

# Cancer Care Ontario Program in Evidence-based Care Practice Guidelines Initiative

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Ontario Ministry of Health and Long-Term Care



## Use of Irinotecan (Camptosar®, CPT-11) Combined with 5-Fluorouracil and Leucovorin (5FU/LV) as First-Line Therapy for Metastatic Colorectal Cancer

### Practice Guideline Report #2-16b

**ORIGINAL GUIDELINE: October 23, 2001**

**MOST RECENT LITERATURE SEARCH: February 19, 2003**

**NEW EVIDENCE ADDED TO THE GUIDELINE REPORT: February 2003**

**New evidence found by update searches since completion of the original guideline is consistent with the original recommendations.**

### SUMMARY

#### Guideline Question

What is the role of irinotecan combined with 5-fluorouracil and leucovorin as first-line systemic therapy in the management of metastatic colorectal cancer? The primary endpoint of interest was survival. Secondary endpoints were response rates, time to disease progression, and quality of life.

#### Target Population

These recommendations apply to adult patients with metastatic colorectal cancer for whom chemotherapy is being considered as a first-line treatment.

#### Recommendations

##### *Key Recommendations*

- It is reasonable to offer the patient a choice between irinotecan/5FU/LV and 5FU/LV. Survival and response improvements with irinotecan/5FU/LV must be balanced against the increased toxicity (more hair loss, diarrhea, and hospitalization with irinotecan versus more mucositis without irinotecan). Excess thrombotic events are also seen with irinotecan.
- For patients offered irinotecan therapy, careful monitoring of adverse effects and early intervention for diarrhea should be part of the treatment process.

### **Qualifying Statement**

- Caution should be exercised in recommending irinotecan to patients with a performance status >1 (ECOG scale). All patients who may be eligible for this treatment should be warned of the adverse effects of irinotecan/5FU/LV.

### **Methods**

Entries to MEDLINE (1976 through January (week 2) 2003), CANCELIT (1983 through October 2002), and Cochrane Library (2002 Issue 4) databases and abstracts published in the proceedings of the annual meetings of the American Society of Clinical Oncology to 2002 were systematically searched for evidence relevant to this practice guideline report.

Evidence was selected and reviewed by two members of the Practice Guidelines Initiative's Gastrointestinal Cancer Disease Site Group and methodologists. This practice guideline report has been reviewed and approved by the Gastrointestinal Cancer Disease Site Group, which comprises medical and radiation oncologists, surgeons, a pathologist, and community representatives.

External review by Ontario practitioners was obtained through a mailed survey. Final approval of the original guideline report was obtained from the Practice Guidelines Coordinating Committee.

The Practice Guidelines Initiative has a formal standardized process to ensure the currency of each guideline report. This process consists of a periodic review and evaluation of the scientific literature and, where appropriate, the integration of this literature with the original guideline information.

### **Key Evidence**

- Irinotecan/5FU/LV is at least as effective as 5FU/LV, which is a standard first-line therapy in patients with metastatic colorectal cancer. Two randomized phase III trials detected improved response rates (pooled data: 37% versus 21%;  $p < 0.0001$ ) and median time to tumour progression (pooled data: 6.9 months versus 4.3 months;  $p < 0.0001$ ) for the combination that contained irinotecan. An individual patient data meta-analysis detected a significant survival advantage for irinotecan/5FU/LV compared with 5FU/LV alone (median survival, 15.9 months versus 13.3 months;  $p < 0.009$ ; hazard ratio, 0.79; 95% confidence interval, 0.66 to 0.94;  $p < 0.009$ ).
- Quality of life was formally measured in both phase III trials, and no difference between arms was detected in either trial.
- Irinotecan/5FU/LV is associated with more grade 3/4 diarrhea, nausea and vomiting, and more grade 1/2 alopecia but less severe mucositis. Hospitalizations were also more frequent with irinotecan.

### **Related Guidelines**

Practice Guidelines Initiative's Practice Guideline Report #2-16: *Use of Irinotecan in the Treatment of Metastatic Colorectal Carcinoma.*

Practice Guidelines Initiative's Practice Guideline Report #2-17: *Use of Raltitrexed (Tomudex) in the Management of Metastatic Colorectal Cancer.*

### **Prepared by the Gastrointestinal Cancer Disease Site Group**

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## **PREAMBLE: About our Practice Guideline Reports**

The Practice Guidelines Initiative (PGI) is a project supported by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care, as part of the Program in Evidence-based Care. The purpose of the Program is to improve outcomes for cancer patients, to assist practitioners to apply the best available research evidence to clinical decisions, and to promote responsible use of health care resources. The core activity of the Program is the development of practice guidelines by multi-disciplinary Disease Site Groups of the PGI using the methodology of the Practice Guidelines Development Cycle.<sup>1</sup> The resulting practice guideline reports are convenient and up-to-date sources of the best available evidence on clinical topics, developed through systematic reviews, evidence synthesis and input from a broad community of practitioners. They are intended to promote evidence-based practice.

This practice guideline report has been formally approved by the Practice Guidelines Coordinating Committee, whose membership includes oncologists, other health providers, community representatives and Cancer Care Ontario executives. Formal approval of a practice guideline by the Coordinating Committee does not necessarily mean that the practice guideline has been adopted as a practice policy of CCO. The decision to adopt a practice guideline as a practice policy rests with each regional cancer network that is expected to consult with relevant stakeholders, including CCO.

### Reference:

<sup>1</sup> 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;13(2):502-12.

**For the most current versions of the guideline reports and information about the PGI and the Program, please visit our Internet site at:**  
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## FULL REPORT

### I. QUESTION

What is the role of irinotecan (Camptosar®, CPT-11) combined with 5-fluorouracil and leucovorin as first-line systemic therapy in the management of metastatic colorectal cancer?

### II. CHOICE OF TOPIC AND RATIONALE

Colorectal cancer is the fourth most prevalent cancer and the second leading cause of cancer death in North America. At some point, 40% of patients will develop metastasis, with a predicted median life span of ten months. Irinotecan has been recommended as second-line therapy in patients with disease progression on anti-thymidylate synthase chemotherapy (1) (see the abstract of Practice Guideline #2-16 in Appendix 1). At the time that Practice Guideline #2-16 was developed, there was insufficient evidence to make a recommendation for the use of irinotecan for first-line treatment. New evidence has emerged regarding the use of irinotecan combined with 5-fluorouracil and leucovorin as first-line therapy in metastatic colorectal cancer. Information on the administration, dosing, and scheduling of irinotecan combined with 5-fluorouracil and leucovorin is included in Appendix 2.

### III. METHODS

#### Guideline Development

This practice guideline report was developed by the Practice Guidelines Initiative (PGI) of Cancer Care Ontario, Gastrointestinal Cancer using methods of the Practice Guidelines Development Cycle (2). Evidence was selected and reviewed by two members of the PGI's Gastrointestinal Cancer Disease Site Group (DSG) and methodologists. Members of the Gastrointestinal DSG disclosed potential conflict of interest information.

