Ontario Health
Cancer Care Ontario

Evidence-Based Series 2-6 Version 2

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Continuous versus Intermittent Chemotherapy Strategies in Inoperable, Advanced Colorectal Cancer

S. Berry, R. Cosby, T. Asmis, K. Chan, M.K. Krzyzanowska, N. Hammad, and the Gastrointestinal Disease Site Group

September 15, 2022

An assessment conducted in December 2023 deferred the review of Evidence Based Series (EBS) 2-6. This means that the document remains current until it is assessed again next year. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol)

EBS 2-6 Version 2 is comprised of 4 sections. You can access the summary and full report here: https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/411

Section 1:	**Guideline Recommendations**
Section 2:	**Evidentiary Base**
Section 3:	**Development Methods, Recommendations Development and External Review Process**
Section 4:	**Document Assessment and Review**

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Guideline Report History

GUIDELINE VERSION	SYSTEMATIC REVIEW		PUBLICATIONS	NOTES AND KEY CHANGES
	Search Dates	Data		
Original version January 8, 2014	2000-2013	Full Report	Web publication	NA
Current Version 2 September 15, 2022	2013-2021	New data found in section 4: Document Assessment and Review	Updated Web publication	2014 recommendations are **ENDORSED**

Section 1: Guideline Recommendations

Evidence-Based Series 2-6: Section 1

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Continuous versus Intermittent Chemotherapy Strategies in Inoperable, Advanced Colorectal Cancer: Guideline Recommendations

S. Berry, R. Cosby, T. Asmis, K. Chan, M.K. Krzyzanowska, N. Hammad, and the Gastrointestinal Disease Site Group

The 2014 guideline recommendations have been ENDORSED, which means that the recommendations are still current and relevant for decision making. Please see Section 4: Document Assessment and Review for a summary of updated evidence published between 2013 and 2022, and for details on how this guideline was ENDORSED.

QUESTION

What is the impact of intermittent strategies of administering systemic therapy on length and quality of survival in patients with untreated, unresectable metastatic colorectal cancer?

TARGET POPULATION

These recommendations apply to adult patients (≥18 years old) with inoperable, advanced (Stage IV) colorectal cancer.

INTENDED USERS

This guideline is intended for use by clinicians and healthcare providers involved in the management of patients with advanced colorectal cancer.

RECOMMENDATIONS AND KEY EVIDENCE

Intermittent strategies of administering first-line systemic therapies to patients with unresectable metastatic colorectal cancer (mCRC) do not result in a statistically significant reduction in overall survival and either improve or maintain quality of life compared to continuous administration of therapy. Patients who want a break from treatment can be reassured that intermittent strategies of administering first-line therapy are a reasonable alternative to continuous administration. Intermittent systemic treatment strategies should be part of an informed discussion of treatment options for this group of patients.

Ten trials (1-10) were identified, and seven (1,2,5-9) had published overall survival hazard ratios (HRs) that could be used for the meta-analysis. Meta-analysis demonstrates no clinically significant survival difference between the continuous and intermittent

chemotherapy strategies (HR, 1.02; 95%CI, 0.95-1.10, p=0.62). No subgroup of trials based on the type of induction or maintenance therapy in the intermittent arm demonstrates a significant difference in overall survival between the two chemotherapy strategies (Figures 2, 3, and 6). Toxicity assessments revealed differential toxicity patterns for the two strategies. However, these toxicity assessments reflect maximal levels of toxicity experienced during exposure to the treatment on that arm of the trial. These measures are important, but for patients on intermittent treatment, duration of exposure to toxicity, or ability of patients to recover from the toxicities after induction treatment, are also important and are likely better captured in quality-of-life (QOL) assessments. Of the two trials that measured quality of life, the Maughan et al. (1) trial demonstrated no difference in QOL, and several benefits were demonstrated for the intermittent chemotherapy arm at 24 weeks in the COIN (6) trial. Specifically, there were statistically significant benefits with respect to role functioning (OR, 0.82; 95%CI, 0.70-0.96, p=0.015) and social functioning (OR, 0.82; 95%CI, 0.70-0.96, p=0.016) as well as for several symptom scales including fatigue, nausea and vomiting, appetite loss, constipation, diarrhea, dry or sore mouth, eating or drinking problems, problems handling small objects, and treatment interfering with activities of daily living (all p<0.04).

QUALIFYING STATEMENTS

- Given that the trials included in this systematic review included a variety of maintenance strategies, a definitive recommendation regarding an optimal maintenance strategy is not possible. However, our analyses of strategies that did not use any maintenance systemic therapy did not demonstrate any statistically significant detriment in overall survival. Therefore, this approach may be preferred by patients, as it offers them a complete break from treatment.
- All but one of the intermittent strategies offered 12 to 18 weeks of induction treatment and were monitored with imaging at least every 8 to 12 weeks during the intermittent phase of treatment, with reintroduction of the induction chemotherapy at disease progression. These represent reasonable guidelines to consider when using an intermittent strategy, but adaptation of a strategy to individual circumstances should always be considered. A longer induction period or closer clinical monitoring of patients on maintenance therapy or chemotherapy-free interval might be appropriate for patients with very bulky or symptomatic disease. For some patients like this, an intermittent strategy may not be appropriate.
- Five of the seven trials that contributed to the meta-analyses were based on treatments with FOLFOX chemotherapy, one of the commonly used first-line chemotherapy regimens for mCRC in Ontario. The other two trials included in the meta-analyses used fluoropyrimidine monotherapy or FOLFIRI as induction chemotherapy regimens. Given the acceptability of fluoropyrimidine monotherapy as one of the options for first-line therapy (see EBS #2-5) and the accepted equivalence of FOLFIRI and FOLFOX as first-line therapies (11,12), extrapolation of our conclusions to all commonly used induction chemotherapy regimens is reasonable.
- During maintenance therapy or a chemotherapy-free interval, best supportive care should be continued for patients.

FUTURE RESEARCH

Future research should include a population study to evaluate the impact of intermittent strategies of administering first-line therapy for mCRC on outcomes in routine practice.

RELATED GUIDELINES

- PEBC Evidence-based Series #2-5: *Strategies of Sequential Therapies in Unresectable, Metastatic Colorectal Cancer Treated with Palliative Intent* (currently under development)

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