Evidence-based Series 2-15 EDUCATION AND INFORMATION 2011

Oral Capecitabine (Xeloda™) in the First-line Treatment of Metastatic Colorectal Cancer

Members of the Gastrointestinal Cancer Disease Site Group

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

Evidence-based Series 2-15 was reviewed in 2010 and put in the Education and Information section by the Gastrointestinal Cancer Disease Site Group (DSG) on July 12, 2010. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment and Review Protocol).

Evidence-based Series (EBS) 2-15 EDUCATION AND INFORMATION 2011, the resulting review report, consists of the following 5 parts:

1. Guideline Report Overview
2. Section 1: Clinical Practice Guideline (February 11, 2005)
3. Section 2: Systematic Review (February 11, 2005)
4. Section 3: Guideline Development and External Review - Methods and Results (February 11, 2005)
5. Document Assessment and Review Tool

and is available on the CCO Web site (http://www.cancercare.on.ca)
PEBC Gastrointestinal Cancer Disease Site Group page at:
http://www.cancercare.on.ca/toolbox/qualityguidelines/diseasesite/gastro-ebs/.

Release Date: September 15, 2011

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Phone: 905-527-4322 ext. 42822   Fax: 905-526-6775   E-mail: ccopgi@mcmaster.ca

Oral Capecitabine (Xeloda™) in the First-line Treatment of Metastatic Colorectal Cancer

Guideline Report History

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Evidence-based Series #2-15 ARCHIVED 2011

Oral Capecitabine (Xeloda™) in the First-line Treatment of Metastatic Colorectal Cancer

Guideline Review Summary
Review Date: July 12, 2010

The 2005 guideline recommendations are
ARCHIVED
This means that the recommendations will no longer be maintained but may still be useful for academic or other information purposes.

OVERVIEW
Evidence-based Series History
This guidance document was originally released by the Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO), in 2003, and its first update was released in February 2005. In June 2010, the PEBC guideline update strategy was applied, and the recommendations were archived in July 2010. The Practice Guideline and the Systematic Review in this review are the same as in the February 2005 version.

Update Strategy
The PEBC update strategy includes an updated search of the literature, the review and interpretation of new eligible evidence by the clinical experts from the authoring panel and consideration of the guideline and its recommendations based on the new available evidence. See the Document Assessment and Review Tool at the end of this document.

DOCUMENT ASSESSMENT AND REVIEW RESULTS
Question Considered
Is there a role for the use of capecitabine (Xeloda™) in the first-line treatment of patients with metastatic colorectal cancer? Survival was the primary outcome of interest and time to progression and tumour response were secondary outcomes.
Literature Search and New Evidence
A search for new literature with respect to this question was not conducted since it was determined that the recommendations regarding this question will be replaced by a new guideline that is currently in production, “Strategies of Sequential Therapy in Advanced Colorectal Cancer”. Therefore, the guideline and its recommendations have been ARCHIVED.

Impact on Guidelines and Its Recommendations
The Gastrointestinal Cancer DSG ARCHIVED the 2005 recommendations. Therefore this guideline will no longer be maintained.
Evidence-based Series #2-15: Section 1

Oral Capecitabine (Xeloda™) in the First-line Treatment of Metastatic Colorectal Cancer: A Clinical Practice Guideline

W Kocha, J Maroun, D Jonker, RB Rumble, L Zuraw, and the Gastrointestinal Cancer Disease Site Group of Cancer Care Ontario’s Program in Evidence-based Care.

A Quality Initiative of the Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)
Developed by the Gastrointestinal Cancer Disease Site Group


Report Date: February 11, 2005

Question
Is there a role for 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? Survival was the primary outcome of interest, and time-to-progression and tumour response were secondary outcomes.

Target Population
These recommendations apply to 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.

Recommendations
- In appropriate patients, standard combination chemotherapy consists of infusional 5-fluouracil plus leucovorin calcium with either irinotecan or oxaliplatin (refer to 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 2500 mg/m²/day in two divided doses for 14 days every three weeks. See Appendix 1 for dosing and dose adjustment information.

Qualifying Statements
- Monotherapy with fluoropyrimidines (e.g. 5-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 ≤ 1, and those with an 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-fluorouracil plus leucovorin, while either capecitabine or 5-fluorouracil 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-fluorouracil 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.

Key Evidence
- 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 re-treatment 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).
• 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.

Treatment Alternatives
In addition to capecitabine, the following treatment alternatives for first-line therapy exist: 5-fluorouracil plus leucovorin, raltitrexed, irinotecan combined with 5-fluorouracil plus leucovorin, and oxaliplatin combined with 5-fluorouracil plus leucovorin. As always, the choice of treatment should be based on the various system factors, patient preferences, and convenience.

Future Research
A study of capecitabine as adjuvant therapy is ongoing (X-ACT trial). Other studies, utilizing capecitabine as a substitute for infusional 5-fluorouracil, are under development. Studies of capecitabine in combination with other agents, such as irinotecan and oxaliplatin, are under consideration. Some of those treatments may be more beneficial than monotherapy for certain patient subgroups, such as the elderly and the frail.

In another guideline (Practice Guideline #2-22: Oxaliplatin Combined with 5-Fluorouracil and Folinic Acid in Advanced Colorectal Cancer [in progress]), there is discussion of the recommended way to administer 5-fluorouracil in combination with irinotecan or oxaliplatin. The evidence now demonstrates that when 5-fluorouracil is to be used, it is best administered via a longer infusion rather than short daily intravenous boluses. That method of administration is both superior in terms of tumour response, and, more importantly, in reducing certain toxicities. Capecitabine is an oral agent converted to an active 5-fluorouracil metabolite. As a daily, low-dose, oral therapy, it mimics infusional 5-fluorouracil in many respects, including the higher tumour response rates and lower toxicity profile. There is now significant ongoing research activity to assess the role of capecitabine as a replacement for 5-fluorouracil in the combination regimens with oxaliplatin and irinotecan in both the advanced and adjuvant settings. Similarly, there is research ongoing to use capecitabine as a substitute for infusional 5-fluorouracil with concurrent radiotherapy for locally advanced or resected rectal adenocarcinoma.

One important area of interest for capecitabine is for frail and elderly patients who are generally not candidates for typical colorectal cancer trials. As that population is underrepresented in trials, it is not possible to adequately assess the risks and benefits of any regimen for those patients. Although capecitabine offers an alternative to intravenous chemotherapy and a generally favourable toxicity profile, it is still associated with important toxicities that impair quality of life and lead to dose adjustments in up to 40% of patients. Research is ongoing to determine the effect of beginning capecitabine at a lower dose, the dose to which many patients are eventually adjusted.

Related Guidelines
Practice Guidelines Initiative’s Practice Guideline Report:
• #2-16: Use of Irinotecan in the Treatment of Metastatic Colorectal Carcinoma.
• #2-16b: Use of Irinotecan (Camptosar®, CPT-11) Combined with 5-fluorouracil and Leucovorin (SFU/LV) as First-line Therapy for Metastatic Colorectal Cancer
• #2-17: Use of Raltitrexed (TomudexTM) in the Management of Metastatic Colorectal Cancer.
• #2-18: Management of Advanced Colorectal Cancer. [future topic]
• #2-22: Oxaliplatin Combined with 5-Fluorouracil and Folinic Acid in Advanced Colorectal Cancer. [in progress]
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Oral Capecitabine (Xeloda™) in the First-line Treatment of Metastatic Colorectal Cancer: A Systematic Review

W Kocha, J Maroun, D Jonker, RB Rumble, L Zuraw, and the Gastrointestinal Cancer Disease Site Group of Cancer Care Ontario’s Program in Evidence-based Care.

