



## Complete Summary

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### GUIDELINE TITLE

Use of irinotecan in the second-line treatment of metastatic colorectal carcinoma.

### BIBLIOGRAPHIC SOURCE(S)

Gastrointestinal Cancer Disease Site Group. Figueredo A, Moore M, Germond C, Kocha W, Maroun J, Zwaal C. Use of irinotecan in the second-line treatment of metastatic colorectal carcinoma. Toronto (ON): Cancer Care Ontario (CCO); 2004 Jul. 21 p. (Practice guideline report; no. 2-16). [40 references]

### GUIDELINE STATUS

This is the current release of the guideline.

The Guideline will expand over time to contain new information emerging from their reviewing and updating activities.

Please visit the [Cancer Care Ontario Web site](#) for details on any new evidence that has emerged and implications to the guidelines.

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## SCOPE

### DISEASE/CONDITION(S)

Metastatic colorectal carcinoma

### GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness  
Treatment

## **CLINICAL SPECIALTY**

Oncology

## **INTENDED USERS**

Physicians

## **GUIDELINE OBJECTIVE(S)**

- To evaluate the role of irinotecan (CPT-11, Camptosar®) in the second-line treatment of metastatic colorectal carcinoma
- To evaluate where second-line treatment with irinotecan is indicated, and if it is used, to evaluate if irinotecan should be administered alone or in combination with other drugs
- To evaluate which patient population is appropriate for monotherapy, and which is appropriate for combination therapy
- To evaluate if there are contraindications to second-line treatment with irinotecan, and what other treatment options exist

## **TARGET POPULATION**

Adult patients with metastatic colorectal carcinoma for whom first-line treatment with either single-agent or combination anti-thymidylate synthase therapy has failed. The patients in whom first-line therapy has failed were those that progressed during first-line chemotherapy or that progressed within six months of completing adjuvant therapy.

## **INTERVENTIONS AND PRACTICES CONSIDERED**

1. Irinotecan alone
2. Irinotecan in combination with other drugs

## **MAJOR OUTCOMES CONSIDERED**

- Overall survival
- Progression-free survival
- Response rates (complete response, partial response)
- Duration of response
- Symptom improvement
- Quality of life
- Adverse effects

## **METHODOLOGY**

### **METHODS USED TO COLLECT/SELECT EVIDENCE**

Hand-searches of Published Literature (Primary Sources)  
Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases  
Searches of Unpublished Data

## **DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE**

### **Original Guideline: April 1999**

A search of MEDLINE, CANCELIT, and the Cochrane Library was conducted for the period from January 1992 to January 1999 using the subject headings "camptothecin", "colonic neoplasms", "rectal neoplasms", and "colorectal neoplasms". Information was requested from Pharmacia & Upjohn, Inc., Canada, the manufacturer of irinotecan. Roussell Laboratories provided data from two randomized controlled trials (RCTs) relating to the adverse effects of irinotecan. Furthermore, personal reprint files, referenced articles, and proceedings of conferences, including the 1998 American Society of Clinical Oncology meeting, were reviewed. The Physician Data Query database was searched for relevant ongoing clinical trials.

### **July 2004 Update**

The original literature search was updated using MEDLINE (through to June [week 2], 2004), EMBASE (through to week 25, 2004), CANCELIT (through to October 2002), the Cochrane Library (through to Issue 2, 2004) databases. Abstracts published in the 1999 through 2004 proceedings of the annual meeting of the American Society of Clinical Oncology have been searched for evidence related to this practice guideline. The National Cancer Institute (NCI) clinical trials database was searched for relevant trial reports. The most recent literature search was performed on June 24, 2004.

### **Inclusion Criteria**

#### **Original Guideline: April 1999**

Articles were selected for inclusion in this systematic review of the evidence if they met the following criteria:

- Articles or abstracts detailing phase II or III trials of irinotecan in patients with metastatic colorectal cancer and articles or abstracts discussing the adverse effects associated with the drug
- Only studies that reported results for the major outcomes of interest (objective response rates, duration of response or progression-free survival, adverse effects, symptom improvement, quality of life, and overall survival) were eligible for review.

#### **July 2004 Update**

Since the Practice Guidelines Coordinating Committee (PGCC) approval and subsequent publication of the original guideline, a companion Gastrointestinal Cancer Disease Site Group (DSG) practice guideline detailing the use of irinotecan combined with 5-fluorouracil/leucovorin (FU/LV) as first-line treatment has also been completed. Therefore, the updated literature search for this guideline was

limited to peer-reviewed abstracts, fully published randomized controlled trials, and meta-analyses using irinotecan alone or in combination with other drugs as second-line treatment only.

## **NUMBER OF SOURCE DOCUMENTS**

### **Original Guideline: April 1999**

Two randomized controlled trials (RCTs), six phase II trials, and one monograph were reviewed.

