (3) if there are any predictors of which patients will undergo treatment modification. To answer these questions, we evaluated patient records and tumor registry data of a population-based cohort from the British Columbia Cancer Agency (BCCA) who were newly diagnosed with mCRC and started a doublet chemotherapy regimen with or without a biologic between 2008 and 2010.

Patients and Methods

Description of the Study Setting

The BCCA is a province-wide cancer agency that provides publicly funded cancer care to 4.7 million people in British Columbia, Canada. It