QUESTION
Is there a role for the use of capecitabine (Xeloda™) in the first-line treatment of patients with metastatic colorectal cancer? Survival was the primary outcome of interest and time to progression and tumour response were secondary outcomes.

INTRODUCTION
For many years, 5-fluorouracil (5-FU) has been the mainstay of treatment of colorectal cancers. Although initially administered by the oral route, that route of administration was largely abandoned when it was found that the serum levels achieved were highly erratic. Further research determined that the mechanism for this erratic bioavailability by the oral route was due to the presence of the enzyme dihydropyrimidine dehydrogenase (DPD) within intestinal mucosa cells.

Several strategies adopted to try to develop drugs that circumvent this problem included using concurrent DPD inhibitors, and undertaking the development of pro-drugs of 5-FU. Capecitabine is an orally administered 5-FU pro-drug that is not subject to metabolism by DPD. Several reviews exist detailing the development, pharmacokinetics, and clinical use of this new oral agent (1-11). Briefly, capecitabine is a precursor of 5’-deoxy-5-fluorouridine that is preferentially converted to the compound 5-FU. There is a >70% oral bioavailability following oral administration, and absorption appears to be rapid and extensive. It is converted to 5-FU in a metabolic pathway involving a four-step process catalyzed by enzymes.
Capecitabine is initially converted in the liver to 5'-deoxy-5-fluorocytidine by carboxylesterase and then to 5'-deoxy-5-fluorouridine by the enzyme cytidine deaminase. This latter conversion may occur either in the liver or the tumour. The conversion to 5-FU within the tumour cell is catalyzed by thymidine phosphorylase (TP). After catalysis by TP, 5-FU is then converted to an active metabolite, which acts directly on tumour cells. Pre-clinical studies suggest that TP levels are higher in tumour tissue than in normal tissue (7,11,12,13). Two such studies have indicated that significantly higher levels of intracellular 5-FU can be achieved with oral administration than with parenteral 5-FU administration (12,13). The possibility that there now could be an oral agent that provides 5-FU in higher intracellular concentrations than the normal parenteral route has generated considerable interest. In addition, because capecitabine is administered orally, there are many advantages to using this drug, aside from treatment outcome. Assuming that treatment with oral capecitabine or infusional 5-FU results in equivalent patient outcomes, patients and practitioners may choose that drug. Oral administration provides more predictable exposure to 5-FU, allows more choice in dosage regimen, and avoids a more invasive intravenous (IV) therapy.

A number of phase II studies of capecitabine have been conducted in breast cancer and metastatic colorectal adenocarcinoma. The drug has been approved in Canada for use in breast cancer and was approved for use in metastatic colorectal cancer in July 2000. This guideline was developed to inform practitioners about the evidence for this new drug.

In addition to capecitabine, the following treatment alternatives for first-line therapy exist: 5-fluorouracil plus leucovorin, raltitrexed, irinotecan combined with 5-fluorouracil plus leucovorin, and oxaliplatin combined with 5-fluorouracil plus leucovorin. As always, the choice of treatment should be based on the various system factors, patient preferences, and convenience. Recent evidence suggests that irinotecan combined with infusional 5-FU and leucovorin (FOLFIRI) has become the standard first-line treatment for metastatic colorectal cancer (14). Due to this change, specific advantages related to the use of capecitabine over 5-FU plus leucovorin in metastatic colorectal cancer treatment as described in this guideline may be less than those obtained when using infusional 5-FU and leucovorin plus irinotecan.

METHODS
Guideline Development
This systematic review was developed by Cancer Care Ontario’s Program in Evidence-based Care (PEBC), using the methods of the Practice Guidelines Development Cycle (15). Evidence was selected and reviewed by two members of the PEBC’s Gastrointestinal Cancer Disease Site Group (DSG) and methodologists.

This systematic review is a convenient and up-to-date source of the best available evidence on capecitabine in colorectal cancer. The body of evidence in this report is primarily comprised of mature randomized controlled trial data (RCT). This evidence forms the basis of a clinical practice guideline developed by the Gastrointestinal Cancer DSG. The systematic review and companion practice guideline are intended to promote evidence-based practice in Ontario, Canada. The PEBC is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

Literature Search Strategy
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://cnetdb.nci.nih.gov/trialsrch.shtml) and abstracts published
in the proceedings of the 1998-2003 annual meetings of the American Society of Clinical Oncology (ASCO) 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.

Update
The literature search was updated on February 11, 2005 using the MEDLINE (through February (week 1) 2005) and EMBASE (through week 7, 2005) databases, as well as the Cochrane Library’s database of Systematic Reviews (through Issue 1, 2005) and the 2004 ASCO abstracts. The National Cancer Institute (NCI®) clinical trials database (http://www.cancer.gov/search/clinical_trials/) was also searched for reports of new and ongoing trials on February 11, 2005. Ongoing trials are listed in Appendix 2.

Study Selection Criteria

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.

Synthesizing 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 (16,17) of capecitabine as first-line treatment for metastatic colorectal cancer (18). This meta-analysis, based on summary data, has been published in full.

RESULTS

Literature Search Results
Capecitabine is a new drug, and no relevant practice guidelines or systematic overviews were available for review. However, a randomized phase II study of capecitabine to determine dose level (11) and two fully-published randomized phase III trials (Trial S014695, Trial S014796) comparing capecitabine to 5-FU plus leucovorin as first-line therapy were obtained (16,17). These two phase III trials had been pooled, and the fully published meta-analysis results were obtained (18). A related meta-analysis report available in abstract form provides data on dose modification for adverse effects (19). Individual patient data was not used in pooling the data presented in either meta-analysis report (18,19). Additionally, an abstract report of interim safety data on the X-ACT (Xeloda as adjuvant treatment for colon cancer) study (20), a phase III trial examining capecitabine versus bolus 5-FU/LV in the adjuvant setting, was obtained.

Update
Two new trial reports were obtained (1u,2u). The first trial, reported in abstract form by Arkenau et al (1u), compared capecitabine combined with oxaliplatin (CAPOX) with 5-fluorouracil combined with leucovorin calcium and oxaliplatin (FUFOX). The Arkenau et al trial (2u) provided preliminary safety data only and efficacy results will be included in a
future update. The second trial, by Van Cutsem et al (1u), is an update and re-analysis of the efficacy data from the SO14695 (17) and SO14796 (16) trials.

