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## Oral Capecitabine (Xeloda™) in the First-line Treatment of Metastatic Colorectal Cancer Practice Guideline Report #2-15

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### SUMMARY

#### Guideline 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-fluorouracil 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/m<sup>2</sup>/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, ECOG performance status  $\leq 1$ , 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.

## Methods

Entries to the MEDLINE (1990 through June (week 3) 2003), CANCERLIT (1990 through October 2002) and Cochrane Library (2003, Issue 2) databases and abstracts published in the proceedings of the 1998 to 2003 annual meetings of the American Society of Clinical Oncology were systematically searched for evidence relevant to this practice guideline report.

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

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

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

## 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 these 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. This 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 this population is underrepresented in trials, it is not possible to adequately assess the risks and benefits of any regimen for these 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 (5FU/LV) as First-line Therapy for Metastatic Colorectal Cancer*

- #2-17: *Use of Raltitrexed (Tomudex™) 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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## **PREAMBLE: About Our Practice Guideline Reports**

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

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

### Reference:

<sup>1</sup> Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. *J Clin Oncol* 1995;13(2):502-12.

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## FULL REPORT

### I. 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.

### II. CHOICE OF TOPIC AND RATIONALE

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. Also, 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.

### **III. METHODS**

#### **Guideline Development**

This practice guideline report was developed by the Practice Guidelines Initiative (PGI) of Cancer Care Ontario's Program in Evidence-based Care, using the methods of the Practice Guidelines Development Cycle (15). Evidence was selected and reviewed by two members of the PGI's Gastrointestinal Cancer Disease Site Group (DSG) and methodologists. Members of the Gastrointestinal Cancer DSG disclosed potential conflicts of interest.

The practice guideline report is a convenient and up-to-date source of the best available evidence on capecitabine in colorectal cancer, developed through systematic reviews, evidence synthesis and input from practitioners in Ontario. The body of evidence in this report is primarily comprised of mature randomized controlled trial data, therefore, recommendations by the DSG are offered. The report is intended to enable evidence-based practice. The PGI is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

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

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

#### **Literature Search Strategy**

MEDLINE (1990 to June (week 3) 2003), CANCELIT (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 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.

#### **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.

## IV. 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.

### 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/m<sup>2</sup>/day as a continuous regimen, capecitabine 2510 mg/m<sup>2</sup>/day as an intermittent regimen, and capecitabine 1657 mg/m<sup>2</sup>/day as an intermittent regimen given along with leucovorin at 30 mg p.o. b.i.d. (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.**

Study Outcome	Treatment Group		
	Capecitabine 1331 mg/m <sup>2</sup> /day Continuous Regimen n=39	Capecitabine 2510 mg/m <sup>2</sup> /day Intermittent Regimen n=34	Capecitabine 1657 mg/m <sup>2</sup> /day Intermittent Regimen + Leucovorin n=35
Response Rate	21%	24%	23%
No. of Responders	8	8	8
Median Time to Progression in Days (95% confidence interval)	127 (84 to 212)	230 (121 to 274)	165 (87 to 174)

### 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/m<sup>2</sup>/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/m<sup>2</sup> of leucovorin and 425 mg/m<sup>2</sup> of 5-FU, both administered daily for five days, in a four-week cycle.

Table 2 summarizes the efficacy data for both trials and the pooled data. All data provided are as calculated by the Independent Review Committee (IRC) for each trial. Both randomized trials and the pooled analysis detected no significant difference in survival for capecitabine compared with 5-FU plus leucovorin. The pooled median survival rates for the two treatment groups were nearly identical. The response rates in one trial (17), and the pooled data (18), indicate a significant difference in favour of capecitabine. The pooled response rates were 22.4% for capecitabine compared with 13.2% for 5-FU plus leucovorin (p≤0.0001). There was no significant difference in median time to progression.