The practice guideline report is a convenient and up-to-date source of the best available evidence on the use of irinotecan in first-line therapy for metastatic colorectal cancer, developed through systematic reviews, evidence synthesis, and input from practitioners in Ontario. The body of evidence in this report is primarily comprised of mature randomized controlled trial data; therefore, recommendations by the DSG are offered. The report is intended to promote evidence-based practice. The Practice Guidelines Initiative is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

External review by Ontario practitioners was obtained through a mailed survey consisting of items that address the quality of the draft practice guideline report and recommendations and whether the recommendations should serve as a practice guideline. Final approval of the original guideline report was obtained from the Practice Guidelines Coordinating Committee (PGCC).

The PGI has a formal standardized process to ensure the currency of each guideline report. This consists of periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original guideline information.

#### Literature Search Strategy

MEDLINE (1976 to November 2000), CANCERLIT (1983 to November 2000), and the Cochrane Library (Issue 4, 2000) were searched with no language restrictions. "Colonic neoplasms" (Medical subject heading [MeSH]), "rectal neoplasms" (MeSH), and "colorectal neoplasms" (MeSH) were combined with "camptothecin" (MeSH) and each of the following phrases used as text words: "irinotecan", "camptosar", "cpt-11". These terms were then combined with the search terms for the following study designs or publication types: practice guidelines, systematic reviews or meta-analyses, randomized controlled trials, and clinical trials. A search of the proceedings from recent international meetings, including the 1999 and 2000 annual meetings of the American Society of Clinical Oncology, was also conducted. In addition,

the Physician Data Query (PDQ) clinical trials database ([http://www.nci.nih.gov/search/clinical\\_trials/](http://www.nci.nih.gov/search/clinical_trials/)) was searched for reports of on-going trials. Reference lists of retrieved papers were also scanned for additional citations. The U.S. Food and Drug Administration (FDA) website was reviewed for additional presented material regarding the application for approval of irinotecan as first-line therapy in the United States.

#### **Update**

Entries to MEDLINE (December 2000 through January (week 2) 2003), CANCELIT (December 2000 through October 2002), and Cochrane Library (2002 Issue 4) databases and abstracts published in the proceedings of the annual meetings of the American Society of Clinical Oncology 2001 and 2002 were systematically searched for evidence relevant to this practice guideline report.

#### **Inclusion Criteria**

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

1. Randomized controlled trials or meta-analyses of an active treatment arm using irinotecan as first-line therapy compared with a control arm without irinotecan in patients with metastatic colorectal cancer. Randomized phase II and phase III trials were eligible as well as published meta-analyses of randomized trials. The primary endpoint of interest was survival. Secondary endpoints were response rates, time to disease progression, and quality of life.
2. Abstracts of trials were also considered.

#### **Synthesizing the Evidence**

It was decided not to pool the data on response or survival from the phase III trials because of the availability of a published meta-analysis using individual patient data (3). Data on toxicity for the irinotecan arms of the phase III trials were pooled by summing the number of adverse events across the phase III trials and dividing this number by the total number of patients included in these arms of the phase III trials. The result was converted to a percentage. It was thought to be inappropriate to combine data on toxicity for the no-irinotecan arms in the phase III trials because the deGramont and Mayo regimens are quite different with respect to toxicity (4).

## **IV. RESULTS**

### **Literature Search Results**

Two phase III randomized trials of irinotecan combined with 5-fluorouracil and leucovorin (5FU/LV) compared with 5FU/LV alone as first-line therapy in patients with metastatic or advanced colorectal cancer met the inclusion criteria (5,6) (Table 1). A combined analysis of these two phase III trials using individual patient data has been published in abstract form (3). In addition, a FDA review of both phase III trials is available on the Internet (7). Two phase II randomized trials published in abstract form also met the inclusion criteria (8,9).

In the phase III study by Saltz et al (n=457 patients), weekly bolus irinotecan/5FU/LV was compared with 5FU/LV (standard full dose Mayo regimen) (6). A third arm in this study evaluated irinotecan alone (n=226 patients). The European phase III trial reported by Douillard et al (n=387 patients) compared irinotecan plus 5FU/LV to the same schedule of 5FU/LV alone (5). As this trial was conducted in two countries with different standards for the use of 5FU/LV, different regimens were used. In France, the 48-hour infusional "deGramont" regimen (n=143 patients) was compared with the same regimen combined with irinotecan (n=145 patients). In Germany, the weekly 24-hour infusional AIO (Association of Medical Oncology of the German Cancer Society) regimen (n=43 patients) was compared with a nearly identical regimen combined with irinotecan (n=54 patients). The random assignment was not entirely successful

in the distribution of baseline prognostic characteristics between arms, with more rectal cancer patients (45% versus 35%; p=0.0042) and fewer women (33% versus 47%; p=0.006) in the irinotecan arm (7). A multivariate analysis controlling for these and other factors was performed.

The Italian phase II study compared the bi-weekly “deGramont regimen” to the same regimen with irinotecan in 102 patients in a 1:2 ratio (8). Graeven et al (9) conducted a three-arm randomized phase II study of combined or alternating irinotecan/5FU/LV versus the Mayo regimen of 5FU/LV.

### Update

Four phase III trials comparing irinotecan containing regimens with other treatments were obtained (1u-4u). The first study compared irinotecan/5FU/LV versus methotrexate/5FU/LV (1u). The second compared irinotecan/5FU/LV versus Oxaliplatin/5FU/LV (2u). The third and fourth studies compared irinotecan/5FU/LV to two different 5FU/LV regimens (AIO and MAYO) (4u,5u). Efficacy results for these new trials appear in Table 4. Data on adverse effects appear in Table 5.

**Table 1. Randomized trials of irinotecan/5FU/LV versus 5FU/LV.**

Trial	Study Period (Years)	Number of Randomized (Evaluable) Patients	Chemotherapy Regimen
<i>Phase III Trials</i>			
Europe / Douillard (5)	1997-1998	199* (169)	Irinotecan 80mg/m <sup>2</sup> +LV 500mg/m <sup>2</sup> +5FU 2300mg/m <sup>2</sup> civ24hr weekly x6 q7w (Germany, weekly AIO, n=54) <b>or</b> Irinotecan 180mg/m <sup>2</sup> d1 + [LV 200mg/m <sup>2</sup> +5FU 400mg/m <sup>2</sup> followed by 600mg/m <sup>2</sup> civ22hr] d1,2 q2w (France, deGramont, n=145)
		188* (169)	LV 500mg/m <sup>2</sup> +5FU 2300mg/m <sup>2</sup> civ24hr weekly x6 q7w (Germany, weekly AIO, n=43) <b>or</b> LV200mg/m <sup>2</sup> +5FU 400mg/m <sup>2</sup> followed by 600mg/m <sup>2</sup> civ22hr d1,2 q2w (France, deGramont, n=143)
North America / Saltz (6)	1997-1998	231 (225)	Irinotecan 125mg/m <sup>2</sup> followed by LV 20mg/m <sup>2</sup> followed by 5FU500mg/m <sup>2</sup> iv weekly x4 q6w
		226 (219)	LV 20mg/m <sup>2</sup> + 5FU 425mg/m <sup>2</sup> iv d1-5 q4w
		226 (223)	Irinotecan 125mg/m <sup>2</sup> iv weeklyx4 q6w
<i>Phase II Trials</i>			
Maiello (8) (abstract)	1997-1999	68 (45)	Irinotecan 180mg/m <sup>2</sup> followed by LV/5FU (as below) q2w
		34 (25)	LV 100mg/m <sup>2</sup> +5FU 400mg/m <sup>2</sup> iv followed by 600mg/m <sup>2</sup> iv civ22hr d1,2 q2w
Graeven (9) (abstract)	NR	NR (33)	Irinotecan 125mg/m <sup>2</sup> + LV 20mg/m <sup>2</sup> +5FU 500mg/m <sup>2</sup> iv weekly x4 q6w
		NR (42)	Irinotecan 350 mg/m <sup>2</sup> <i>alternating with</i> LV 20mg/m <sup>2</sup> +5FU 425mg/m <sup>2</sup> q6w
		NR (42)	LV 20 mg/m <sup>2</sup> +5-FU 425 mg/m <sup>2</sup> iv q4w