### **July 2004 Update**

Of the nine monotherapy RCTs obtained for this update, six were either duplicate publications of trials or cost-effectiveness analyses of a study. The other three reports were new trials and are included in Table 1 of the original guideline document.

Two trial reports were obtained describing the use of irinotecan in combination with other drugs in the second-line treatment of metastatic colorectal cancer.

## **METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE**

Expert Consensus (Committee)

## **RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE**

Not applicable

## **METHODS USED TO ANALYZE THE EVIDENCE**

Systematic Review with Evidence Tables

## **DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE**

### **Original Guideline: April 1999**

A meta-analysis of efficacy data from the randomized controlled trials (RCTs) could not be conducted because irinotecan was compared with two different control regimens. However, response rates, median time to disease progression, adverse effects, and median survival times in the phase II trials were pooled using an average weighted for study population size to estimate the overall effect of irinotecan.

### **July 2004 Update**

Data on the median number of cycles administered were added to the tables during subsequent updates.

## **METHODS USED TO FORMULATE THE RECOMMENDATIONS**

Expert Consensus

## **DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS**

### **Original Guideline: April 1999**

After an intense debate about the risks, benefits, and costs of palliative chemotherapy, the Gastrointestinal Cancer Disease Site Group members agreed that irinotecan may be indicated in some patients with metastatic colorectal cancer for whom 5-fluorouracil (5-FU) chemotherapy failed. Patients must be made aware that there are significant adverse effects requiring intense supervision and adjuvant medications. Patients must also be advised that responses are usually transient but associated with improved one-year survival and quality of life, especially when compared with best supportive care (BSC). The high cost of the drug must be considered in policy development.

### **July 2004 Update**

The major discussion among the Gastrointestinal Cancer Disease Site Group (DSG) members centered around scenarios where it would be appropriate to administer an irinotecan-containing regimen, either as monotherapy or in combination with other drugs, where no randomized trial data are available to support any recommendations.

Members of the Gastrointestinal Cancer DSG also noted that there are several new drugs indicated for the first and second-line treatment of metastatic colorectal cancer that are available to clinicians. Guidelines on the role of bevacizumab combined with IFL or FOLFIRI in the first-line treatment of colorectal cancer (Draft Practice Guideline 2-25, in progress), and the role of cetuximab (C225) in the second and third-line treatment of metastatic colorectal cancer (Draft Practice Guideline Report 2-27, in progress) are being developed by the Gastrointestinal Cancer Disease Site Group. The role of second-line treatment using irinotecan will be contextualized in all relevant documents.

## **RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS**

Not applicable

## **COST ANALYSIS**

Published cost analyses were reviewed.

## **METHOD OF GUIDELINE VALIDATION**

External Peer Review  
Internal Peer Review

## **DESCRIPTION OF METHOD OF GUIDELINE VALIDATION**

## **Original Guideline: April 1999**

Practitioner feedback was obtained through a mailed survey of 26 practitioners in Ontario (26 medical oncologists). The survey consisted of items evaluating the methods, results and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a practice guideline. Written comments were invited. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The results of the survey were reviewed by the Gastrointestinal Cancer Disease Site Group (DSG).

The Practice Guidelines Coordinating Committee formally approved the practice guideline report but made suggestions for minor revisions to the recommendations. The main points concerned a need to include the tumour response rate and one-year survival rates in the recommendation, as well as a need for a more explicit definition of the patient population to which the recommendation applies. The Gastrointestinal Cancer DSG agreed with the suggestions, and these changes were made to the guideline to incorporate this feedback.

These practice guideline recommendations reflect the integration of the draft recommendations with feedback obtained from the external review process. They have been approved by the Gastrointestinal Cancer DSG and the Practice Guidelines Coordinating Committee.

## **July 2004 Update**

New evidence has emerged on the use of irinotecan as first-line therapy for metastatic colorectal cancer. That evidence has been reviewed by the Gastrointestinal Cancer DSG, and a separate practice guideline on the use of irinotecan for the first-line treatment of metastatic colorectal cancer has been developed. For this reason, the bullet indicating insufficient evidence on irinotecan for first-line treatment was removed from the original guideline recommendations.

# **RECOMMENDATIONS**

## **MAJOR RECOMMENDATIONS**

- The Gastrointestinal Cancer Disease Site Group (DSG) recommends second-line treatment with irinotecan, either alone or in combination with 5-fluorouracil/leucovorin, to selected patients in whom first-line therapy has failed.
- It is appropriate to offer irinotecan monotherapy as second-line treatment to patients following failure of first-line treatment with:
  - Infusional 5-fluorouracil/leucovorin and oxaliplatin (FOLFOX)
  - Bolus or infusional 5-fluorouracil/leucovorin (Mayo or de Gramont schedule)
  - Oral capecitabine
  - Raltitrexed
- Although based on non-randomized controlled trial evidence, the Gastrointestinal Disease Site Group supports second-line treatment with

irinotecan, either alone or in combination with infusional 5-fluorouracil/leucovorin, as second-line treatment to patients following failure of first-line treatment with:

- Infusional 5-fluorouracil/leucovorin and oxaliplatin.