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

Study Outcome	Treatment Group		
	Capecitabine	5-FU + LV	p-value
<i>Trial SO14796 (16)</i>	n=301	n=301	
Survival (median)	13.2 months	12.1 months	p=0.33
Response Rate % (CR + PR)	18.9 (1 + 56)	15 (2 + 43)	p>0.05
Time to Progression (median)	5.2 months	4.7 months	p=0.17
<i>Trial SO14695 (17)</i>	n=302	n=303	
Survival (median)	12.5 months	13.3 months	log-rank p=0.97
Response Rate % (CR + PR)	25.8 (1 + 77)	11.6 (1 + 34)	X <sup>2</sup> p=0.005
Time to Progression (median)	4.3 months	4.7 months	log-rank p=0.72
<i>Pooled Data (18)</i>	n=603	n=604	
Survival (median)	12.9 months	12.8 months	p>0.05
Response Rate %	22.4	13.2	p<0.0001
Time to Progression (median)	4.6 months	4.7 months	p>0.05

Note: CR, complete response; PR, partial response.

#### *Adverse effects*

Table 3 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).

**Table 3. Most frequent adverse effects leading to dose reduction and/or treatment interruption.**

Adverse Event	Study Group				p value (ref)
	Capecitabine n=603		5-FU + LV n=604		
Diarrhea	48%		58%		p<0.001 (18)
Nausea	38%		47%		p<0.001 (18)
Stomatitis	All Grades 24% (17)	Grade3/4 2.0% (18)	All Grades 62% (17)	Grade 3/4 14.7% (18)	p<0.001 (18)
Alopecia	6%		21%		p<0.001 (18)
Neutropenia leading to infection or sepsis	2.2%		21.1%		p<0.05 (18)
Hospitalization for treatment-related adverse effects	11.6%		18%		p=0.002 (18)
Patient required dose modification due to adverse effects	34%		42%		p<0.004 (18)
Median time to dose reduction	2.5 months		1.2 months		p=NR (18)
Grade 3 Hand-Foot syndrome	17%		1%		p=NR (18)
Patient required to withdraw due to adverse treatment effects	9.6%		6.7%		P=NS (19)

NR, not reported; NS, not significant.

**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 re-treatment 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 4. Response rates by prior 5-FU-based adjuvant chemotherapy.**

Subgroup	Trial SO14796 (16)		Trial SO14695 (17)	
	Capecitabine (N=301)	5-FU + LV (N=301)	Capecitabine (N=302)	5-FU + LV (N=303)
<i>Prior adjuvant chemotherapy</i>				
Number of patients	56	41	85	110
Response rate	21.0%	11.1%	21.2%	8.2%
<i>No prior adjuvant chemotherapy</i>				
Number of patients	245	260	217	193
Response rate	28.0%	19.1%	26.3%	19.7%

**V. INTERPRETIVE SUMMARY**

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.

## VI. ONGOING TRIALS

The PDQ<sup>®</sup> database was searched on July 2, 2003 for records of ongoing and recently closed phase II and III trials using capecitabine alone or in combination with other drugs. The protocol ID of the trials, a brief description including projected or actual accrual, and the trials' current status are all detailed in Table 5.

**Table 5. Ongoing trials.**

<b>Protocol ID</b>	<b>Description</b>	<b>Status</b>
<b>Roche-ML 16323</b>	<p><b>Phase II study of capecitabine and irinotecan in patients with locally advanced or metastatic colorectal cancer.</b> (summary last modified June 2002)</p> <ul style="list-style-type: none"> <li>• This is a multicentre study</li> <li>• Projected accrual is 14-50 patients.</li> <li>• Pharmaceutical sponsorship [Hoffmann-La Roche, Inc.]</li> </ul>	<ul style="list-style-type: none"> <li>• recruiting</li> </ul>
<b>SWOG-S0030</b>	<p><b>Phase II study of capecitabine in elderly patients with unresectable metastatic or recurrent colorectal cancer.</b> (summary last modified February 2003)</p> <ul style="list-style-type: none"> <li>• This is a multicentre study</li> <li>• Patients are stratified according to age (70 and over vs. 18 to 59)</li> <li>• A total of 80 patients (60 patients aged 70 and over, 20 patients aged 18 to 59) will be accrued for this study</li> <li>• Southwest Oncology Group sponsorship</li> </ul>	<ul style="list-style-type: none"> <li>• recruiting</li> </ul>