Notes: 5FU, 5-fluorouracil; civ, continuous intravenous; d, day; LV, leucovorin; iv, intravenous; q, every; w, week(s); NR, not reported.

\* One patient in each group did not receive study treatment and one patient in the non-irinotecan arm received irinotecan.

## Survival

The European trial (5) demonstrated a survival benefit favouring irinotecan (Table 2). Partial analysis of the European trial controlling for the imbalance in the proportion of patients with rectal cancer was performed and reported in the FDA review (7). The median survival times for the subgroup of patients with rectal tumours were 18.3 months with irinotecan and 17.4 months without irinotecan. The unadjusted median survival times for all patients were 17.4 months for 5FU/LV/irinotecan and 14.1 months for 5FU/LV. Since the rectal cancer patients in the 5FU/LV arm had superior survival compared with the colon cancer patients, the lower percentage of rectal cancer patients randomized to 5FU/LV (35% no irinotecan versus 45% with irinotecan) may mean the difference in the observed survival curves may overestimate the true difference.

The FDA reviewers (7) noted that the endpoint of survival was added to the North American trial in May 1998 as an amendment after the trial was initiated. The decision mid-way through the trial (in December 1997) to limit the statistical analysis to irinotecan/5FU/LV compared with 5FU/LV (i.e. excluding the irinotecan-alone arm) was also done in an effort to bolster the statistical significance of the study by avoiding adjustments for multiple comparisons. Early results of the North American trial, reported in abstract form, showed similar median survival times between arms (median, 14.4 months with irinotecan/5FU/LV versus 12.6 months with 5FU/LV;  $p=0.173$ ) (11). Results at the specified cut-off date of September 1999, reported in abstract form, demonstrated a non-significant trend towards improved survival with irinotecan/5FU/LV compared with 5FU/LV (median, 14.5 months versus 12.6 months;  $p=0.097$ ) (10). A subsequent analysis of the data (cut-off date of December 1999), published in full, detected a significant survival benefit favouring irinotecan/5FU/LV compared with 5FU/LV (median, 14.8 months versus 12.6 months;  $p=0.04$ ) (6). This survival benefit remained significant after adjustment for baseline patient characteristics (hazard ratio [HR], 0.78; 95% confidence interval [CI], 0.63 to 0.97;  $p=0.03$ ) (6).

An individual patient data meta-analysis of the two phase III trials (5,6) has been published in abstract form (3). The results detected a significant survival benefit favouring irinotecan/5FU/LV compared with 5FU/LV alone (HR, 0.79; 95% CI, 0.66 to 0.94;  $p<0.009$ ).

**Table 2. Results of randomized trials of irinotecan/5FU/LV versus 5FU/LV.**

Trial	Treatment Group	Number of Randomized Patients (Evaluable)	Overall Response Rate	Confirmed* Response Rate	Median Time to Tumour Progression (months)	Median Survival (months)
<i>Phase III Trials</i>						
Europe / Douillard (5)	Irinotecan/5FU/LV	199 (169)	49%	41%	6.7	17.4
	5FU/LV	188 (169)	31% p<0.001	23% p<0.001	4.4 p<0.001	14.1 p=0.031
North America / Saltz (6) †	Irinotecan/5FU/LV	231 (225)	50%	39%	7.0	14.8
	5FU/LV	226 (219)	28% p<0.001	21% p<0.001	4.3 p=0.004	12.6 p=0.04‡
Pooled Analysis (3) § (abstract)	Irinotecan/5FU/LV	430 (429)	NR	37%	6.9	15.9
	5FU/LV	414 (413)		21% p<0.0001	4.3 p<0.0001	13.3 p<0.009
<i>Phase II Trials</i>						
Maiello (8) (abstract)	Irinotecan/5FU/LV	68 (45)	42%	NR	NR	NR
	5FU/LV	35 (25)	20%			
Graeven (9) (abstract)	Irinotecan/5FU/LV (combined)	NR (33)	47%	NR	NR	NR
	Irinotecan/5FU/LV (alternating)	NR (42)	39%			
	5FU/LV	NR (42)	24%			

Notes: 5FU, 5-fluorouracil; LV, leucovorin; NR, not reported.

\* Duration greater than or equal to four weeks after initial objective response.

† P-values shown are for the two-way comparison of irinotecan/5FU/LV versus 5FU/LV. It was decided mid-way through the trial (in December 1997) to limit the statistical analysis to irinotecan/5FU/LV compared with 5FU/LV (i.e. excluding the irinotecan-alone arm).

‡ Results at the specified cut-off date of September 1999, reported in abstract form, demonstrated a non-significant trend towards improved survival with irinotecan/5FU/LV compared with 5FU/LV (median, 14.5 months versus 12.6 months; p=0.097) (10).

§ Data available at: [http://www.conference-cast.com/asco/vm2000/post\\_0922\\_0972.htm](http://www.conference-cast.com/asco/vm2000/post_0922_0972.htm). All randomized patients were included in the pooled analysis except for two patients in the European trial (one from each arm) who did not receive study treatment.

## Response Rates

Both investigator-assessed *objective response rates* and *confirmed response rates* (the latter is defined as response lasting greater than or equal to four weeks after initial objective response) were reported for the two phase III trials (5,6). Both trials detected significant improvements in objective and confirmed response rates favouring irinotecan/5FU/LV compared with 5FU/LV alone (p<0.001) (Table 2). The difference in response rates between treatment groups in the European phase III trial remained significant in the multivariate analysis, which adjusted for known imbalance in the pre-treatment characteristics. The individual patient data meta-analysis of the two phase III trials demonstrated an odds ratio for confirmed tumour response of 2.2 (95% CI, 1.6 to 3.0; p<0.0001) favouring irinotecan/5FU/LV compared with 5FU/LV (3).