## **CLINICAL ALGORITHM(S)**

None provided

## **EVIDENCE SUPPORTING THE RECOMMENDATIONS**

### **TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS**

#### **Original Guideline: April 1999**

Two randomized controlled trials (RCTs), six phase II trials, and one monograph were reviewed. The randomized controlled trials compared irinotecan with best supportive care (BSC) or 5-fluorouracil (5-FU) infusional chemotherapy in patients for whom first-line 5-FU bolus therapy failed. Three phase II studies also presented data on chemotherapy-naïve patients.

#### **July 2004 Update**

The recommendations are supported by randomized controlled trials.

## **BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS**

### **POTENTIAL BENEFITS**

#### **Second-line Irinotecan Monotherapy**

It is appropriate to offer irinotecan monotherapy as second-line treatment to patients following failure of first-line treatment with: infusional 5-fluorouracil/leucovorin and oxaliplatin (FOLFOX), bolus or infusional 5-fluorouracil/leucovorin (Mayo or de Gramont schedule), oral capecitabine, or intravenous (IV) raltitrexed.

- Following first-line treatment failure with FOLFOX, the Gastrointestinal Disease Site Group (DSG) recommends second line irinotecan monotherapy for those patients with contraindications to 5-fluorouracil/leucovorin, but randomized data are unavailable to support this.
- Two randomized trials involving 535 patients detected a median survival benefit for irinotecan monotherapy compared with best supportive care ( $p=0.0001$ ) and three different 5-fluorouracil containing regimens ( $p=0.035$ ).
- As oral capecitabine has both pharmacokinetic and adverse effects similar to infusional 5-fluorouracil, the Gastrointestinal Disease Site Group recommends second-line irinotecan monotherapy; however, randomized trial data are unavailable to support this.
- As intravenous raltitrexed has the same enzyme target and similar adverse effects as 5-fluorouracil, the Gastrointestinal Disease Site Group recommends

second-line irinotecan monotherapy; however, randomized trial data are unavailable to support this.

- When irinotecan was compared with BSC, quality of life scores favoured irinotecan. An exception was diarrhea, which was significantly better for BSC ( $p=0.02$ ). Irinotecan compared with 5-FU demonstrated no difference in quality of life scores, but cases of vomiting and diarrhea were significantly worse for irinotecan than for 5-FU-treated patients. Only two trials obtained during the update reported data on quality of life and both found no significant difference between the treatment groups.

### **Second-line Irinotecan, either as a Single-agent or in Combination**

- Although based on non-randomized controlled trial evidence, the Gastrointestinal Disease Site Group supports second-line treatment with irinotecan, either alone or in combination with infusional 5-fluorouracil/leucovorin, as second-line treatment to patients following failure of first-line treatment with FOLFOX (infusional 5-fluorouracil/leucovorin/oxaliplatin).
- There is evidence from a single randomized crossover trial involving 220 patients that where FOLFOX is given as first-line treatment, it is appropriate to offer second-line infusional 5-fluorouracil/leucovorin and irinotecan (FOLFIRI) to patients. Where there are contraindications to administering irinotecan in combination with 5-fluorouracil and folinic acid, single-agent irinotecan therapy is recommended by the Gastrointestinal Disease Site Group, despite the absence of randomized trial data.

### **POTENTIAL HARMS**

#### **Original Guideline: April 1999**

- Some form of adverse effect was found in most treated patients. They included nausea/vomiting, diarrhea, neutropenia, alopecia, asthenia, and a cholinergic syndrome occurring during drug administration (which consisted of abdominal cramps, diarrhea, nausea/vomiting, salivation, sweating, and lacrimation). Stomatitis, thrombocytopenia, anemia, and other toxic events were rare. Severe diarrhea, febrile neutropenia, and the cholinergic syndrome require immediate treatment.
- The major adverse effects observed in all studies were delayed diarrhea, nausea and vomiting, neutropenia, and leukopenia. The most frequent severe adverse effects (NCI grades 3 and 4) are presented in Tables 4 and 5 in the original guideline document. The randomized controlled trials (RCTs) demonstrated that 19% of patients experienced neutropenia, 14% vomiting, and 22% diarrhea. Pooled results from the phase II studies demonstrated that 33% of patients experienced diarrhea, 17% vomiting, 38% neutropenia, and 18% leukopenia.
- In a monograph that reported pooled data from three American phase II studies involving 304 patients, 17% of patients experienced cholinergic syndrome, 12% asthenia, and 3% febrile neutropenia. Potentially drug-related fatalities were experienced by 1.6% of patients, usually due to diarrhea and/or neutropenia. Dose reductions were required in 63% of patients, and 4.3% discontinued treatment due to adverse effects.