<p><b>NCCTG-N9945, NSABP-CI-66</b></p>	<p><b>Phase II study of hepatic arterial infusion with floxuridine and dexamethasone followed by systemic therapy with oxaliplatin and capecitabine in patients with surgically resected liver metastases from primary colorectal carcinoma.</b> (summary last modified February 2003)</p> <ul style="list-style-type: none"> <li>• This is a multicentre study</li> <li>• A total of 15-75 patients will be accrued for this study within 9 months-3.25 years</li> <li>• North Central Cancer Treatment Group and National Surgical Adjuvant Breast and Bowel Project sponsorship</li> </ul>	<ul style="list-style-type: none"> <li>• recruiting</li> </ul>
<p><b>SWS-SAKK-41/99, EU-99026</b></p>	<p><b>Phase I/II study of capecitabine and oxaliplatin in patients with chemotherapy naive or thymidylate synthase inhibitor pretreated unresectable, advanced or metastatic colorectal cancer</b> (summary last modified July 2000)</p> <ul style="list-style-type: none"> <li>• This is a dose escalation, multicentre study of capecitabine</li> <li>• Approximately 18 patients will be accrued for phase I of the study and a total of 27-68 patients (14-25 thymidylate synthase inhibitor pretreated patients and 13-43 chemotherapy naive patients) will be accrued for phase II of the study</li> <li>• Swiss Institute for Applied Cancer Research sponsorship</li> </ul>	<ul style="list-style-type: none"> <li>• closed</li> </ul>
<p><b>SWS-SAKK-41/00, EU-20141</b></p>	<p><b>Phase II randomized multicentre trial investigating capecitabine and irinotecan as first-line therapy in patients with advanced or metastatic colorectal cancer</b> (summary last modified December 2002)</p> <ul style="list-style-type: none"> <li>• This is a randomized, multicentre study</li> <li>• Projected accrual is 28-74 patients (14-37 per treatment arm).</li> <li>• Swiss Institute for Applied Cancer Research sponsorship</li> </ul>	<ul style="list-style-type: none"> <li>• closed</li> </ul>
<p><b>ROCHE-SO14695, NCI-V97-1320</b></p>	<p><b>Phase III open label randomized study comparing capecitabine and fluorouracil in combination with leucovorin calcium as first line chemotherapy in patients with advanced and/or metastatic colorectal carcinoma</b> (summary last modified May 1998)</p> <ul style="list-style-type: none"> <li>• This is an open label, multicentre, multinational, randomized, parallel group study</li> <li>• This study will accrue approximately 524 evaluable patients or a maximum of 604 randomized patients, whichever occurs first</li> <li>• Pharmaceutical sponsorship [Hoffmann-La Roche, Inc.]</li> </ul>	<ul style="list-style-type: none"> <li>• closed</li> </ul>
<p><b>ROCHE-M66001</b></p>	<p><b>Phase III randomized study of adjuvant capecitabine versus fluorouracil and low-dose leucovorin calcium in chemotherapy naive patients with previously resected stage III colon cancer</b> (summary last modified December 2001)</p> <ul style="list-style-type: none"> <li>• This is a randomized, open-label, multicentre study. Patients are randomized to one of two treatment arms</li> <li>• A total of 1,956 (978 per treatment arm) will be accrued for this study within 2.3 years</li> <li>• Pharmaceutical sponsorship [Hoffmann-La Roche, Inc.]</li> </ul>	<ul style="list-style-type: none"> <li>• closed</li> </ul>

