Complete Summary

GUIDELINE TITLE

Oral capecitabine (Xeloda™) in the first-line treatment of metastatic colorectal cancer.

BIBLIOGRAPHIC SOURCE(S)

Gastrointestinal Cancer Disease Site Group. Kocha W, Maroun J, Jonker D, Rumble RB, Zuraw L. Oral capecitabine (Xeloda) in the first-line treatment of metastatic colorectal cancer [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2003 Dec 5. 19 p. (Practice guideline report; no. 2-15). [26 references]

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SCOPE

DISEASE/CONDITION(S)

Metastatic colorectal cancer

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Gastroenterology
Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To evaluate the use of oral capecitabine (Xeloda™) in the first-line treatment of patients with metastatic colorectal cancer where monotherapy with fluoropyrimidines or other thymidylate synthase inhibitors is favoured

TARGET POPULATION

Adult patients with metastatic colorectal cancer who have not received prior chemotherapy for metastatic disease in whom monotherapy with fluoropyrimidines or other thymidylate synthase inhibitors is favoured. For patients who are at a high risk following curative resection and who received adjuvant chemotherapy, adjuvant treatment should have been completed at least six months prior to being diagnosed with metastatic disease.

INTERVENTIONS AND PRACTICES CONSIDERED

Single agent capecitabine (Xeloda™) as first-line therapy as compared to 5-fluorouracil (5-FU) plus leucovorin

MAJOR OUTCOMES CONSIDERED

- Survival (primary)
- Time to progression (secondary)
- Tumour response (secondary)

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Searches of Unpublished Data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

MEDLINE (1990 to June [week 3] 2003), CANCERLIT (1990 to October 2002), and the Cochrane Library (2003, Issue 2) databases were searched. "Colorectal neoplasms" (Medical subject heading [MeSH]) was combined with the text words "capecitabine" and "xeloda". Search terms for study designs were not used because of the relatively small number of papers on capecitabine in colorectal cancer. In addition, the Physician Data Query (PDQ) clinical trials database on the Internet http://www.cancer.gov/search/clinical_trials/ and abstracts published in the proceedings of the 1998 to 2003 annual meetings of the American Society of Clinical Oncology were searched for reports of new or ongoing trials. Relevant articles and abstracts were selected and reviewed by one reviewer, and the reference lists from these sources were searched for additional trials. Hoffman-La Roche Limited provided information on this drug from their investigator´s brochure.

Inclusion Criteria

Articles were selected for inclusion in this systematic review of the evidence if they were fully published reports or published abstracts of randomized trials of capecitabine in patients with previously untreated metastatic colorectal cancer.

Exclusion Criteria

1. Phase I and non-randomized phase II studies were not considered for inclusion in this report because of the availability of randomized controlled trials.
2. Letters and editorials were not considered.
3. Papers published in a language other than English were not considered.

NUMBER OF SOURCE DOCUMENTS

A randomized phase II study, two fully-published randomized phase III trials, a meta-analysis combining the two phase III trials, and a related meta-analysis in abstract form were reviewed. In addition, an abstract report of interim safety data and a phase III study examining capecitabine in the adjuvant setting were 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

The results of phase III trials of capecitabine as first-line therapy for metastatic colorectal cancer were not pooled because of the availability of an up-to-date, published meta-analysis of two randomized phase III trials of capecitabine as first-line treatment for metastatic colorectal cancer. This meta-analysis, based on summary data, has been published in full.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The data from the two phase III trials revealed no statistically significant difference between capecitabine and 5-fluorouracil (FU) plus leucovorin as first-line therapy for metastatic colorectal cancer. Although irinotecan has now moved into first-line therapy (given in combination with 5-FU plus leucovorin), a subgroup of patients will select or be selected for thymidylate synthase-inhibitor monotherapy because of age, frailty, coexistent morbid conditions, or preference. Capecitabine would certainly be one of the alternatives to consider, and may be preferable to many patients because it is taken orally. Its pharmacokinetics and toxicity pattern are concordant with 5-FU administered as a continuous infusion. There is evidence that 5-FU continuous infusions have some activity where there is resistance to 5-FU bolus therapy. Capecitabine may therefore have similar activity.

There was speculation that capecitabine might replace or represent an alternative to 5-FU therapy given as a continuous infusion in combination with other chemotherapy or with radiation therapy. The Gastrointestinal Cancer Disease Site Group (DSG) will integrate the results of trials exploring the effects of capecitabine in combination with other drugs, such as irinotecan and oxaliplatin, when available.

Opinions in the Disease Site Group differed as to the effect of the dominant toxicity of palmar-plantar erythrodysesthesia (hand-foot syndrome). Some felt the syndrome was a major drawback to the use of the drug while others believed it to be a minor discomfort that is easy to manage and not life threatening.

As patients with colorectal cancer frequently have liver involvement with consequent effects on liver function, it was felt that more data should be included on the use of capecitabine in this group of patients, but little evidence exists on the subject. A section on the management of hyperbilirubinemia was added.