In the European trial, the median duration of response was not statistically different between groups (9.3 months for irinotecan/5FU/LV versus 8.8 months for 5FU/LV; p=0.08). However, there was heavy censoring of patients in both arms due to inadequate documentation of the time of tumour progression (7). This occurred in 58% of responders in the

irinotecan/5FU/LV arm and 41% of responders in the 5FU/LV arm. The FDA review of the European trial downgraded the confirmed response rates. The overall response rate in the irinotecan arm was 35% versus 22% in the no-irinotecan arm ( $p < 0.005$ ) (7).

Improvement in response rate with irinotecan was also reported for the phase II trials although p-values were not reported (Table 2).

### **Time to Tumour Progression**

There was a significant improvement in median time to tumour progression favouring irinotecan in both phase III trials (5,6) (Table 2). In the European trial, the difference in median time to progression between groups remained significant in the multivariate analysis (5). This was also true for the North American trial as reported in the FDA review (7). The FDA reviewers noted that evaluation of time to progression in the European trial may be tainted by the fact that 33% to 44% of all patients did not have a time of progression documented by the cut-off date (7). The published pooled analysis of the phase III trials demonstrated a significant improvement in time to tumour progression with irinotecan/5FU/LV compared with 5FU/LV (HR, 0.67; 95% CI, 0.57 to 0.79;  $p < 0.001$ ) (3).

### **Quality of Life**

In both phase III trials, quality of life, as measured by the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30, did not differ significantly between the treatment groups (5,6).

The FDA reviewers noted that the scales that were analyzed in the North American trial (pain, role functioning, and global health status) were selected while the trial was ongoing rather than prospectively (7). In addition, some imputed means had to be used in the 5FU/LV arm to match the timing of the quality-of-life testing in the irinotecan arm. This method of data analysis was not pre-specified, and the FDA reviewers concluded that the results were unclear.

### **Adverse Effects**

Adverse effects differed between treatment groups in the phase III trials. In the European trial, there was more grade 3/4 diarrhea (13% versus 6%;  $p = 0.028$ ), asthenia (6% versus 1%;  $p = 0.011$ ), neutropenia (46% versus 13%;  $p = 0.001$ ), leukopenia (17% versus 4%;  $p = 0.001$ ), and grade 1-2 alopecia (57% versus 17%; p-value not reported) with the deGramont regimen of irinotecan (5). There was less toxicity with the AIO regimen of irinotecan, with the only significant differences between the irinotecan/5FU/LV arm versus the 5FU/LV arm for grade 3/4 neutropenia (29% versus 2%;  $p = 0.001$ ) and leukopenia (20% versus 2%;  $p = 0.009$ ). Grade 3/4 adverse events for the irinotecan group combined across regimen compared with the no-irinotecan group were reported in the FDA review and are as follows: diarrhea (23% versus 11%;  $p = 0.0026$ ), asthenia (10% versus 3%;  $p = 0.013$ ), thrombosis (4% versus 1%;  $p = 0.038$ ), and cardiovascular disorders (6% versus 1%;  $p = 0.0059$ ) (7). There was also more grade 1/2 alopecia with irinotecan (51% versus 17%;  $p < 0.001$ ). The FDA reviewers felt that 2% of patients in the irinotecan arm may have had treatment-related deaths in the European trial (7).

In the North American trial, there was more grade 3/4 diarrhea (23% versus 13%) and vomiting (10% versus 4%) but less neutropenic fever (7% versus 15%) and mucositis (2% versus 17%) with irinotecan/5FU/LV compared with 5FU/LV (6). Rates of severe neutropenia were similar (54% versus 67%). The FDA reviewers noted that hospitalizations were more frequent with irinotecan (total number of hospitalizations were 193 for irinotecan/5FU/LV versus 121 for 5FU/LV) (7).

The data on toxicity in the irinotecan arms for the two phase III trials as reported in the FDA review (7) were pooled and the results are as follows: grade 3/4 diarrhea in 23% of patients, grade 3/4 asthenia in 15%, grade 3/4 vomiting in 8%, grade 3/4 mucositis in 3%, and grade 1/2 alopecia in 47%.

In the Italian phase II trial (8), grade 3/4 diarrhea (9% versus 2%) and nausea and vomiting (7% versus 0%) were more frequent with irinotecan. Graeven et al (9) reported the following grade 3/4 adverse effects for the combined irinotecan/5FU/LV arm versus the alternating irinotecan/5FU/LV arm versus the 5FU/LV arm: diarrhea 6%/22%/19%, stomatitis 0%/7%/10%, and neutropenia 2%/15%/2%.

### **Subgroup Analyses**

For both of the phase III trials, the FDA review presented a stratified analysis of survival according to baseline patient characteristics (7). In the North American trial, the following subgroups did not appear to benefit from irinotecan/5FU/LV: performance status > 0 (median survival was 9.4 months with irinotecan versus 10.4 months without irinotecan); age  $\geq$  65 (median survival was 14.8 months with irinotecan versus 15.1 months without irinotecan); prior adjuvant therapy (median survival was 12.4 months with irinotecan versus 18.8 months without irinotecan); LDH > upper limit of normal (median survival was 10.7 months with irinotecan versus 10.4 months without irinotecan). Subgroups that appear to derive greater benefit include: age < 65; performance status 0; no prior adjuvant therapy; LDH < upper limit of normal. In the European trial, patients with performance status > 0 did not appear to benefit from combination therapy (median survival was 13 months in both arms). Subgroups that appear to derive greater benefit include patients with good performance status, normal LDH, or a low number of organs involved.

When the two European regimens were compared separately, the AIO regimen appeared to perform better than the deGramont regimen, with and without irinotecan. This difference may represent chance or patient selection factors used by different investigators. This group also made up only 25% of the total patients in the European study. Concern was raised about recommending the AIO irinotecan regimen as only 50 patients received this treatment.

## **V. INTERPRETIVE SUMMARY**

The combination of irinotecan/5FU/LV by either schedule represents a reasonable alternative to 5FU/LV. With maturation of the phase III trials, there now appears to be a survival advantage with the combination of irinotecan/5FU/LV. Although questions remain regarding sequential versus combined therapy, the new data supports the use of irinotecan as first-line therapy in combination with 5FU and leucovorin.

### **Combined (First-Line) Versus Sequential (Second-Line) Use of Irinotecan**

It is unknown whether combined (first-line) or sequential (second-line) use of irinotecan and 5FU/LV is superior. Less than half (31% to 40%) of patients in the 5FU/LV-alone arms received irinotecan as second-line therapy in the reported trials, which is lower than one might expect in current clinical practice with widespread availability of irinotecan. Some patients may not have been offered irinotecan off-study as second-line therapy for resource reasons. This may have exaggerated the true survival benefit of combination therapy (first-line irinotecan) over a sequential (second-line irinotecan) approach.

If used in a first-line strategy, all patients would receive irinotecan. If used as second-line therapy (as has been the practice in Ontario), fewer patients receive irinotecan, perhaps only 30% to 40% of patients as was the case in these trials.

Since combined irinotecan/5FU/LV as first-line therapy is associated with much higher tumour response rates, it may be a more appropriate option for those with symptomatic disease in whom greater tumour shrinkage would result in superior palliation. Similarly, it may be superior for those at risk for imminent decompensation due to disease for which no second-line therapy would be possible if deterioration were to occur. In asymptomatic patients and those

not at risk for imminent decompensation, either first- or second-line use of irinotecan are acceptable options.