<p><b>London Regional Cancer Centre (Dr. M. Vincent, PI)</b></p>	<p><b>A Phase I/II study of capecitabine (Xeloda®) in patients with advanced colorectal cancer not known to derive survival benefits from combination therapy with 5-FU and irinotecan.</b></p> <ul style="list-style-type: none"> <li>• Non-randomized parallel phase I/II study of 5 subgroups of patients</li> <li>• Projected accrual is 175 patients (35 per sub-group)</li> <li>• Pharmaceutical sponsorship [Hoffman-La Roche, Inc.]</li> </ul>	<ul style="list-style-type: none"> <li>• recruiting</li> </ul>
<p><b>Roche NO16968</b></p>	<p><b>An open-label randomized phase III study of intermittent oral capecitabine in combination with intravenous oxaliplatin (q3w) ("XELOX") versus fluorouracil/leucovorin as adjuvant therapy for patients who have undergone surgery for colon carcinoma, AJCC/UICC stage III (Dukes stage C).</b></p> <ul style="list-style-type: none"> <li>• This is a randomized controlled trial</li> <li>• A total of 1850 patients will be accrued for this study</li> <li>• Pharmaceutical sponsorship [Hoffman-La Roche, Inc.]</li> </ul>	<ul style="list-style-type: none"> <li>• recruiting</li> </ul>
<p><b>Roche NO16967A</b></p>	<p><b>An open-label randomized phase III study of intermittent oral capecitabine in combination with intravenous oxaliplatin (q3w) ("XELOX") versus bolus and continuous infusion fluorouracil/intravenous leucovorin with intravenous oxaliplatin (q2w) ("FOLFOX4") as second-line treatment for patients with metastatic colorectal cancer who have received prior CPT-11 plus 5-FU+LV as first-line therapy.</b></p> <ul style="list-style-type: none"> <li>• This is a randomized controlled trial</li> <li>• A total of 610 patients will be accrued for this study</li> <li>• Pharmaceutical sponsorship [Hoffman-La Roche, Inc.]</li> </ul>	<ul style="list-style-type: none"> <li>• recruiting</li> </ul>
<p><b>Roche</b></p>	<p><b>An open-label randomized phase III study of intermittent oral capecitabine in combination with intravenous oxaliplatin (q3w) ("XELOX") versus bolus and continuous infusion fluorouracil/intravenous leucovorin with intravenous oxaliplatin (q2w) ("FOLFOX4") as first-line treatment for patients with metastatic colorectal cancer.</b></p> <ul style="list-style-type: none"> <li>• A randomized controlled trial</li> <li>• A total of 1000 patients will be accrued for this trial</li> <li>• Pharmaceutical sponsorship [Hoffman-La Roche, Inc.]</li> </ul>	<ul style="list-style-type: none"> <li>• recruiting</li> </ul>
<p><b>Pharmacia CPTAIV-0020-411</b></p>	<p><b>A randomized, multi-center phase III trial of irinotecan in combination with three different methods of administration of fluoropyrimidine: Infusional 5-FU (FOLFIRI), bolus 5-FU (day 1 &amp; 8), and oral capecitabine (day 1-14); with celecoxib versus placebo as first line treatment for patients with metastatic colorectal cancer.</b></p> <ul style="list-style-type: none"> <li>• A randomized, multicentre trial</li> <li>• A total of 900 patients will be accrued for this trial</li> <li>• Pharmaceutical sponsorship: Pfizer-Pharmacia</li> </ul>	<ul style="list-style-type: none"> <li>• recruiting</li> </ul>

Notes: AJCC/UICC, American Joint Committee on Cancer/ Union Internationale Contre le Cancer; w, week(s).

## **VII. DOSING AND SCHEDULING**

As determined from the randomized phase II trial summarized previously (11), the recommended dose of capecitabine is 2510 p.o. mg/m<sup>2</sup>/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<sup>®</sup> 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.

## **VIII. 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.

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

### **Draft Recommendations**

Based on the evidence described above, the Gastrointestinal Cancer DSG drafted the following recommendations:

#### ***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.

#### ***Draft Recommendations***

- 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.

#### ***Practitioner Feedback***

Based on the evidence and the draft recommendations presented above, feedback was sought from Ontario clinicians.

