



Evidence-Based Series 2-5

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

Strategies of Sequential Therapies in Unresectable, Metastatic Colorectal Cancer Treated with Palliative Intent

*T. Asmis, S. Berry, R. Cosby, K. Chan, N. Coburn, M. Rother,
and the Gastrointestinal Disease Site Group*

Report Date: January 28, 2014

An assessment conducted in December 2024 deferred the review of Evidence-based Series (EBS) 2-5. 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](#))

Evidence-Based Series 2-5 is comprised of 3 sections. You can access the summary and full report here:

<https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/396>

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

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Evidence-Based Series 2-5: Section 1

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

**Strategies of Sequential Therapies in Unresectable, Metastatic
Colorectal Cancer Treated with Palliative Intent:
Guideline Recommendations**

*T. Asmis, S. Berry, R. Cosby, K. Chan, N. Coburn, M. Rother,
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QUESTION

What is the impact of different strategies of sequential and combination chemotherapy on efficacy (including overall survival), toxicity and quality of life in unresectable metastatic colorectal cancer treated with palliative intent?

TARGET POPULATION

These recommendations apply to adult patients (≥ 18 years old) with unresectable metastatic colorectal cancer. The cytotoxic agents covered in this guideline include initial fluoropyrimidine (5-FU or capecitabine) either alone or in combination, irinotecan and oxaliplatin.

INTENDED USERS

This guideline is intended for use by clinicians and healthcare providers involved in the management of patients with unresectable, metastatic colorectal cancer treated with palliative intent.

RECOMMENDATIONS AND KEY EVIDENCE

Planned sequential chemotherapy and upfront combination chemotherapy are both acceptable standards of care. While there is a statistically significant difference in overall survival in favour of combination chemotherapy, the magnitude of the difference between the two strategies may not be clinically significant. Furthermore, sequential therapies may reduce upfront toxicities. Therefore, choice of treatment should be made on a case-by-case basis based on considerations that include patient and tumour characteristics, toxicity of each strategy and patient preference.

Sequential chemotherapy consists of a fluoropyrimidine monotherapy followed by either:

- a. another monotherapy with irinotecan *OR*
- b. combination chemotherapy consists of a doublet of a fluoropyrimidine with irinotecan or oxaliplatin

Combination chemotherapy consists of an upfront doublet of a fluoropyrimidine with irinotecan or oxaliplatin.

A meta-analysis of five trials (1-5) demonstrates a survival advantage for combination chemotherapy (HR, 0.92; 95%CI, 0.86-0.99, $p=0.02$). Median survival advantage in most trials is 3 to 6 weeks (range <1 week to 12 weeks). Therefore, any survival advantage that exists is likely to be very small and not clinically significant. First-line toxicities are reported by three trials (1,2,4). Hematological toxicities include significantly more neutropenia (1,4), febrile neutropenia (1) and thrombocytopenia (4) with upfront combination chemotherapy. Non-hematological toxicities include significantly more diarrhea (1), nausea (1,4), vomiting (1,4) and sensory neuropathy (4) in the upfront combination chemotherapy arm, and significantly more hand-foot syndrome in the sequential chemotherapy arm (1).

QUALIFYING STATEMENTS

- The FOCUS (2) trial is the largest trial of the five included trials. The individual hazard ratio for the FOCUS (2) trial only includes two arms of this trial. Therefore, one third of the data from this trial is missing from the overall meta-analysis of the five trials.
- Based on the results of this systematic review, patients should have access to all effective cytotoxic drugs using a sequential strategy.
- Combination chemotherapy may be more appropriate for patients with rapidly progressing, very symptomatic or bulky life-threatening visceral disease given their higher overall response rates.
- The studies included in this systematic review were done in an era prior to the use of biologics in the treatment of mCRC. Definitive statements about the integration of biologics into a sequential strategy cannot be made at this time.

FUTURE RESEARCH

Future research of strategies of care should also include biologically targeted therapies.

RELATED GUIDELINES

- PEBC Evidence-based Series #2-25: *The Role of Bevacizumab (Avastin®) Combined with Chemotherapy in the Treatment of Patients with Advanced Colorectal Cancer* (available from: <https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/1506?redirect=true>).

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