Single-Agent Capecitabine as First-Line Therapy
Randomized Phase II Study
In contrast to most other new agents, there is almost no phase II data for capecitabine as a single agent, specifically because this drug is, in fact, metabolized to 5-FU for which there is a considerable amount of such data. The one existing randomized phase II study compared two different regimens of capecitabine as a single agent and one regimen of capecitabine plus leucovorin (11). The results are summarized in Table 1. This study compared capecitabine at 1331 mg/m²/day as a continuous regimen, capecitabine 2510 mg/m²/day as an intermittent regimen, and capecitabine 1657 mg/m²/day as an intermittent regimen given along with leucovorin at 30 mg orally, twice daily. The study arms were well balanced with respect to patient, disease, and pretreatment characteristics (p-values not reported). The reported response rates ranged from 20.5% to 23.5%, and time to progression ranged from 127 days to 230 days. Capecitabine administered using an intermittent regimen demonstrated nearly a two-fold increase in time to progression compared with continuous use. Capecitabine plus leucovorin was associated with considerably greater toxicity compared with capecitabine alone. Therefore, intermittent, single-agent capecitabine was selected as the arm with the best therapeutic benefit-to-toxicity ratio for further studies.

Table 1. Summary of randomized phase II study on capecitabine regimen and dosing.

<table>
<thead>
<tr>
<th>Study Outcome</th>
<th>Treatment Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Capecitabine 1331 mg/m²/day Continuous Regimen n=39</td>
</tr>
<tr>
<td>Response Rate</td>
<td>21%</td>
</tr>
<tr>
<td>No. of Responders</td>
<td>8</td>
</tr>
<tr>
<td>Median Time to Progression in Days</td>
<td>127 (84 to 212)</td>
</tr>
<tr>
<td>(95% confidence interval)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Capecitabine 2510 mg/m²/day Intermittent Regimen n=34</td>
</tr>
<tr>
<td>Response Rate</td>
<td>24%</td>
</tr>
<tr>
<td>No. of Responders</td>
<td>8</td>
</tr>
<tr>
<td>Median Time to Progression in Days</td>
<td>230 (121 to 274)</td>
</tr>
<tr>
<td>(95% confidence interval)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Capecitabine 1657 mg/m²/day Intermittent Regimen + Leucovorin n=35</td>
</tr>
<tr>
<td>Response Rate</td>
<td>23%</td>
</tr>
<tr>
<td>No. of Responders</td>
<td>8</td>
</tr>
<tr>
<td>Median Time to Progression in Days</td>
<td>165 (87 to 174)</td>
</tr>
<tr>
<td>(95% confidence interval)</td>
<td></td>
</tr>
</tbody>
</table>

Phase III Trials
Efficacy data
Two randomized phase III trials, both sponsored by Hoffman - La Roche, Inc., compared capecitabine with 5-FU plus leucovorin (Trial SO14695, Trial SO14796). The eligible patient population was patients with metastatic colorectal cancer who had not received prior chemotherapy for metastatic disease. For high-risk patients who had received 5-FU-based adjuvant chemotherapy following curative resection, adjuvant treatment was completed at least six months before trial entry. The same dose and dose intensity of capecitabine (2500 mg/m²/day over two weeks followed by a one-week break) was used in both trials. The 5-FU plus leucovorin arm, also identical in both trials, utilized the classic Mayo regimen of 20 mg/m² of leucovorin and 425 mg/m² of 5-FU, both administered daily for five days, in a four-week cycle.

Table 2 summarizes the efficacy data for both trials. All data provided are as calculated by the Independent Review Committee (IRC) for each trial. Both randomized trials detected no significant difference in survival for capecitabine compared with 5-FU plus leucovorin. The response rates in one trial indicate a significant difference in favour of capecitabine.
Update
The trial found in the update search, Arkenau et al (1u), is a preliminary report, and no efficacy data were given. Complete data will be added in a future update.

Table 2. Summary of efficacy results from two randomized phase III trials of capecitabine.

<table>
<thead>
<tr>
<th>Study Author (ref) [location] year protocol ID</th>
<th>Treatment</th>
<th>Number of patients</th>
<th>Median survival (months)</th>
<th>Overall Response Rate% [CR + PR]</th>
<th>Median time to disease progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van Cutsem et al [multinational] 2001 SO14796</td>
<td>Capecitabine 5-FU/LV</td>
<td>301</td>
<td>13.2</td>
<td>18.9 [1 + 56]</td>
<td>5.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>301</td>
<td>12.1</td>
<td>15 [2 + 43]</td>
<td>4.7</td>
</tr>
<tr>
<td>Hoff et al [multinational] 2001 SO14695</td>
<td>Capecitabine 5-FU/LV</td>
<td>302</td>
<td>12.5</td>
<td>25.8 [1 + 77]</td>
<td>4.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>303</td>
<td>13.3</td>
<td>11.6 [1 + 34]</td>
<td>4.7</td>
</tr>
<tr>
<td>Arkenau et al [Germany] 2004</td>
<td>CAPOX FUFOX</td>
<td>140</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>135</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

Note: CR, complete response; PR, partial response; 5-FU, 5-fluorouracil; LV, leucovorin calcium; ns, not significant; \( \chi^2 \), chi-square test; CAPOX, capecitabine combined with oxaliplatin; FUFOX, 5-fluorouracil combined with leucovorin calcium and oxaliplatin; NR, not reported.

Meta-analysis of the Phase III trials
Update
Two papers have reported the pooled results from the SO14695 (17) and SO14796 (16) trials, Twelves et al (18) in 2002 and Van Cutsem et al (2u) in 2004. As the report by Van Cutsem et al represents the most recent publication, only it will be discussed, as both meta-analyses reported identical results. As shown in Table 3, there were no statistically significant differences between the treatment groups for median survival or median time to progression. However, a treatment benefit in favour of capecitabine was detected in overall response (26% versus [vs.] 17%; \( p<0.0002 \)).

Table 3. Summary of pooled efficacy data from two randomized phase III trials.

<table>
<thead>
<tr>
<th>Meta-analysis Author (ref)</th>
<th>Treatment</th>
<th>Number of patients</th>
<th>Median survival (months)</th>
<th>Overall Response Rate% [CR + PR]</th>
<th>Median time to disease progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van Cutsem et al (2u)</td>
<td>Capecitabine 5-FU/LV</td>
<td>603</td>
<td>12.9</td>
<td>26</td>
<td>4.6</td>
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<td></td>
<td></td>
<td>604</td>
<td>12.8</td>
<td>17</td>
<td>4.7</td>
</tr>
</tbody>
</table>

Note: CR, complete response; PR, partial response; 5-FU, 5-fluorouracil; LV, leucovorin calcium; ns, not significant.
Adverse effects
Table 4 provides a summary of the most frequent adverse effects leading to a reduction in dosage and/or a treatment interruption, along with median time to dose-reduction information. The incidence rates of diarrhea, nausea, stomatitis, and alopecia were lower with capecitabine than with 5-FU plus leucovorin (18,19). Capecitabine was associated with a lower incidence of grade 3/4 stomatitis (2% versus 14.7%) (19), neutropenia leading to infection or sepsis (2.2% versus 21.1%) (18) and a lower rate of hospitalization for treatment-related adverse events (11.6% versus 18%) (18).

Twelves et al (18) evaluated the occurrence of dose modification in the phase III trials. In a pooled analysis of 1207 patients, dose modification for adverse effects occurred in significantly fewer patients on capecitabine compared to patients on 5-FU plus leucovorin, and the median time to dose reduction was significantly greater in the capecitabine group compared to the 5-FU plus leucovorin group. There was a significantly higher incidence of grade 3 hand-foot syndrome in the capecitabine group (17% versus 1%) (18). Patients on capecitabine withdrew due to treatment-related adverse events at a slightly higher rate than patients on 5-FU plus leucovorin, but this difference was not statistically significant (19).