#### ***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.**

Item	Number (%)*		
	Rated “strongly agree” or “agree”	Rated “neither agree nor disagree”	Rated “disagree” or “disagree strongly”
The rationale for developing a CPG, as stated in the “Choice of Topic” section of the report, is clear.	27(96)	0(0)	1(4)
There is a need for a CPG on this topic.	23(85)	2(7)	2(7)
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.	22(83)	5(19)	0(0)
I agree with the methodology used to summarize the evidence included in this PGIP report.	27(100)	0(0)	0(0)
The results of the trials described in the PGIP report are interpreted according to my understanding of the data.	25(93)	2(7)	0(0)
The DRs in this report are clear.	24(89)	2(7)	1(4)
I agree with the DRs as stated.	21(78)	6(22)	0(0)
The DRs are suitable for the patients for whom they are intended.	23(86)	3(11)	1(4)
The DRs are too rigid to apply to individual patients.	1(4)	5(19)	20(75)
When applied, the DRs will produce more benefits for patients than harms.	16(60)	10(37)	1(4)
The PGIP report presents options that will be acceptable to patients.	23(85)	3(11)	1(4)
To apply the DRs will require reorganization of services/care in my practice setting. [2(7)†]	3(11)	2(7)	20(75)
To apply the DRs will be technically challenging. [1(4)†]	3(11)	3(11)	20(75)
The DRs are too expensive to apply. [1(4)†]	3(11)	8(30)	14(52)
The DRs are likely to be supported by a majority of my colleagues.	21(78)	5(19)	1(4)
If I follow the DRs, the expected effects on patient outcomes will be obvious.	7(26)	18(67)	2(7)
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). [5(19)†]	10(37)	10(37)	2(8)
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). [4(15)†]	11(41)	10(37)	1(4)
This PGIP report should be approved as a practice guideline.	18(66)	6(22)	3(11)
If this PGIP report were to become a practice guideline, how likely would you be to make use of it in your own practice?	Rated “likely” or “very likely”	Rated “unsure”	Rated “not at all likely” or “unlikely”
	19(71)	4(15)	4(15)

DR – draft recommendation, CPG – clinical practice guideline, PGIP – practice-guideline-in-progress

\* 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 1<sup>st</sup> 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-fluouracil 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.

## **X. PRACTICE GUIDELINE**

This practice guideline reflects the integration of the draft recommendations with feedback obtained from the external review process. It has been approved by the Gastrointestinal Cancer DSG and the PGCC.

### **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-fluorouracil plus leucovorin calcium with either irinotecan or oxaliplatin (refer to 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/m<sup>2</sup>/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, ECOG performance status  $\leq 1$ , 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.

### **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 these treatments may be more beneficial than monotherapy for certain patient subgroups, such as the elderly and the frail.

In another guideline (PG #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. This 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 this population is underrepresented in trials, it is not possible to adequately assess the risks and benefits of any regimen for these 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 Combined with 5-fluorouracil and Leucovorin as First-Line Therapy for Metastatic Colorectal Cancer.*
- #2-17: *Use of Raltitrexed (Tomudex™) 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].

## **XI. JOURNAL REFERENCE**

Publication in progress.

## **XII. ACKNOWLEDGEMENTS**

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For a complete list of the Gastrointestinal Cancer Disease Site Group members and the Practice Guidelines Coordinating Committee members, please visit the Cancer Care Ontario Web site at [http://www.cancercare.on.ca/access\\_PEBC.htm](http://www.cancercare.on.ca/access_PEBC.htm).