**Patients with Poorer Performance Status**

As patients with high performance status (ECOG 0-2) were selected for these trials, there are no data on patients with poor performance status (ECOG 3). In the sub-group analysis performed by the FDA, there was no survival benefit for patients with performance status > 0, though improvements were seen in response and time to progression. No subgroups analysis for toxicity has been made available. It is possible that improvements in response were countered by an increase in toxicity resulting in a neutral effect on survival. Decisions regarding the use of irinotecan in these patients should be left to the clinical judgement of the physician.

**VI. ADMINISTRATION, DOSING AND SCHEDULING**

Information on the administration, dosing and scheduling of irinotecan, 5-fluorouracil and leucovorin is presented in Appendix 2.

**VII. ONGOING TRIALS**

Protocol ID	Description	Status
<p><b>NCCTG-N9741, CAN-NCIC- CO13, CLB- 89804, E-N9741, SWOG-N9741</b></p>	<p><b>Phase III Randomized Study of Combinations of Oxaliplatin, Fluorouracil, Leucovorin Calcium, and Irinotecan as Initial Therapy in Patients With Advanced Adenocarcinoma of the Colon and Rectum (Summary Last Modified September 1, 2002)</b></p> <ul style="list-style-type: none"> <li>• a randomized, multi-centre study</li> <li>• a total of 825 patients (275 per arm) have been accrued for this study thus far. Additional patients are being accrued on arm II (Arms I and III closed to accrual as of March 15, 2002.)</li> <li>• Intergroup trial sponsorship</li> </ul> <p><u>Preliminary reports published as:</u>            Goldberg R. Oxaliplatin in colorectal cancer: current studies. <i>Oncology</i> 2000;14(12 Suppl 11):42-7            Goldberg RM, Morton RF, Sargent D, et al. N9741: oxaliplatin (oxal) or CPT-11 + 5-fluorouracil (5FU)/leucovorin (LV) or oxal + CPT-11 in advanced colorectal cancer (CRC). Initial toxicity and response data from a GI Intergroup study. [Abstract] <i>Proc Am Soc Clin Oncol</i> 2002;21:A-511            Morton RF, Goldberg RM, Sargent DJ, et al. Oxaliplatin (OXAL) or CPT-11 combined with 5FU/leucovorin (LV) in advanced colorectal cancer (CRC): an NCCTG/CALGB study. [Abstract] <i>Proc Am Soc Clin Oncol</i> 2001;20:A-495</p>	<ul style="list-style-type: none"> <li>• closed</li> </ul>

Protocol ID	Description	Status
EORTC-40986	<p><b>Phase III Randomized Study of High-Dose Fluorouracil and Leucovorin Calcium With or Without Irinotecan in Patients With Metastatic Adenocarcinoma of the Colon or Rectum (Summary Last Modified 02/2002)</b></p> <ul style="list-style-type: none"> <li>• a randomized, multi-centre study</li> <li>• A total of 430 patients (215 per arm) will be accrued for this study within 2 years.</li> <li>• EORTC Gastrointestinal Tract Cancer Group sponsorship</li> </ul> <p><u>Preliminary report published as:</u> Köhne C, van Cutsem E, Wils J, et al. Weekly high dose infusional 5-FU plus folinic acid (FA) with or without irinotecan (IRI) in metastatic colorectal cancer (MCR): interim safety results of EORTC study 40986. [Abstract] <i>Proc Am Soc Clin Oncol</i> 2002;21:A-532 (3u)</p>	<ul style="list-style-type: none"> <li>• closed</li> </ul>
FRE-FNCLCC-ACCORD-2, EU-20014, FFCD-9802	<p><b>Phase III Randomized Study of Adjuvant Leucovorin, Calcium, and Fluorouracil With or Without Irinotecan in Patients With Resected Stage III Colon Cancer at High Risk of Recurrence (Summary Last Modified July 1, 2002)</b></p> <ul style="list-style-type: none"> <li>• a randomized, multi-centre study</li> <li>• a total of 400 patients (200 per arm) will be accrued for this study within 3 years</li> <li>• Fédération Nationale des Centres de Lutte Contre le Cancer, Fédération Francophone de Cancerologie Digestive sponsorship</li> </ul>	<ul style="list-style-type: none"> <li>• active</li> </ul>
MRC-CR08-FOCUS, EU-20038	<p><b>Phase III Randomized Study of Fluorouracil With Leucovorin Calcium and Either Irinotecan or Oxaliplatin in Patients With Unresectable Metastatic Colorectal Cancer (Summary Last Modified 01, 2002)</b></p> <ul style="list-style-type: none"> <li>• a randomized, open-label, multi-centre study</li> <li>• a total of 2,100 patients (700 in arm I and 350 each in arms II-V) will be accrued for this study</li> </ul> <p><u>Preliminary reports published as:</u> Seymour M. An update on the MRC FOCUS/CR08 trial: the first 300 patients. <i>Br J Cancer</i> 2001;85(Suppl 1):A-P45,44</p>	<ul style="list-style-type: none"> <li>• active</li> </ul>

Protocol ID	Description	Status
NCCTG-N9841, E-N9841, SWOG-N9841	<p><b>Phase III Randomized Study of Irinotecan Versus Oxaliplatin, Fluorouracil, and Leucovorin Calcium in Patients With Advanced Colorectal Cancer Previously Treated With Fluorouracil</b></p> <ul style="list-style-type: none"> <li>• a randomized, multi-centre study</li> <li>• a total of 560 patients will be accrued for this study within 2 years</li> <li>• a randomized, multi-centre study</li> <li>• an Intergroup study</li> </ul> <p><u>Preliminary reports published as:</u> Goldberg R. Oxaliplatin in colorectal cancer: current studies. <i>Oncology</i> 2000;14(12 Suppl 11):42-7</p>	<ul style="list-style-type: none"> <li>• active</li> </ul>
SANOFI-EFC4585	<p><b>Phase III Randomized Study of Irinotecan With or Without Oxaliplatin in Patients With Metastatic Colorectal Cancer (Summary May 1, 2001)</b></p> <ul style="list-style-type: none"> <li>• a randomized, open label, multi-centre study</li> <li>• a total of 596 patients (298 per arm) will be accrued for this study within 18 months</li> <li>• pharmaceutical sponsorship</li> </ul>	<ul style="list-style-type: none"> <li>• active</li> </ul>

### VIII. DISEASE SITE GROUP CONSENSUS PROCESS

The Gastrointestinal Cancer Disease Site Group (DSG) discussed three options for the recommendation: (i) irinotecan/5FU/LV as the standard first-line treatment; (ii) irinotecan/5FU/LV as an option for first-line treatment; or (iii) there is insufficient data at the present time to make a recommendation. The DSG members agreed that irinotecan/5FU/LV should be available as an option for first-line treatment in patients with good performance status and adequate social and medical support to monitor adverse effects. There was general agreement with the recommendation as written.