Update
The Arkenau et al trial (1u), a preliminary report available in abstract form only, provided early safety data on an RCT comparing CAPOX with FUFOX. Results appear in Table 4. Results show that CAPOX and FUFOX have a comparable toxicity profile, for the outcomes reported only neutropenia leading to infection or sepsis showed a significant difference between the treatment arms favouring treatment with CAPOX (10% CAPOX vs. 24% FUFOX; p=0.004, reviewer’s calculation).
Table 4. Most frequent adverse effects leading to dose reduction and/or treatment interruption.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Adverse effects</th>
<th>Diarrhea %</th>
<th>Nausea %</th>
<th>Stomatitis %</th>
<th>Alopecia %</th>
<th>Neutropenia (leading to infection or sepsis) %</th>
<th>Treatment leads to hospitalization %</th>
<th>Dose modification due to adverse effects %</th>
<th>Median time to dose reduction (months)</th>
<th>Grade 3+ hand-foot syndrome %</th>
<th>Patients required to withdraw due to adverse effects %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Twelves et al (18)</td>
<td>Capecitabine (n=603)</td>
<td>48</td>
<td>38</td>
<td></td>
<td>6</td>
<td>2.2</td>
<td>11.6</td>
<td>34</td>
<td>2.5</td>
<td>17</td>
<td>9.6 (19)</td>
</tr>
<tr>
<td>5-FU/LV (n=604)</td>
<td></td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>All Grades - 24 Grade 3/4 - 2 21</td>
<td>21.1</td>
<td>18</td>
<td>42</td>
<td>1.2</td>
<td>p=NR</td>
<td>p=NR</td>
<td>p=ns</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>All Grades - 62 Grade 3/4 - 14.7</td>
<td>p&lt;0.05</td>
<td>p&lt;0.05</td>
<td>p&lt;0.05</td>
<td>p=NR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arkenau et al (2u)</td>
<td>CAPOX (n=140)</td>
<td>43</td>
<td>NR</td>
<td></td>
<td>NR</td>
<td>10</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>FUFOX (n=135)</td>
<td></td>
<td>35</td>
<td>NR</td>
<td>All Grades - 4 Grade 3/4 - 1 24</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>0</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>p=ns</td>
<td></td>
<td>All Grades - 4 Grade 3/4 - 2</td>
<td>p=0.004</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NOTE: 5-FU, 5-fluorouracil; LV, leucovorin calcium; NR, not reported; CAPOX, capecitabine combined with oxaliplatin; FUFOX, 5-fluorouracil combined with leucovorin calcium and oxaliplatin.
Subgroup Analysis: Capecitabine After Adjuvant 5-FU Therapy

Patients who had received 5-FU and leucovorin as adjuvant therapy were entered into both phase III trials, providing such therapy had been completed at least six months prior to trial entry. Response based on previous adjuvant therapy with 5-FU and leucovorin at least six months previous to metastatic recurrence is shown in Table 4. 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 (p-values not reported). Pooled response rates were 21.2% with capecitabine versus 8.2% with 5-fluorouracil plus leucovorin in the subgroup of patients with prior 5-FU-based adjuvant therapy (p-value not reported) (18).

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Trial SO14796 (16)</th>
<th>Trial SO14695 (17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior adjuvant chemotherapy</td>
<td>Capecitabine (N=301)</td>
<td>5-FU + LV (N=301)</td>
</tr>
<tr>
<td>Number of patients</td>
<td>56</td>
<td>41</td>
</tr>
<tr>
<td>Response rate</td>
<td>21.0%</td>
<td>11.1%</td>
</tr>
<tr>
<td>No prior adjuvant chemotherapy</td>
<td>Number of patients</td>
<td>245</td>
</tr>
<tr>
<td>Response rate</td>
<td>28.0%</td>
<td>19.1%</td>
</tr>
</tbody>
</table>

DISCUSSION

In appropriate patients, standard combination chemotherapy for the first-line treatment of metastatic colorectal cancer consists of infusional 5-FU plus leucovorin calcium with either irinotecan or oxaliplatin (refer to the PGI’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]).

Although the two individual studies (16,17) comparing capecitabine to 5-FU/LV were not designed to establish equivalence, a pooled analysis of both trials detected no difference in survival (18). A finding of no statistically significant difference is of high clinical importance due to the many benefits that could be obtained from oral administration of a drug therapy regimen, as discussed previously. Where monotherapy is deemed the therapy of choice, the data support capecitabine as an alternative choice to a 5-FU and leucovorin regimen. Moreover, the data indicate that it may be more active in patients who have previously received 5-FU and leucovorin as adjuvant therapy for resected disease.

There is insufficient evidence to recommend the use of capecitabine as second-line therapy after the failure of bolus 5-FU. There is evidence that capecitabine is active in patients who have previously received 5-FU plus leucovorin as adjuvant therapy (Table 4). However, a recent phase II trial showed that patients given capecitabine as second-line therapy after first-line treatment with 5-FU achieved stable disease but showed no objective response (21).

No data are available on the use of capecitabine in combination with other chemotherapy drugs or radiation therapy. Capecitabine may find a role as a replacement for prolonged, continuous, parenteral infusions of 5-FU. Capecitabine may also be a replacement for 5-FU infusions currently given as standard therapy concurrent with radiation therapy. There is also evidence from a phase III trial that the use of capecitabine over 5-FU/LV will provide a treatment cost savings as hospital visits for IV therapy would be unnecessary and the fewer toxic side effects would reduce treatment requirements both at home and in hospital (22). The Gastrointestinal Cancer DSG will continue to monitor the potential roles of this drug as data emerge.
ONGOING TRIALS
The NCI ® database was searched on February 11, 2005 for records of ongoing or recently closed phase III trials using capecitabine alone or in combination with other drugs. A brief description of the trials including projected or actual accrual, and current status are all detailed in Appendix 2.

CONCLUSIONS
Dosing and Scheduling
As determined from the randomized phase II trial summarized previously (11), the recommended dose of capecitabine is 2510 p.o. mg/m2/day for 14/21 days per 21-day cycle.

The absorption of capecitabine is affected by food intake, and the effects appear complex. It is currently recommended that capecitabine be administered orally with food, as done in the clinical trials (23). A concern about Maalox® intake interfering with capecitabine absorption does not appear to have been borne out experimentally (24).

Use in Hepatic Insufficiency, Hyperbilirubinemia and Renal Insufficiency
Capecitabine and its metabolites are extensively excreted by the urinary route (25). Pharmacokinetic studies demonstrate the need for 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.

There appears to be no significant difference in pharmacokinetic values for patients receiving capecitabine in situations of “mild” or “moderate” hepatic insufficiency. Specifically, no dose reductions are necessary. The use of capecitabine in severe hepatic failure has not been formally studied, and therefore, the effect of severe hepatic dysfunction is unknown (26).