## REFERENCES

1. Benson AB, 3rd. Regional and systemic therapies for advanced colorectal carcinoma: randomized clinical trial results. *Oncology* 1998;12:28-34.
2. Bajetta E, Carnaghi C, Somma L, Stampino CG. A pilot safety study of capecitabine, a new oral fluoropyrimidine, in patients with advanced neoplastic disease. *Tumori* 1996;82:450-2.
3. Budman DR, Meropol NJ, Reigner B, Creaven PJ, Lichtman SM, Berghorn E, et al. Preliminary studies of a novel oral fluoropyrimidine carbamate: capecitabine. *J Clin Oncol* 1998;16:1795-802.
4. Ignoffo RJ. Novel oral fluoropyrimidines in the treatment of metastatic colorectal cancer. *Am J Health Syst Pharm* 1999;56:2417-28.
5. Diasio RB. Improving fluorouracil chemotherapy with novel orally administered fluoropyrimidines. *Drugs* 1999;58:119-26.
6. Kaye SB. Oral tumoractivated chemotherapy--an introduction. *Oncology* 1999; 57 Suppl 1:1.
7. Lamont EB, Schilsky RL. The oral fluoropyrimidines in cancer chemotherapy. *Clin Cancer Res* 1999;5:2289-96.
8. Pazdur R, Hoff PM, Medgyesy D, Royce M, Brito R. The oral fluorouracil prodrugs. *Oncology* 1998;12:48-51.
9. Von Hoff DD. Promising new agents for treatment of patients with colorectal cancer. *Semin Oncol* 1998;25:47-52.
10. Verweij J. Rational design of new tumoractivated cytotoxic agents. *Oncology* 1999;57 Suppl 1:9-15.
11. Van Cutsem E, Findlay M, Osterwalder B, Kocha W, Dalley D, Pazdur R, et al. Capecitabine, an oral fluoropyrimidine carbamate with substantial activity in advanced colorectal cancer: results of a randomized phase II study. *J Clin Oncol* 2000;18:1337-45.
12. Ishikawa T, Utoh M, Sawada N, Nishida M, Fukase Y, Sekiguchi I, et al. Tumor selective delivery of 5-fluorouracil by capecitabine, a new oral fluoropyrimidine carbamate, in human cancer xenografts. *Biochem Pharmacol* 1998;55:1091-7.
13. Schuller J, Cassidy J, Dumont E, Roos B, Durston S, Banken L, et al. Preferential activation of capecitabine in tumor following oral administration to colorectal cancer patients. *Cancer Chemother Pharmacol* 2000;45:291-7.
14. Jonker D, Earle C, Kocha W, Moore M, Maroun J, Zuraw L, and the Gastrointestinal Cancer Disease Site Group. Use of irinotecan combined with 5-fluorouracil and leucovorin as first-line therapy for metastatic colorectal cancer. *Curr Oncol* 2001;8:60-8.
15. 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;13:502-12.
16. Van Cutsem E, Twelves C, Cassidy J, Allman D, Bajetta E, Boyer M, et al. Oral capecitabine compared with intravenous fluorouracil plus leucovorin in patients with metastatic colorectal cancer: results of a large phase III study. *J Clin Oncol* 2001;19(21):4097-106.  
Update of:  
Twelves C, Harper P, Van Cutsem E, Thibault A, Shelygin YA, Burger HU, et al. A phase III trial (S014796) of Xeloda™ (capecitabine) in previously untreated advanced/metastatic colorectal cancer [abstract]. *Proc Ann Meet Am Soc Clin Oncol* 1999;18:263a. Abstract 1010.
17. Hoff M, Ansari R, Batist G, Cox J, Kocha W, Kuperminc M, et al. Comparison of Oral Capecitabine Versus Intravenous Fluorouracil Plus Leucovorin as First-Line Treatment in 605 Patients With Metastatic Colorectal Cancer: Results of a Randomized Phase III Study. *J Clin Oncol* 2001; 19(8):2282-92.  
Update of:

