Complete Summary

GUIDELINE TITLE

Use of irinotecan (Camptosar®, CPT-11) combined with 5-fluorouracil and leucovorin (5FU/LV) as first-line therapy for metastatic colorectal cancer.

BIBLIOGRAPHIC SOURCE(S)

Gastrointestinal Cancer Disease Site Group. Use of irinotecan (camptosar, CPT-11) combined with 5-fluorouracil and leucovorin (5FU/LV) as first-line therapy for metastatic colorectal cancer [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2003 Feb [online update]. 20 p. (Practice guideline; no. 2-16b). [17 references]

GUIDELINE STATUS

This is the current release of the guideline.

The FULL REPORT, initially the full original Guideline or Evidence Summary, over time will expand 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.

COMPLETE SUMMARY CONTENT

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SCOPE

DISEASE/CONDITION(S)

Metastatic colorectal cancer

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To make evidence-based recommendations about the use of irinotecan combined with 5-fluoruoracil and leucovorin as first-line systemic therapy for the management of metastatic colorectal cancer

TARGET POPULATION

Adult patients with metastatic colorectal cancer for whom chemotherapy is being considered as a first-line treatment

INTERVENTIONS AND PRACTICES CONSIDERED

1. Irinotecan (CPT-11, Camptosar®) combined with 5-fluorouracil and leucovorin
2. 5-fluorouracil and leucovorin alone

MAJOR OUTCOMES CONSIDERED

- Survival
- Response rates (both objective and confirmed)
- Time to tumor progression
- Quality of life
- Toxicity (adverse effects of treatment)

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

October 2001 Guideline

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 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) Web site was reviewed for additional presented material regarding the application for approval of irinotecan as first-line therapy in the United States.

February 2003 Update

Entries to MEDLINE (December 2000 through January [week 2] 2003), CANCERLIT (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.

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.

NUMBER OF SOURCE DOCUMENTS

October 2001 Guideline

- Two phase III randomized trials
- A combined analysis (in abstract form) of two phase III trials using individual patient data
- A U.S. Food and Drug Administration (FDA) review of both phase III trials
- Two phase II randomized trials (both abstracts)

February 2003 Update

Four additional phase III trials were obtained and reviewed.

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

Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE 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. 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 were quite different with respect to toxicity.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The Gastrointestinal Cancer Disease Site Group (DSG) discussed three options for the recommendation: (i) irinotecan/5-fluorouracil (5FU)/leucovorin (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. 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 U.S. 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.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

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 21 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 Disease Site Group.

The practice guideline recommendations reflect the integration of the draft recommendations with feedback obtained from the external review process.

Final approval of the original guideline report was obtained from the Practice Guidelines Coordinating Committee (PGCC).

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

- It is reasonable to offer the patient a choice between irinotecan/5-fluorouracil/leucovorin (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.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

October 2001 Guideline

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, a combined analysis (in abstract form) of these two phase III trials using individual patient data, a U.S. Food and Drug Administration review of both phase III trials (available on the internet), and two phase II randomized trials (both abstracts) were reviewed.

February 2003 Update

Four phase III trials comparing irinotecan containing regimens with other treatments were obtained. The first study compared irinotecan/5FU/LV versus methotrexate/5FU/LV. The second compared irinotecan/5FU/LV versus Oxaliplatin/5FU/LV. The third and fourth studies compared irinotecan/5FU/LV to two different 5FU/LV regimens (AIO and MAYO).

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Irinotecan/5-fluorouracil/leucovorin (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; $p<0.009$).

POTENTIAL HARMS

Irinotecan/5-fluorouracil and leucovorin 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.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- Caution should be exercised in recommending irinotecan to patients with a performance status Eastern Cooperative Oncology Group >1. All patients who may be eligible for this treatment should be warned of the adverse effects of irinotecan/5-fluorouracil and leucovorin.
- 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)

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ADAPTATION

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

DATE RELEASED

2001 Oct 23 (updated online 2003 Feb)

GUIDELINE DEVELOPER(S)

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

GUIDELINE DEVELOPER COMMENT

The Practice Guidelines Initiative (PGI) is the main project of the Program in Evidence-based Care (PEBC), a Province of Ontario initiative sponsored 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 members, please see the Cancer Care Ontario Web site.

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

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

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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 (Camptosar®, CPT-11) combined with 5-fluorouracil and leucovorin (5FU/LV) as first-line therapy for metastatic colorectal cancer. Summary. Toronto (ON): Cancer Care Ontario (CCO), 2001 Oct 23 (revised 2003 Feb). Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.
- 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.

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on July 19, 2002. The information was verified by the guideline developer on August 19, 2002. This summary was updated on August 6, 2003. The updated information was verified by the guideline developer on September 2, 2003.

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Date Modified: 9/22/2008