Where there is hyperbilirubinemia with bilirubin values exceeding 1.5 times normal, it has been recommended that treatment be interrupted until the bilirubin drops below the 1.5 times normal value. Company-supplied recommendations suggest that in such cases, following recovery of bilirubin values, capecitabine doses should be reduced.

JOURNAL REFERENCE

ACKNOWLEDGEMENTS
The Gastrointestinal Cancer Disease Site Group would like to thank Dr. W. Kocha, Dr. J. Maroun, Dr D. Jonker, Mr. R. Bryan Rumble, and Ms. Lisa Zuraw for taking the lead in drafting and revising this practice guideline report.

For a complete list of the Gastrointestinal Cancer Disease Site Group members and the Report Approval Panel members, please visit the CCO Web site at http://www.cancercare.on.ca/toolbox/qualityguidelines/pebc/

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The PEBC is supported by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC is editorially independent from its funding agencies.
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For information about the PEBC and the most current version of all reports, please visit the CCO Web site at http://www.cancerca.re.on.ca/ or contact the PEBC office at:
Phone: 905-527-4322 ext. 42822 Fax: 905-526-6775 E-mail: ccopgi@mcmaster.ca
REFERENCES


Update of:


Update of:

Update of:

Update of:

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


Appendix 1. Dosage and dose modification.

**Dosage and administration**
The recommended dose of capecitabine is 1250 mg/m$^2$ administered twice daily (morning and evening; equivalent to 2500 mg/m$^2$ total daily dose) for 14 days followed by a seven-day rest period. Capecitabine is intended for long-term administration unless clinically inappropriate. Capecitabine tablets should be swallowed with water within 30 minutes after the end of a meal. The following table displays the total daily dose by body surface area and the number of tablets to be taken at each dose.

**Calculated capecitabine dose, standard starting dose.**

<table>
<thead>
<tr>
<th>Body surface area (m$^2$)</th>
<th>Dose per administration</th>
<th>Number of tablets administered in the morning</th>
<th>Number of tablets administered in the evening</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>150 mg</td>
<td>500 mg</td>
<td>150 mg</td>
</tr>
<tr>
<td>≤ 1.25</td>
<td>1500</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>1.26 - 1.37</td>
<td>1650</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>1.38 - 1.51</td>
<td>1800</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>1.52 - 1.65</td>
<td>2000</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>1.66 - 1.77</td>
<td>2150</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>1.78 - 1.91</td>
<td>2300</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>1.92 - 2.05</td>
<td>2500</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>2.06 - 2.17</td>
<td>2650</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>≥ 2.18</td>
<td>2800</td>
<td>2</td>
<td>5</td>
</tr>
</tbody>
</table>

**Dose modification guidelines**
Patients should be monitored carefully for toxicity. Any adverse effects due to capecitabine administration may be managed by symptomatic treatment, dose interruptions, and dose adjustment. Once a dose reduction has been made, it should not be increased at a later time.

**Recommended dose modifications for oral capecitabine monotherapy.**

<table>
<thead>
<tr>
<th>NCIC-CTC* Toxicity Grade</th>
<th>During a course of therapy</th>
<th>Dose adjustment for next cycle (% of starting dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>Maintain dose level</td>
<td>Maintain dose level</td>
</tr>
<tr>
<td>Grade 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• 1st appearance</td>
<td>Interrupt until resolved to grade 0-1</td>
<td>100%</td>
</tr>
<tr>
<td>• 2nd appearance</td>
<td>Interrupt until resolved to grade 0-1</td>
<td>75%</td>
</tr>
<tr>
<td>• 3rd appearance</td>
<td>Interrupt until resolved to grade 0-1</td>
<td>50%</td>
</tr>
<tr>
<td>• 4th appearance</td>
<td>Discontinue treatment permanently</td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• 1st appearance</td>
<td>Interrupt until resolved to grade 0</td>
<td>75%</td>
</tr>
<tr>
<td>• 2nd appearance</td>
<td>Interrupt until resolved to grade 0</td>
<td>50%</td>
</tr>
<tr>
<td>• 3rd appearance</td>
<td>Discontinue treatment permanently</td>
<td></td>
</tr>
<tr>
<td>Grade 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• 1st appearance</td>
<td>Discontinue treatment permanently</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td>or If physician deems it to be in the patient’s best interest to continue, interrupt until resolved to grade 0-1</td>
<td></td>
</tr>
</tbody>
</table>

*NCIC-CTC, National Cancer Institute of Canada - Common Toxicity Criteria (version 1, December 1994) grades were used for all adverse effects except hand and foot syndrome. The toxicity grades for hand and foot syndrome were defined as follows: Grade 1 - numbness, dysesthesia/parasthesia, tingling, or erythema of the hands and/or feet and/or discomfort which does not disrupt normal activities; Grade 2 - painful erythema and swelling of the hands and/or feet that results in discomfort affecting the patient’s activities of daily living; Grade 3 - moist desquamation, ulceration, blistering or severe pain of the hands and/or feet that results in severe discomfort and causes the patient to be unable to work or perform activities of daily living.
Dose modifications are not recommended for grade 1 events.

Therapy with capecitabine should be interrupted upon the first occurrence of a grade 2 or 3 adverse event. Once resolved or decreased to Grade 1, capecitabine may begin again at full dose, or as adjusted according to the above table on dose modifications.

If a Grade 4 adverse event occurs, therapy should be discontinued or interrupted until resolved or decreased to grade 1, then therapy should begin again at 50% of the original dose. Doses of capecitabine omitted for toxicity are not replaced, the patient resumes the originally planned treatment cycles.

Appendix 2. Ongoing trials.

<table>
<thead>
<tr>
<th>Protocol ID:</th>
<th>Date last modified:</th>
<th>Type of trial:</th>
<th>Accrual:</th>
<th>Sponsorship:</th>
<th>Status:</th>
</tr>
</thead>
<tbody>
<tr>
<td>EORTC-40015; NCT00064181</td>
<td>December 30, 2004</td>
<td>Randomized, double-blind, multicentre study</td>
<td>A total of 692 patients (173 per treatment arm) will be accrued for this study within 3.5 years</td>
<td>European Organization for Research and Treatment of Cancer</td>
<td>Open, recruiting</td>
</tr>
<tr>
<td>NCRI-FOCUS2; EU-20303; NCT00070213; MRC-CR09</td>
<td>December 3, 2003</td>
<td>Randomized, multicentre study</td>
<td>A total of 460 patients (115 per treatment arm) will be accrued for this study within 2 years</td>
<td>National Cancer Research Institute and Medical Research Council Clinical Trials Unit sponsorship</td>
<td>Open, recruiting</td>
</tr>
<tr>
<td>NO16966; NCT00069095</td>
<td>January 18, 2005</td>
<td>Randomized</td>
<td></td>
<td>Pharmaceutical sponsorship [F. Hoffmann - La Roche, Ltd.]</td>
<td>Open, recruiting</td>
</tr>
<tr>
<td>NO16967; NCT00069108</td>
<td>January 26, 2005</td>
<td>Randomized</td>
<td></td>
<td>Pharmaceutical sponsorship [F. Hoffmann - La Roche, Ltd.]</td>
<td>Open, recruiting</td>
</tr>
</tbody>
</table>
Evidence-based Series #2-15: Section 3

Oral Capecitabine (Xeloda™) in the First-line Treatment of Metastatic Colorectal Cancer: Guideline Development and External Review - Methods and Results

W Kocha, J Maroun, D Jonker, RB Rumble, L Zuraw, and the Gastrointestinal Cancer Disease Site Group of Cancer Care Ontario’s Program in Evidence-based Care.