One issue that was raised was the question of the appropriateness of the control arms in each of the randomized trials. The deGramont regimen has been compared with the Mayo regimen in a published randomized controlled trial (4). This study demonstrated that the regimens appeared to be equivalent in terms of survival, but the deGramont regimen may be associated with both less toxicity and a superior response rate. As the Mayo regimen is the FDA standard at present, it is an appropriate standard for the North American trial. The performance of the deGramont regimen also appears to justify its use as a standard control, which it is throughout much of Europe. Some DSG members continue to disagree with its use as a standard therapy.

The DSG noted that the subgroup analysis as published in the FDA review must be interpreted with caution and must be considered secondary to the analysis of the major endpoints in the entire population studied. This data did influence the final recommendation, however, in that an earlier draft of the recommendations had suggested a particular benefit might be expected for symptomatic or decompensating patients, a conclusion based on the theoretical benefit for these subgroups due to the higher response rates with combination therapy. However, the subgroup data presented in the FDA review suggested the opposite, resulting in a modification of the practice guideline.

## **IX. EXTERNAL REVIEW OF THE PRACTICE GUIDELINE REPORT**

This section describes the external review activities undertaken for the original guideline report.

### **Draft Recommendations**

Based on the evidence described in the original report above, the Gastrointestinal Cancer DSG drafted the following recommendations. At the time when the draft recommendations were developed, the two randomized phase III trials were published only in abstract form and the FDA review of these trials was not available.

### **Target Population**

These draft recommendations apply to adult patients with metastatic colorectal cancer for whom chemotherapy is being considered as a first-line treatment.

### **Draft Recommendations**

- Irinotecan/5FU/LV is at least as effective as 5FU/LV, which is the standard first-line therapy in patients with metastatic colorectal cancer. Three randomized trials (reported in abstract form) demonstrated improved response rates for the combination that contained irinotecan. Preliminary analysis detected a survival advantage for irinotecan/5FU/LV in one trial but not the other, and a pooled analysis of both trials did not show a survival benefit in favour of irinotecan/5FU/LV.
- It is reasonable for the oncologist to offer the patient a choice between irinotecan/5FU/LV and 5FU/LV after discussion of the difference in adverse effects (more hair loss and diarrhea with irinotecan versus more neutropenia, febrile neutropenia, and mucositis without irinotecan) between the two types of treatments. Excess thrombotic events are also seen with irinotecan.
- Irinotecan may be especially beneficial for patients for whom a tumour response in the short term will have important clinical benefit, such as the decompensating patient for whom the clinical course can potentially be reversed in the opinion of the oncologist.
- Caution should be exercised in recommending irinotecan to patients with a performance status > 2 (ECOG scale), and these patients should be warned of the risks of this treatment.

### **Related Guideline**

Practice Guidelines Initiative's Practice Guideline Report #2-16: *Use of Irinotecan in the Treatment of Metastatic Colorectal Carcinoma.*

### **Practitioner Feedback**

Based on the evidence contained in the original report and the draft recommendations presented above, feedback was sought from Ontario clinicians. Feedback was received on an earlier draft based on initial data from these trials, and not this final recommendation.

### **Methods**

Practitioner feedback was obtained through a mailed survey of 40 practitioners in Ontario (28 medical oncologists, three radiation oncologists, eight surgeons, and one gastroenterologist). The survey consisted of eight items evaluating the methods, results, and interpretive summary used to inform the draft recommendations outlined and whether the draft recommendations above 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 have been reviewed by the Gastrointestinal Cancer DSG.

## Results

Key results of the practitioner feedback survey are summarized in Table 3. A total of 20 (50%) surveys were returned. Of this sample, 15 (75%) respondents indicated that the practice-guideline-in-progress report was relevant to their clinical practice and they completed the survey. Of the 15 clinicians who completed the survey, 53% agreed that the document should be approved as a practice guideline and 80% agreed that they would use it in their own clinical practice.

**Table 3. Practitioner responses to eight items on the practitioner feedback survey.**

Item	Number (%)*		
	Strongly agree or agree	Neither agree nor disagree	Strongly disagree or disagree
The rationale for developing a clinical practice guideline, as stated in the “ <i>Choice of Topic</i> ” section of the report, is clear.	14 (93.3%)	1 (6.7%)	0
There is a need for a clinical practice guideline on this topic.	12 (80%)	3 (20%)	0
The literature search is relevant and complete.	14 (93.3%)	1 (6.7%)	0
The results of the trials described in the report are interpreted according to my understanding of the data.	15 (100%)	0	0
The draft recommendations in this report are clear.	14 (93.3%)	1 (6.7%)	0
I agree with the draft recommendations as stated.	14 (93.3%)	1 (6.7%)	0
This report should be approved as a practice guideline.	8 (53.3%)	6 (40%)	0
If this report were to become a practice guideline, how likely would you be to make use of it in your own practice?	<b>Very likely or likely</b>	<b>Unsure</b>	<b>Not at all likely or unlikely</b>
	12 (80%)	2 (13.3%)	1 (6.7%)

\* Percentages may not add up to 100% due to missing data.

## Summary of Written Comments

Three (20%) respondents provided written comments. One respondent thought it was inappropriate to pool the survival data in a meta-analysis because two different regimens of irinotecan/5FU/LV were used. This respondent also disagreed with the pooling of the toxicity data from the 5FU/LV arms of the randomized trials since the toxicity of 5FU/LV is dependent on the regimen. The two other respondents also commented on toxicity issues. Given the toxicity of irinotecan, one respondent indicated a preference, if time permits, for the sequential use of irinotecan and 5FU/LV, while combined irinotecan/5FU/LV be used in patients with rapidly progressing disease for whom it is urgent to achieve tumour reduction. The other respondent suggested the addition of a cautionary note regarding the administration of irinotecan to patients with significant peritoneal carcinomatosis resulting in gastrointestinal stasis in conjunction with significant ascites.

## Modifications/Actions

Updated data from two phase III trials, an individual patient data meta-analysis of these phase III trials and the availability of a detailed FDA review led to minor revisions of the guideline after practitioner feedback. Because of further evidence supporting a survival benefit with combination therapy, a more inclusive recommendation was developed. This same recommendation was more clearly qualified with a reminder of toxicity concerns with the use of this palliative regimen, particularly in patients with poorer performance status (ECOG >1).

Subsequent to these changes, cautions were issued by the data and safety monitoring boards of 2 large on-going trials using bolus irinotecan/5FU/LV as a treatment arm (12). Analysis of the current data from each study revealed an excess number of deaths occurring within 60 days after the initiation of treatment. Deaths were primarily related to dehydration (resulting from

diarrhea, nausea and vomiting), neutropenic sepsis (alone or in combination with shock), and thrombotic events (myocardial infarction, cerebrovascular accident, bowel ischemia, and pulmonary emboli). An independent panel recommended close clinical monitoring, early recognition of toxicities and toxicity syndromes, aggressive therapeutic intervention, and withholding therapy in the presence of unresolved drug-related toxicities for patients receiving irinotecan/5FU/LV or other intensive chemotherapy regimens (13). It stopped short of recommending initial dose reductions with re-escalation in the presence of toxicity, though this was instituted for all new patients entering the ongoing trials and has been adopted by some outside of the trial setting for patients with metastatic colorectal cancer (e.g. Irinotecan 100mg/m<sup>2</sup>). It is unclear whether a dose reduced bolus irinotecan/5FU/LV regimen would also lose its survival advantage. No recommendation can be made with respect to this strategy. A statement regarding the increase in thrombotic events shown with irinotecan was also added to the key recommendations.