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 103 practitioners in Ontario (29 medical oncologists, 3 gastroenterologists, and 71 surgeons). The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations 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 Gastrointestinal Cancer Disease Site Group (DSG) reviewed the results of the survey.

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

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

- In appropriate patients, standard combination chemotherapy consists of infusional 5-fluorouracil plus leucovorin calcium with either irinotecan or oxaliplatin (refer to the National Guideline Clearinghouse summary of the Program in Evidence-based Care´s Practice Guideline #2-16b: Use of Irinotecan (Camptosar®, CPT-11) Combined with 5-fluorouracil and Leucovorin (5FU/LV) as First-line Therapy for Metastatic Colorectal Cancer, and Practice Guideline #2-22: Oxaliplatin Combined with 5-fluorouracil and Folinic Acid in Advanced Colorectal Cancer [in progress]).
- If infusion therapy with 5-fluorouracil plus leucovorin calcium with either irinotecan or oxaliplatin is not reasonable, then treatment using oral capecitabine is appropriate.
- The standard dose for capecitabine is 2,500 mg/m^2/day in two divided doses for 14 days every three weeks. See Appendix 1 in the original guideline document for dosing and dose adjustment information.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by randomized controlled trials and meta-analyses.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Two randomized phase III trials demonstrate that single-agent capecitabine administered orally yields higher response rates than 5-fluorouracil plus leucovorin. Pooled response rates were 26% with capecitabine versus 17% with 5-fluorouracil plus leucovorin ($p<0.0002$) in a meta-analysis of both trials that has been published in abstract form. Similar median time to progression and median duration of survival was observed with capecitabine and 5-fluorouracil plus leucovorin.
- In the subgroup of patients who relapsed more than six months after completing adjuvant therapy with 5-fluorouracil and leucovorin, capecitabine

was associated with higher response rates compared with retreatment with 5-fluorouracil plus leucovorin. Pooled response rates were 21% with capecitabine versus 9% with 5-fluorouracil plus leucovorin in this subgroup of patients (p-value not reported).

POTENTIAL HARMS

Capecitabine appears to have a lower incidence of stomatitis, alopecia, and neutropenia compared with 5-fluorouracil and leucovorin. There is, however, a considerably higher incidence of hand-foot syndrome with capecitabine.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- Monotherapy with fluoropyrimidines (e.g., 5-fluorouracil [FU], capecitabine) or other thymidylate synthase inhibitors (e.g. raltitrexed, pemetrexed) may be favoured in patients with prior pelvic radiotherapy, elevated liver enzymes, age greater than 65 years, Eastern Cooperative Oncology Group (ECOG) performance status $\leq$1, and those with a lactate dehydrogenase (LDH) above the upper limit normal. This may also include patients who prefer to avoid intravenous therapy, where travel to a chemotherapy unit would be difficult, or who live in remote locations where an infusional pump program is not available, or in whom placement of a central line catheter is contraindicated. It is also an option for patients with concerns about the toxicity profile of combination chemotherapy (such as hair loss or risk of toxic death), or for whom there is insufficient data regarding the use of combination chemotherapy, or in those subgroups of patients for whom there is no clear survival benefit over single agent anti-thymidylate synthase therapy.
- Preliminary data from a subgroup analysis suggest that capecitabine may be the preferred treatment for patients who had received prior adjuvant therapy at least six months earlier with 5-FU plus leucovorin, while either capecitabine or 5-FU plus leucovorin therapy is reasonable for patients who have never received adjuvant therapy. Further trials are needed to confirm this observation.
- The decision to use capecitabine may be influenced by its toxicity. While capecitabine is associated with a lower incidence of stomatitis, alopecia, and neutropenia compared with 5-FU plus leucovorin, the incidence of hand-foot syndrome is considerably higher with capecitabine.
- Using capecitabine will require dose adjustments in patients with a creatinine clearance less than 60%. This is particularly important in thin elderly patients in whom reductions in creatinine clearance are not adequately reflected in the serum creatinine level alone.
- Where there is hyperbilirubinemia with bilirubin values exceeding 1.5 times normal, it has been recommended that capecitabine treatment be interrupted until the bilirubin drops below the 1.5 times normal value.
- 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. Kocha W, Maroun J, Jonker D, Rumble RB, Zuraw L. Oral capecitabine (Xeloda) in the first-line treatment of metastatic colorectal cancer [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2003 Dec 5. 19 p. (Practice guideline report; no. 2-15). [26 references]

ADAPTATION

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

DATE RELEASED

2003 Dec

GUIDELINE DEVELOPER(S)

Practice Guidelines Initiative - 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 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 conflicts of interest.

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.

GUIDELINE AVAILABILITY

Electronic copies: Available from the Cancer Care Ontario Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Oral capecitabine (Xeloda™) in the first-line treatment of metastatic colorectal cancer. Summary. Toronto (ON): Cancer Care Ontario, 2003 Dec. Electronic copies: Available 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 Feb;13(2):502-12.

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on May 14, 2004. The information was verified by the guideline developer on June 2, 2004.

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