A Quality Initiative of the Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO) Developed by the Gastrointestinal Cancer Disease Site Group


Report Date: February 11, 2005

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO) (1). The PEBC mandate is to improve the lives of Ontarians affected by cancer, through the development, dissemination, implementation, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer care.

The PEBC supports a network of disease-specific panels, called Disease Site Groups (DSGs) and Guideline Development Groups (GDGs), mandated to develop the PEBC products. These panels are comprised of clinicians, methodologists, and community representatives from across the province.

The PEBC is well known for producing evidence-based practice guideline reports, using the methods of the Practice Guidelines Development Cycle (1,2). The PEBC reports consist of a comprehensive systematic review of the clinical evidence on a specific cancer care topic, an interpretation of and consensus agreement on that evidence by our DSGs and GDGs, the resulting clinical recommendations, and an external review by Ontario clinicians in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each clinical practice guideline report, through the routine periodic
review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original clinical practice guideline information.

The Evidence-based Series: A New Look to the PEBC Practice Guidelines
Each Evidence-based Series is comprised of three sections.
- **Section 1: Clinical Practice Guideline.** This section contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its interpretation by the DSG or GDG involved and a formalized external review by Ontario practitioners.
- **Section 2: Systematic Review.** This section presents the comprehensive systematic review of the clinical and scientific research on the topic and the conclusions reached by the DSG or GDG.
- **Section 3: Guideline Development and External Review: Methods and Results.** This section summarizes the guideline development process and the results of the formal external review by Ontario practitioners of the draft version of the clinical practice guideline and systematic review.

DEVELOPMENT OF THIS EVIDENCE-BASED SERIES
Development and Internal Review
This evidence-based series was developed by the Gastrointestinal Cancer Disease Site Group of CCO's PEBC. The series is a convenient and up-to-date source of the best available evidence on capecitabine for colorectal cancer, developed through systematic review, evidence synthesis, and input from practitioners in Ontario.

Disease Site Group Consensus Process
The data from the two phase III trials, revealed no statistically significant difference between capecitabine and 5-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 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 DSG 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.
External Review by Ontario Clinicians
Following review and discussion of sections 1 and 2 of this evidence-based series, the Gastrointestinal Cancer Disease Site Group circulated the clinical practice guideline and systematic review to clinicians in Ontario for review and feedback. Box 1 summarizes the draft clinical recommendations and supporting evidence developed by the panel.

**BOX 1: DRAFT RECOMMENDATIONS** (approved for external review January 2, 2002)

**Target Population**
These recommendations apply to adult patients with metastatic colorectal cancer who have not received prior chemotherapy for metastatic disease. 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.

**Recommendation**
It is reasonable to use capecitabine as a single-agent in the first-line therapy of advanced or metastatic colorectal cancer, where monotherapy with fluoropyrimidines or other thymidylate synthase inhibitors is favoured.

**Qualifying Statements**
- Preliminary data from a subgroup analysis suggest that capecitabine may be the preferred treatment for patients who had received prior adjuvant therapy with 5-fluorouracil (5-FU) plus leucovorin (LV), while either capecitabine or 5-FU plus LV therapy is reasonable for patients who have never received adjuvant therapy. Further trials are needed to confirm this observation.
- It should be noted that since the development of this guideline began, irinotecan combined with 5-FU/LV for many practitioners has become the standard first-line treatment for metastatic colorectal cancer. Due to this change, specific advantages relating to the use of capecitabine over 5-FU plus leucovorin in metastatic colorectal cancer treatment may be less than that which would be obtained when using 5-FU plus leucovorin plus irinotecan.
- 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.

**Methods**
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 DSG reviewed the results of the survey.
Results
Fifty-one responses were received out of the 103 surveys sent (49.5% response rate). Responses include returned completed surveys as well as phone, fax, and email responses. Of the practitioners who responded, 27 indicated that the report was relevant to their clinical practice and completed the survey. Key results of the practitioner feedback survey are summarized in Table 6.

Table 6. Practitioner responses to the 20 items on the practitioner feedback survey.

<table>
<thead>
<tr>
<th>Item</th>
<th>Number (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rated “strongly agree” or “agree”</td>
</tr>
<tr>
<td>The rationale for developing a CPG, as stated in the “Choice of Topic” section of the report, is clear.</td>
<td>27(96)</td>
</tr>
<tr>
<td>There is a need for a CPG on this topic.</td>
<td>23(85)</td>
</tr>
<tr>
<td>The literature search is relevant and complete (i.e., no key trials were missed nor any included that should not have been) in this PGIP report.</td>
<td>22(83)</td>
</tr>
<tr>
<td>I agree with the methodology used to summarize the evidence included in this PGIP report.</td>
<td>27(100)</td>
</tr>
<tr>
<td>The results of the trials described in the PGIP report are interpreted according to my understanding of the data.</td>
<td>25(93)</td>
</tr>
<tr>
<td>The DRs in this report are clear.</td>
<td>24(89)</td>
</tr>
<tr>
<td>I agree with the DRs as stated.</td>
<td>21(78)</td>
</tr>
<tr>
<td>The DRs are suitable for the patients for whom they are intended.</td>
<td>23(86)</td>
</tr>
<tr>
<td>The DRs are too rigid to apply to individual patients.</td>
<td>1(4)</td>
</tr>
<tr>
<td>When applied, the DRs will produce more benefits for patients than harms.</td>
<td>16(60)</td>
</tr>
<tr>
<td>The PGIP report presents options that will be acceptable to patients.</td>
<td>23(85)</td>
</tr>
<tr>
<td>To apply the DRs will require reorganization of services/care in my practice setting.</td>
<td>3(11)</td>
</tr>
<tr>
<td>To apply the DRs will be technically challenging.</td>
<td>3(11)</td>
</tr>
<tr>
<td>The DRs are too expensive to apply.</td>
<td>3(11)</td>
</tr>
<tr>
<td>The DRs are likely to be supported by a majority of my colleagues.</td>
<td>21(78)</td>
</tr>
<tr>
<td>If I follow the DRs, the expected effects on patient outcomes will be obvious.</td>
<td>7(26)</td>
</tr>
<tr>
<td>The DRs reflect a more effective approach for improving patient outcomes than is current usual practice (if DRs are the same as current practice, please tick NA).</td>
<td>10(37)</td>
</tr>
<tr>
<td>When applied, the DRs will result in better use of resources than current usual practice (if DRs result in the same outcomes as current practice, please tick NA).</td>
<td>11(41)</td>
</tr>
<tr>
<td>This PGIP report should be approved as a practice guideline.</td>
<td>18(66)</td>
</tr>
</tbody>
</table>

If this PGIP report were to become a practice guideline, how likely would you be to make use of it in your own practice?