### **Approved Practice Guideline Recommendations**

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.

### **Recommendations**

#### ***Key Recommendations***

- It is reasonable to offer the patient a choice between irinotecan/5FU/LV and 5FU/LV. Survival and response improvements with irinotecan/5FU/LV must be balanced against the increased toxicity (more hair loss, diarrhea and hospitalization with irinotecan versus more mucositis without irinotecan). Excess thrombotic events are also seen with irinotecan.
- For patients offered irinotecan therapy, careful monitoring of adverse effects and early intervention for diarrhea should be part of the treatment process.

#### ***Qualifying Statement***

- Caution should be exercised in recommending irinotecan to patients with a performance status >1 (ECOG scale). All patients who may be eligible for this treatment should be warned of the adverse effects of irinotecan/5FU/LV.

## **X. PRACTICE GUIDELINE**

This practice guideline reflects the most current information reviewed by the Gastrointestinal Cancer DSG.

### **Target Population**

These recommendations apply to adult patients with metastatic colorectal cancer for whom chemotherapy is being considered as a first-line treatment.

### **Recommendations**

#### ***Key Recommendations***

- It is reasonable to offer the patient a choice between irinotecan/5FU/LV and 5FU/LV. Survival and response improvements with irinotecan/5FU/LV must be balanced against the increased toxicity (more hair loss, diarrhea and hospitalization with irinotecan versus more mucositis without irinotecan). Excess thrombotic events are also seen with irinotecan.
- For patients offered irinotecan therapy, careful monitoring of adverse effects and early intervention for diarrhea should be part of the treatment process.

### **Qualifying Statement**

- Caution should be exercised in recommending irinotecan to patients with a performance status >1 (ECOG scale). All patients who may be eligible for this treatment should be warned of the adverse effects of irinotecan/5FU/LV.

### **Related Guideline**

Practice Guidelines Initiative's Practice Guideline Report #2-16: *Use of Irinotecan in the Treatment of Metastatic Colorectal Carcinoma.*

Practice Guidelines Initiative's Practice Guideline Report #2-17: *Use of Raltitrexed (Tomudex) in the Management of Metastatic Colorectal Cancer.*

### **XI. JOURNAL REFERENCE**

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### **XII. ACKNOWLEDGMENTS**

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The Gastrointestinal Cancer Disease Site Group would like to thank Dr. D. Jonker and Mr. R.B. Rumble for taking the lead in updating this practice guideline report.

For a complete list of Gastrointestinal Cancer Disease Site Group members, please visit our web site at <http://www.cancercare.on.ca/ccopgi>.

For a listing of the Practice Guidelines Coordinating Committee Members, please visit our web site at <http://www.cancercare.on.ca/ccopgi>.

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## Update

This section includes all references obtained from the review and updating activities.

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- 2u. Comella P, Massidda B, Farris A, Palmeri S, Filippelli G, Russo A, et al. Oxaliplatin plus leucovorin/fluorouracil I.V. bolus (OXAFUFU) versus irinotecan plus leucovorin/fluorouracil I.V. bolus (IRIFUFU) as first-line treatment of advanced colorectal carcinoma (ACC): SICOG 0103 randomised study [abstract]. *Proc Annu Meet Am Soc Clin Oncol* 2002;21:Abstract 645.
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**Table 4. Efficacy data from randomized controlled trials of irinotecan in metastatic colorectal cancer.**

Author Trial # (ref)	Median Follow-up (months)	Number of Patients	Treatment Groups	Median Survival (months)	One-year Survival (%)	Median Progression-Free Survival (months)
Comella et al. (1u)	23	118	Irinotecan 200mg/m <sup>2</sup> (90 min i.v. inf.) d1 + 5FU 850 mg/m <sup>2</sup> (bolus i.v. inf.) d2 + LV 250 mg/m <sup>2</sup> (2hr i.v. inf.) d2, q2week.	14.7	NR	7.2
		116	Methotrexate 750 mg/m <sup>2</sup> (2hr i.v. inf.) d1 + 5FU 800 mg/m <sup>2</sup> (i.v. bolus) d2 + LV 250 mg/m <sup>2</sup> (2hr i.v. inf.).	14.8	NR	4.8
Comella et al. (2u)	NR	Final accrual of 53 pts per arm not yet completed	Irinotecan 200mg/m <sup>2</sup> d1 + 5FU 850mg/m <sup>2</sup> i.v. bolus inf. d2 + LV 250 mg/m <sup>2</sup> d2, q2weeks.	NR	NR	NR
			Oxaliplatin 100mg/m <sup>2</sup> d1 + 5FU 1050mg/m <sup>2</sup> i.v. bolus inf. d2 + LV 250 mg/m <sup>2</sup> d2, q2weeks.	NR	NR	NR
Köhne et al. (3u)	NR	179	Irinotecan 80 mg/m <sup>2</sup> + 5FU 2300* mg/m <sup>2</sup> (24hr inf.) + LV 500 mg/m <sup>2</sup> weekly, q6week, q50d. (AIO 2.3 + IRI)	NR	NR	NR
		188	5FU 2600 mg/m <sup>2</sup> (24hr inf.) + LV 500 mg/m <sup>2</sup> , weekly, q6week, q50d. (AIO)	NR	NR	NR
			* after three toxic deaths, AIO 2.3 was reduced to AIO 2.0			
Pozzo et al. (4u)	NR	76	Irinotecan 350 mg/m <sup>2</sup> d1 + 5FU 425 mg/m <sup>2</sup> (bolus i.v.) + LV 20mg/m <sup>2</sup> d21-25, q6weeks (IRI + MAYO)	17.1	NR	8.5
		80	5FU 425 mg/m <sup>2</sup> (bolus i.v.) + LV 20mg/m <sup>2</sup> d21-25, q4weeks (MAYO)	14.5 (p=0.99)	NR	8.4 (p=0.897)

Note: i.v., intravenous; inf., infusion; d, day; 5FU, 5-fluorouracil; LV, leucovorin calcium; q, every; AIO, Arbeitsgemeinschaft Internistische Onkologie.

**Table 5. Most common grade 3/4 toxicity experienced by patients participating in randomized controlled trials of irinotecan in metastatic colorectal cancer.**

Author Trial # (ref)	Treatment regimens of Irinotecan	Number of patients	Neutropenia (%)	Vomiting (%)	Diarrhea (%)
Comella et al. (1u)	Irinotecan/5FU/LV	118	40	NR	13
	Methotrexate/5FU/LV	116	9 (p=0.001)	NR	4 (p=0.024)
Comella et al. (2u)	Irinotecan/5FU/LV	Final accrual of 53 pts per arm not yet completed	46	NR	27
	Oxaliplatin/5FU/LV		63	NR	19
Köhne et al. (3u)	Irinotecan/5FU/LV	179	NR	NR	51.6
	5FU/LV	188	NR	NR	32.7
Pozzo et al. (4u)	Irinotecan/5FU/LV	76	14	NR	4 (cycles)
	5FU/LV	80	18	NR	1.2 (cycles)

Note: 5FU, 5-fluorouracil; LV, leucovorin calcium.