- Similar adverse effects were observed in a French phase II study. Severe diarrhea was more common in patients older than 65 years ( $p=0.059$ ) and in those with previous abdominal or pelvic radiation ( $p < 0.0001$ ), but not in those who received previous chemotherapy. Four deaths among 213 (1.9%) patients were considered likely related to treatment, and three deaths were associated with diarrhea. Neutropenia was short-lived, not cumulative, and less common in patients younger than 65 years with a performance status of 0. Febrile neutropenia was experienced by patients in 9% of 40 cycles when diarrhea accompanied neutropenia but only in 2% of 1013 cycles when neutropenia occurred alone ( $p < 0.0001$ ).
- Immediate attention to gastrointestinal adverse effects has led to better drug tolerance. The early cholinergic syndrome was responsive to immediate administration of intravenous atropine in doses of 0.25 to 1.00 mg. Delayed diarrhea was found to be controllable with the intensive use of loperamide: 4 mg at the start of loose stools and repeating 2 mg doses every two hours until 12 hours without diarrhea. Other measures to control diarrhea have been investigated in phase I trials and have been suggested for investigation. Use of dexamethasone and ondansetron prior to irinotecan administration relieved most severe cases of nausea and vomiting. Granulocyte colony-stimulating factor (G-CSF) has been determined to decrease the incidence of neutropenia and infection.

### **July 2004 Update**

The adverse effects observed in the updated trials were similar to those in the original guideline report and are detailed in the updated Table 4 in the original guideline document.

## **QUALIFYING STATEMENTS**

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Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult these guidelines is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or warranties of any kind whatsoever regarding their content or use or application and disclaims any responsibility for their application or use in any way.

## **IMPLEMENTATION OF THE GUIDELINE**

### **DESCRIPTION OF IMPLEMENTATION STRATEGY**

An implementation strategy was not provided.

## **INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES**

### **IOM CARE NEED**

Living with Illness

**IOM DOMAIN**

Effectiveness

**IDENTIFYING INFORMATION AND AVAILABILITY**

**BIBLIOGRAPHIC SOURCE(S)**

Gastrointestinal Cancer Disease Site Group. Figueredo A, Moore M, Germond C, Kocha W, Maroun J, Zwaal C. Use of irinotecan in the second-line treatment of metastatic colorectal carcinoma. Toronto (ON): Cancer Care Ontario (CCO); 2004 Jul. 21 p. (Practice guideline report; no. 2-16). [40 references]

**ADAPTATION**

Not applicable: The guideline was not adapted from another source.

**DATE RELEASED**

1999 Apr 30 (revised 2004 Jul)

**GUIDELINE DEVELOPER(S)**

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

**GUIDELINE DEVELOPER COMMENT**

The Program in Evidence-based Care (PEBC), is a project supported by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

**SOURCE(S) OF FUNDING**

Cancer Care Ontario  
Ontario Ministry of Health and Long-Term Care

**GUIDELINE COMMITTEE**

Provincial Gastrointestinal Cancer Disease Site Group

**COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE**

For a current list of past and present members, please see the [Cancer Care Ontario Web site](#).

**FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST**

Members of the Gastrointestinal Cancer Disease Site Group disclosed potential conflict of interest information.

## **GUIDELINE STATUS**

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## **GUIDELINE AVAILABILITY**

Electronic copies: Available in Portable Document Format (PDF) from the [Cancer Care Ontario Web site](#).

## **AVAILABILITY OF COMPANION DOCUMENTS**

The following are available:

- Use of irinotecan in the second-line treatment of metastatic colorectal carcinoma. Summary. Toronto (ON): Cancer Care Ontario (CCO). Electronic copies: Available in Portable Document Format (PDF) from the [Cancer Care Ontario Web site](#).
- Figueredo A, Moore M, Germond C, Kocha W, Maroun J, Zwaal C, and the Gastrointestinal Cancer Disease Site Group. Use of irinotecan in second-line treatment of metastatic colorectal carcinoma. *Curr Oncol* 2000;7:29-36.
- Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. *J Clin Oncol* 1995 Feb;13(2):502-12.

## **PATIENT RESOURCES**

None available

## **NGC STATUS**

This summary was completed by ECRI on August 19, 1999. The information was verified by the guideline developer as of September 17, 1999. This NGC summary was updated by ECRI on December 3, 2001. The updated information was reviewed by the guideline developer as of January 10, 2002. This information was updated again by ECRI on May 14, 2004. The updated information was verified by the guideline developer on June 2, 2004. This NGC summary was updated on August 12, 2005. The updated information was verified by the guideline developer on September 13, 2005.

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