<table>
<thead>
<tr>
<th>Rated “likely” or “very likely”</th>
<th>Rated “unsure”</th>
<th>Rated “not at all likely” or “unlikely”</th>
</tr>
</thead>
<tbody>
<tr>
<td>19(71)</td>
<td>4(15)</td>
<td>4(15)</td>
</tr>
</tbody>
</table>

* Percentages may not add up to 100% due to missing data
† Number of practitioners (%) who indicated “NA= not applicable”
Summary of Written Comments
Seven respondents (26%) provided written comments. The main points contained in the written comments were:

- The comparisons made in the data analysis for this guideline may have been made obsolete given that a combination 5-FU, leucovorin, and irinotecan has become the standard 1st line therapy.
- More detail needs to be given in the discussion of median survival, since the guideline shows that it is the same in both groups.
- There could be more discussion on effective management of adverse effects, such as hand and foot syndrome and diarrhea.
- More discussion regarding the economic impact of capecitabine implementation needs to be made. For example, would the cost savings in treatment be offset by the costs of the drug itself?

Modifications/Actions
No substantial changes were made to the guideline based on the practitioner feedback survey for the following reasons. Although combination therapy with 5-FU, leucovorin, and irinotecan has become standard treatment for metastatic colorectal cancer, this guideline only considers those patients for whom monotherapy is the treatment method of choice, and this patient population is described. The most commonly reported adverse effects with capecitabine treatment are not life-threatening and can be successfully managed in most cases. The question of economics is beyond the scope of this guideline.

Practice Guidelines Coordinating Committee Approval Process
The practice guideline report was circulated to 14 members of the Practice Guidelines Coordinating Committee (PGCC) for review and approval. Eleven out of 14 PGCC members returned ballots. Three PGCC members approved the practice guideline report as written, and eight members approved the guideline conditional on the Gastrointestinal Cancer DSG addressing the following specific concerns:

- Information on dosing and scheduling need to be included in the recommendations.
- Please add a recommendation stating what the current standard therapy is, and refer to the relevant guideline.
- The target population and recommendation may be at a variance—please review.
- On page iii of the Summary under Future Research, the section below needs clarification: “capecitabine is an oral agent converted to an active 5-flouracil metabolite.”
- Please provide examples of other fluoropyrimidines where they are mentioned in the text.
- As capecitabine is an oral agent, this should be clearly stated in the report.
- The caveats re: hepatic insufficiency, hyperbilirubinemia and renal insufficiency should be stated in the recommendations.
- The qualifying statement indicates that monotherapy may be favoured in patients for whom there is insufficient data for a clear survival benefit of combination over single-agent activity. Several criteria are listed, but it is not clear where this data came from. Please clarify.

Modifications/Actions
In response, the Gastrointestinal Cancer DSG has:

- Provided guidance regarding dosing in the Recommendations, which now appear on the Summary page and in the main document. An appendix was added to the document clearly stating recommended dosages and recommended dose adjustments in case of adverse effects.
• Changed the first bullet under the Recommendations to state that standard combination chemotherapy consists of either irinotecan, leucovorin, and 5-FU and (FOLFIRI) or oxaliplatin, leucovorin, and 5-FU (FOLFOX), and directs the reader to the other guidelines (PG #2-16b and PG #2-22 [in progress]) for further information.
• Not changed the target population as recommended, but instead added, “at least six months earlier” to the bullet in the Qualifying Statement.
• Rewritten some sections of Future Research. The infusion information requested now appears in a bullet under the main Recommendations.
• Provided two examples each of fluoropyrimidines (5-FU, capecitabine) and thymidylate synthase inhibitors (raltitrexed, pemetrexed) in the first bullet of the Qualifying Statements.
• Added the word “oral” to the Practice Guideline title, Guideline Question, and in most instances where the word “capecitabine” appears.
• Added two bullets to the Qualifying Statements providing guidance for clinicians for those patients with renal insufficiency and/or hyperbilirubinemia. A bullet providing guidance for hepatic insufficiency was not added because, in patients with mild to moderate hepatic dysfunction, no dose adjustment is necessary, and patients with severe hepatic dysfunction have not been carefully studied.
• Reworded the first bullet under the Qualifying Statements as suggested.

Funding
The PEBC is supported by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC is editorially independent from its funding agencies.

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Contact Information
For further information about this series, please contact Dr. Jean Maroun, Chair, Gastrointestinal Cancer Disease Site Group, Ottawa Regional Cancer Centre, General Division, 503 Smyth Road, Ottawa, Ontario, K1H 1C4; TEL (613) 737-7700, ext. 6708; FAX (613) 247-3511.

For information about the PEBC and the most current version of all reports, please visit the CCO Web site at http://www.cancercare.on.ca/ or contact the PEBC office at:
Phone: 905-527-4322 ext. 42822 Fax: 905-526-6775 E-mail: ccopgi@mcmaster.ca
REFERENCES


EBS 2-15 Document Assessment and Review Tool

<table>
<thead>
<tr>
<th>Number and title of document under review</th>
<th>EBS #2-15 Oral Capecitabine in the First-Line Treatment of Metastatic Colorectal Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date of current version</td>
<td>February 11, 2005</td>
</tr>
<tr>
<td>Clinical reviewer</td>
<td>Dr. J. Biagi</td>
</tr>
<tr>
<td>Research coordinator</td>
<td>Rovena Tey</td>
</tr>
<tr>
<td>Date initiated</td>
<td>June 16, 2010</td>
</tr>
<tr>
<td>Date and final results / outcomes</td>
<td>July 12, 2010 (ARCHIVED)</td>
</tr>
</tbody>
</table>

Beginning at question 1, below, answer the questions in sequential order, following the instructions in the black boxes as you go.

1. Is there still a need for a guideline covering one or more of the topics in this document? Answer Yes or No, and explain if necessary:
   - **1. YES**
     - However, the recommendations in this guideline do not take into account newer treatment strategies (e.g., biologics) that might be used in combination.
     - Guideline 2-15 can be ARCHIVED because components of this guideline will be replaced by a new guideline that is currently in production, “Strategies of Sequential Therapy in Advanced Colorectal Cancer”
     - The new guideline is expected to be completed in 2011 and will update the literature search to address the research questions from guideline EBS #2-15
     - In the meantime, guideline 2-15 will still be available to view on the CCO website

   If No, then the document should be ARCHIVED with no further action; go to 11. If Yes, then go to 2.

2. Are all the current recommendations based on the current questions definitive or sufficient, and have less than 5 years elapsed since the latest search? Answer Yes or No, and explain if necessary:
   - **2.**
   - If Yes, the document can be ENDORSED with no further action; go to 11. If No, go to 3.

3. Is there expected or known evidence that contradicts the current recommendations, such that they may cause harm or lead to unnecessary or improper treatment if followed? Answer Yes or No, and explain if necessary, providing references of known evidence:
   - **3.**
   - If Yes, the document should be taken off the website as soon as possible. A WARNING should be put in its place informing a user that the document is only available by email, with a brief explanation of the reasons. If No, go to 4.

4. Do current resources allow for an updated literature search to be conducted at this time? Answer Yes or No, and explain if necessary:
   - **4.**
No, and explain as necessary. Provide an expected date of completion of the updated search, if applicable: If No, a **DEFERRAL** should be placed on the document indicating it cannot be updated at this time, but will be reviewed again on a yearly basis. If Yes, go to 5.