## **Appendix 1. Practice Guideline Report 2-16: Use of irinotecan in the treatment of metastatic colorectal carcinoma.**

### **Guideline Question**

What is the role of irinotecan (Camptosar®, CPT-11) in the management of metastatic colorectal carcinoma?

### **Outcomes**

Outcomes of interest were survival, time to disease progression, response rate, response duration, adverse effects, symptom improvement, and quality of life.

### **Perspective (Values)**

Evidence was collected and reviewed by one member of the Cancer Care Ontario Practice Guidelines Initiative □ Provincial Gastrointestinal Cancer Disease Site Group (GI DSG). The GI DSG is comprised of medical and radiation oncologists, surgeons, and epidemiologists. Community representatives did not participate in the development of this report but will in future reports.

### **Quality of Evidence**

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

### **Benefits**

One RCT, involving 279 patients with a World Health Organization (WHO) performance status of 0 to 2, compared irinotecan given once every three weeks with BSC. Results demonstrated statistically significant improvement in one-year survival (36% versus 14%,  $p=0.0001$ ) and all domains of quality of life measures (except diarrhea) favouring irinotecan. Another RCT, with participation by 256 patients with a WHO performance status of 0 to 2, compared irinotecan with 5-FU infusional chemotherapy. Results demonstrated statistically significant improvement in one-year survival (45% versus 32%,  $p=0.035$ ) and time to disease progression (4.2 versus 2.9 months,  $p=0.030$ ) favouring irinotecan. Quality of life scores were not different from those of patients treated with 5-FU infusional chemotherapy. Among 617 patients assessed in phase II trials, 26% had complete or partial tumour response to irinotecan. The pooled median time to disease progression for 497 patients with prior 5-FU failure was four months and the pooled median survival time was ten months.

### **Harms**

During treatment with irinotecan, most patients experienced adverse effects, consisting of an early cholinergic syndrome, delayed diarrhea, nausea and vomiting, neutropenia, asthenia, and/or alopecia. The RCTs used a three-week schedule of irinotecan and detected grade 3/4 severe toxicity as follows: neutropenia in 19%, vomiting in 14%, and diarrhea in 22% of patients. Pooled results from phase II studies revealed that grade 3/4 severe toxicity included diarrhea in 33%, vomiting in 17%, and neutropenia in 38% of patients. A monograph reporting pooled data from three American phase II studies found cholinergic syndrome in 17% and asthenia in 12% of patients. Febrile neutropenia occurred in approximately 3% of patients and together with severe diarrhea accounted for a <2% treatment-related fatality rate. About 5% of patients discontinued treatment due to toxicity. More recent studies have documented lower grades of cholinergic syndrome which can be well controlled with the early use of intravenous atropine. Delayed diarrhea can be adequately controlled with the use of an intense schedule of oral loperamide. Nausea and vomiting are improved by prophylactic dexamethasone and ondansetron.

### **Practice Guideline**

This practice guideline applies to patients with metastatic colorectal cancer for whom treatment with 5-fluorouracil has failed:

- Irinotecan can induce objective tumour responses in approximately 15% of patients with metastatic colorectal cancer after failure of 5-fluorouracil plus leucovorin (5-FU+LV) chemotherapy. Two randomized trials used a three-week schedule of irinotecan in patients for whom treatment with 5-FU failed. Results demonstrated a significant increase in one-year survival for patients treated with irinotecan compared with patients treated with best supportive care (BSC) (36% versus 14%) or patients who were retreated with 5-FU infusion regimens (45% versus 32%). The quality of life of patients on irinotecan was better than that of patients on BSC but not different from that of patients on 5-FU chemotherapy.
- Irinotecan is associated with serious side effects which require significant supervision and immediate treatment for severe drug-induced diarrhea and neutropenia, which occur in 22% and 19% of patients, respectively (see Appendix 2 of the full report for recommendations on the prevention and management of adverse effects of irinotecan).
- After full consideration of expected benefits and harms, it is appropriate to offer treatment with irinotecan to selected patients in whom 5-FU-based chemotherapy has failed. The patients in whom 5-FU-based chemotherapy failed were those that progressed during palliative chemotherapy or within six months of completing adjuvant therapy. Patients should also have good performance status (2 or better) and should be able to have close medical supervision of treatment.
- There is insufficient evidence to make a recommendation for the use of irinotecan for first-line treatment of metastatic colorectal cancer.

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## **Appendix 2. Administration, dosing, and scheduling of irinotecan, 5-fluorouracil and leucovorin.**

Irinotecan is supplied in 40 mg and 100 mg vials. For administration, the dose is diluted in 250 ml 0.9% saline solution and infused intravenously over 30 to 90 minutes.

5-fluorouracil is supplied as a 50 mg/ml solution in 500 mg, 2.5 g and 5 g vials. For bolus administration, the dose is given undiluted as a rapid intravenous push over roughly 5 minutes. For 5-fluorouracil infusions, the dose is diluted to 50 ml in D5W solution and administered intravenously over 1 to 7 days through a pump such as a Travenol Infuser® (an elastomeric pump).

Calcium leucovorin is supplied as a 10 mg/ml solution in 50 ml vials. For bolus administration, the dose is given undiluted as a rapid intravenous push over roughly 5 minutes. For high dose leucovorin, the dose may be diluted in 250 ml of 0.9% saline solution and administered intravenously through a pump such as an Intermate Infuser® over 2 hours.

The three most common schedules of administration are as follows:

1. Weekly x4 schedule: Irinotecan 125 mg/m<sup>2</sup>, calcium leucovorin 20 mg/m<sup>2</sup> and 5-fluorouracil 500 mg/m<sup>2</sup> weekly for 4 weeks followed by a 2-week rest period. The cycle is repeated every 6 weeks. This schedule was used in the North American randomized phase III trial (6).
2. Two-weekly schedule: Irinotecan 180 mg/m<sup>2</sup> day 1 with leucovorin 200 mg/m<sup>2</sup> and 5-fluorouracil 400 mg/m<sup>2</sup> intravenous push followed by 5-fluorouracil 600 mg/m<sup>2</sup> as a 22 hour continuous intravenous infusion both on days 1 and 2 every two weeks. This is the schedule used by the French investigators in the European randomized phase III trial (5).
3. Weekly x6 schedule: Irinotecan 80mg/m<sup>2</sup>, leucovorin 500 mg/m<sup>2</sup>, and then 5-fluorouracil 2300mg/m<sup>2</sup> as a 24 hour continuous intravenous infusion weekly for 6 weeks. The cycle is repeated every 7 weeks. This schedule was used by the German investigators in the European randomized phase III trial (5).