- Cox JV, Pazdur R, Thibault A, Maroun J, Weaver C, Jahn MW, et al. A phase III trial of Xeloda™ (capecitabine) in previously untreated advanced/metastatic colorectal cancer [Abstract]. *Proc Ann Meet Am Soc Clin Oncol* 1999:Abstract 1016.
18. Twelves C, on behalf of the Xeloda Colorectal Cancer Group. Capecitabine as first-line treatment in colorectal cancer: pooled data from two large, phase III trials. *Eur J Cancer* 2002;38:S15-S20.  
Update of:  
Hoff PM. Capecitabine as first-line treatment for colorectal cancer: integrated results of 1207 patients from 2 randomized, phase III studies [abstract]. *Ann Oncol* 2000;11 (Suppl 4):60. Abstract 263.
  19. Cassidy J, Twelves C, Van Cutsem E, Hoff P, Bajetta E, Boyer M, et al. First-line oral capecitabine therapy in metastatic colorectal cancer: a favorable safety profile compared with intravenous 5-fluorouracil/leucovorin. *Ann Oncol* 2002;13:566-75.  
Update of:  
Cassidy J, Twelves C. Effective dose-modification scheme for the management of toxicities with capecitabine therapy: data from metastatic colorectal cancer phase III trials. Capecitabine CRC Study Group [abstract]. *Ann Oncol* 2000;11 (Suppl 4):62. Abstract 271.
  20. Twelves C, Wong A, Nowacki MP, Cassidy J, Cervantes A, Koralewski P, et al. Improved safety results of a phase III trial of capecitabine vs bolus 5-FU/leucovorin (LV) as adjuvant therapy for colon cancer (the X-ACT Study) [abstract]. *Proc Ann Meet Am Soc Clin Oncol* 2003:Abstract 1182.
  21. Hoff P, Abbruzzese JL, Medgyesy D, Thomas M, Carter S. A phase II study of Xeloda (capecitabine) in patients with metastatic colorectal cancer demonstrating progression on 5-FU therapy [abstract]. *Proc Ann Meet Am Soc Clin Oncol* 2000;19:256a. Abstract 993.
  22. Twelves C, Boyer M, Findlay M, Cassidy J, Weitzel C, Barker C, et al. Capecitabine (Xeloda™) improves medical resource use compared with 5-fluorouracil plus leucovorin in a phase III trial conducted in patients with advanced colorectal carcinoma. *Eur J Cancer* 2001; 37:597-604.
  23. Reigner B, Verweij J, Dirix L, Cassidy J, Twelves C, Allman D, et al. Effect of food on the pharmacokinetics of capecitabine and its metabolites following oral administration in cancer patients. *Clin Cancer Res* 1998;4:941-8.
  24. Reigner B, Clive S, Cassidy J, Jodrell D, Schulz R, Goggin T. Influence of the antacid Maalox on the pharmacokinetics of capecitabine in cancer patients. *Cancer Chemother Pharmacol* 1999;43:309-15.
  25. Judson IR, Beale PJ, Trigo JM, Aherne W, Crompton T, Jones D, et al. A human capecitabine excretion balance and pharmacokinetic study after administration of a single oral dose of <sup>14</sup>C-labelled drug. *Invest New Drugs* 1999; 17:49-56.
  26. Twelves C, Glynne-Jones R, Cassidy J, Schuller J, Goggin T, Roos B, et al. Effect of hepatic dysfunction due to liver metastases on the pharmacokinetics of capecitabine and its metabolites. *Clin Cancer Res* 1999; 5:1696-702.

## Appendix 1. Dosage and dose modification.

### Dosage and administration

The recommended dose of capecitabine is 1250 mg/m<sup>2</sup> administered twice daily (morning and evening; equivalent to 2500 mg/m<sup>2</sup> 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.

Dose level 1250 mg/m <sup>2</sup> twice daily		Number of tablets administered in the morning		Number of tablets administered in the evening	
Body surface area (m <sup>2</sup> )	Dose per administration	150 mg	500 mg	150 mg	500 mg
≤ 1.25	1500	0	3	0	3
1.26 – 1.37	1650	1	3	1	3
1.38 – 1.51	1800	2	3	2	3
1.52 – 1.65	2000	0	4	0	4
1.66 – 1.77	2150	1	4	1	4
1.78 – 1.91	2300	2	4	2	4
1.92 – 2.05	2500	0	5	0	5
2.06 – 2.17	2650	1	5	1	5
≥ 2.18	2800	2	5	2	5

### 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.

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

\* 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.

Source: Xeloda [Product Monograph]. Mississauga, Ontario: Hoffman-La Roche Limited; 2002.