### 5a.
List below any new, relevant questions that have arisen since the last version of the document. List any changes to the original research questions that now must be considered.

### 5b.
List below any changes to the selection criteria in the original version made necessary by new questions, changes to existing questions, or changes in available evidence (e.g., limit a search to randomized trials that originally included non-randomized evidence).

### 5c.
Conduct an updated literature search based on that done for the current version and modified by 5a and 5b above. Report the results below.

**Go to 6.**

### 6.
Are the volume and content of the newly identified evidence such that a new document is necessary to address the topic?

If Yes, then the document should be **ARCHIVED** with no further action; go to 11. If No, go to 7.

### 7.
On initial review, does the newly identified evidence support the **existing recommendations**? Do the current recommendations cover all relevant subjects addressed by the evidence, such that no new recommendations are necessary? Answer Yes or No, and explain if necessary:

If Yes, the document can be **ENDORSED**. If No, go to 8.

### 8.
Does any of the newly identified evidence, on initial review, contradict the current recommendations, such that the current recommendations may cause harm or lead to unnecessary or improper treatment if followed? Answer Yes or No, and explain if necessary, citing newly identified references:

If Yes, a **WARNING** note will be placed on the website. If No, go to 9.

### 9.
Is there a good reason (e.g., new stronger evidence will be published soon, changes to current recommendations are trivial or address very limited situations) to postpone updating the guideline? Answer Yes or No, and explain if necessary:

If Yes, the document update will be **DEFERRED**, indicating that the document can be used for decision making and the update will be deferred until the expected evidence becomes available. If No, go to 10.

### 10.
An update should be initiated as soon as possible. List the expected date of completion of the update:

An **UPDATE** will be posted on the website, indicating an update is in progress.

### 11.
Circulate this form to the appropriate Disease Site Group for their approval. Once approved, a copy of this form should be placed behind the cover page of the current document on the website. Notify the original authors of the document about this review.

**DSG Approval Date:** July 12, 2010
# DOCUMENT ASSESSMENT & REVIEW 5-STEP FLOW CHART

## STEPS

### STEP 1: Initiation of the Document Assessment & Review process

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>Archive¹</td>
</tr>
<tr>
<td>No</td>
<td>Endorse²</td>
</tr>
</tbody>
</table>

### STEP 2: First teleconference to determine:

- the clinical relevance of the guideline,
- if a new literature search is needed, and
- if Yes, the search criteria.

1. **#1.** Is there still a NEED for a guideline covering one or more of the topics in this document?
   - Yes
   - No

2. **#2.** Are all the current recommendations based on the current questions definitive* or sufficient§, and have less than 5 years elapsed since the latest search?
   - Yes
   - No

3. **#3.** Is there expected or known evidence that contradicts the current recommendations, such that they may cause harm or lead to unnecessary or improper treatment if followed?
   - Yes
   - No

4. **#4.** Do current resources allow for an updated literature search to be conducted at this time?
   - Yes
   - No

5. **#5.** List any new and relevant questions that have arisen since the last version of the document. List any changes to the original research questions that now must be considered. Determine the search criteria.

### STEP 3: A NEW literature search based on input from #5 will be conducted, and the result will be sent to the reviewers with a follow-up date.

- RC emails DSG reviewer(s) the protocol
- Discuss questions #1-5
- Please note: No teleconference needed, IF the answers lead to one of these outcomes, PLUS the reviewer(s) complete & return the form with the answers & explanations.
- Teleconference with the reviewer(s) will focus the discussion on #5: the search strategies, i.e., scope, key word(s), and inclusion and exclusion criteria.
FLOW CHART (cont.)

STEP 4: Second teleconference to determine the ultimate status of the document

<table>
<thead>
<tr>
<th>STEPS</th>
<th>Outcomes</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>#6.</strong> Are the volume and content of the newly identified evidence such that a new document is necessary to address the topic?</td>
<td>Yes</td>
<td>Archive</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>Teleconference with the reviewer(s) to discuss the type of update, priority, and resources.</td>
</tr>
<tr>
<td></td>
<td><strong>#7.</strong> Does the newly identified evidence support the existing recommendations? Do the current recommendations cover all relevant subjects addressed by the evidence, such that no new recommendations are necessary?</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>Please note: No teleconference needed, IF the reviewer(s) complete and return the form with answers &amp; explanations.</td>
</tr>
<tr>
<td></td>
<td><strong>#8.</strong> Does any of the newly identified evidence, on initial review, contradict the current recommendations, such that the current recommendations may cause harm or lead to unnecessary or improper treatment if followed?</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>Teleconference with the reviewer(s) to discuss the type of update, priority, and resources.</td>
</tr>
<tr>
<td></td>
<td><strong>#9.</strong> Is there a good reason (e.g., new, stronger evidence will be published soon, changes to current recommendations are trivial or address very limited situations) to postpone updating the guideline?</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>#10.</strong> An update should be initiated as soon as possible. List the expected date of completion of the update.</td>
<td>Yes</td>
</tr>
</tbody>
</table>

STEP 5: Final outcome approval; Document Assessment & Review questions #11

**#11.** Circulate this form, the new evidence, and a draft document for approval by the appropriate DSG. Once approved, a copy of this form should be placed behind the cover page of the current document on the Web site. Notify the original authors of the document about this review.
DOCUMENT ASSESSMENT AND REVIEW DEFINITIONS

Document Assessment and Review Terms

* DEFINITIVE RECOMMENDATIONS - Definitive means that the current recommendations address the relevant subject area so fully that it would be very surprising to identify any contradictory or clarifying evidence.

§ SUFFICIENT RECOMMENDATIONS - Sufficient means that the current recommendations are based on consensus, opinion and/or limited evidence, and the likelihood of finding any further evidence of any variety is very small (e.g., in rare or poorly studied disease).

¶ WARNING - A warning indicates that, although the topic is still relevant, there may be, or is, new evidence that may contradict the guideline recommendations or otherwise make the document suspect as a guide to clinical decision making. The document is removed from the Web site, and a warning is put in its place. A new literature search may be needed, depending on the clinical priority and resources.

Document Assessment and Review Outcomes

1. ARCHIVED - An archived document is a document that will no longer be tracked or updated but may still be useful for academic or other informational purposes. The document is moved to a separate section of the Web site and each page is watermarked with the phrase “ARCHIVED”.

2. ENDORSED - An endorsed document is a document that the DSG/GDG has reviewed for currency and relevance and determined to be still useful as guidance for clinical decision making. A document may be endorsed because the DSG/GDG feels the current recommendations and evidence are sufficient, or it may be endorsed after a literature search uncovers no evidence that would alter the recommendations in any important way.

3. DEFERRAL - A Deferral means that the clinical reviewers feel that the document is still useful and the decision has been made to postpone further action for a number of reasons. The reasons for the deferral are in the Document Assessment and Review Tool (Appendix 2).

4. UPDATE - An Update means that the DSG/GDG recognizes that there is new evidence that makes changes to the existing recommendations in the guideline necessary but these changes are more involved and significant than can be accomplished through the Document Assessment and Review process. The DSG/GDG will rewrite the guideline at the earliest opportunity to reflect this new evidence. Until that time, the document will still be available as its existing recommendations are still of some use in clinical decision making.