Guidelines for the use of Capecitabine in Metastatic Colorectal Cancer
QEII Health Sciences Centre/Cancer Care Nova Scotia

**Guideline Questions**

- Does capecitabine provide response, improvement in time to disease progression, lengthen duration of response and prolong survival in patients with previously untreated metastatic colorectal cancer (MCRC) over standard therapy?
- Should this oral agent be offered to a selected patient population with MCRC?
- Does the magnitude of benefit in terms of toxicity and quality of life (QOL) warrant the routine use of this agent?
- Is there sufficient evidence to recommend the use of capecitabine in place of protracted infusions of 5-Fluorouracil (5-FU) after failure of 5-FU/irinotecan based therapy?

**Objectives**

- To make recommendations regarding the use of capecitabine in patients with MCRC.

**Outcome Measures**

- To review response, time to disease progression and survival.
- Toxicity and QOL are considered.

**Quality of Evidence**

- Phase I, Phase II and Phase III studies in colorectal cancer have been reported.
  - Phase I studies determined dose in patients with advanced metastatic cancer (Level V evidence) (Published)
  - Phase II randomized study (34 patients) evaluated three dosing schedules in patients with advanced colorectal cancer (Level II-III Evidence) (Published).
  - Two Phase III randomized, controlled, multicentre studies have been reported. The first trial (Study 1 - Cox et al 1999) randomized previously untreated MCRC patients in USA, Canada, Brazil and Mexico, to capecitabine vs 5-FU/leucovorin (LV) (Mayo regimen). The second trial (Study 2 - Twelves et al 1999) randomized previously untreated MCRC patients in Western Europe, Russia, Israel, Taiwan and Australia to capecitabine vs 5-FU/LV. (Level II evidence) (Published in abstract form).
  - One Phase II study (22 patients) of capecitabine in MCRC patients demonstrating progression on 5-FU bolus chemotherapy (Level V evidence) (Published in abstract form).
  - An integrated report of the results of the two Phase III trials was published in abstract form and presented at the European Society Medical Oncology (ESMO) meeting in 2000.
  - A medical resource abstract was published and presented at the European Cancer Conference (ECCO) 1999 in previously untreated advanced/metastatic colorectal cancer patients.
  - No Quality of Life (QOL) assessments have been published.

**Benefit**

- The end point of overall response (OR) rate, median time to progression (TTP) and median survival was reported in both Phase III trials. The OR rate was statistically superior in the capecitabine arm of both trials with very similar values. The results reported for capecitabine (Study 1 - 21%, Study 2 - 21%) versus 5-FU/LV (Study 1 - 11%, Study 2 - 14%) demonstrating superiority for the capecitabine arm.
There did not appear to be any difference in the median TTP (4.6 and 4.7 months) or median survival (12.9 months in each group).

- Response rates to capecitabine were superior to those for 5-FU/LV in patients with liver metastases (25.2% vs 17.1%) and lung metastases (29.7% vs 8%). In those patients who had received prior adjuvant chemotherapy (completed at least 6 months before enrollment), the response rate was 15.3% and 14.5% for capecitabine and 5.5% and 4.4% for 5-FU/LV. Stable disease rates were very similar for all groups in both studies with 49% and 52% for capecitabine and 52% and 52% (Study 1 and 2, respectively) for 5-FU/LV.

- A Phase II abstract reported on the experience of the use of capecitabine in patients with MCRC who had progressed on initial 5-FU based therapy. Of the twenty two patients enrolled, no objective responses were noted but a number of patients (32%) experienced disease stabilization for ≥ 6 cycles of capecitabine therapy.

**Adverse Effects**

- Capecitabine was associated with a statistically significant lower incidence of diarrhea, stomatitis, nausea and alopecia compared to 5-FU/LV. Grade 3 / 4 stomatitis, severe neutropenia and leukopenia were significantly less frequent in the capecitabine arm.

- Capecitabine treatment led to a higher incidence of hand foot syndrome (HFS), however, only 2 patients were hospitalized for HFS and all other cases were managed with treatment interruption or dose reduction. Patients treated with 5-FU/LV experienced significantly more Grade 3 / 4 stomatitis (14.7% vs 2.2%) and neutropenia (23.1% vs 2.4%) with only a small number experiencing neutropenic fever (3.4% vs 0.2%). Treatment related hospitalization rates were significantly lower in patients receiving capecitabine (11.6% vs 18%) compared to 5-FU/LV.

**Evidence Based Recommendation**

Currently, treatment for MCRC is in evolution. Limited progress has been made over the past 40 years since the introduction of 5-FU. Intervention with 5-FU-based chemotherapy has been shown to prolong survival by approximately 6 months. Modulation of 5-FU has improved response rates but not overall survival. Infusional 5-FU has demonstrated a notable but modest benefit. New agents, such as irinotecan, (topoisomerase I inhibitor) have demonstrated the value of second line therapy in patients with MCRC who have progressed following first line therapy. The introduction of irinotecan to first line combination therapy has resulted in a statistically significant but modest improvement in median overall survival when compared to 5-FU/LV alone. The benefits are most evident in those patients with an ECOG performance status of 0 to 1. For many patients, particularly those with a poor performance status unable to tolerate an irinotecan/5-FU/LV combination regimen, an orally administered well tolerated agent such as capecitabine would be a reasonable treatment option. Two Phase III trials comparing capecitabine to 5-FU/ LV have demonstrated improvements in response rates and toxicity profiles. The response rates observed in the Phase III trials in patients have been consistent with the published literature.

Capecitabine may “mimic” a continuous infusion of 5-FU and, therefore, the toxicity profile is very different from modulated bolus 5-FU. Most notably, patients in the capecitabine groups experienced significantly less diarrhea, stomatitis, nausea and alopecia of any grade compared to the 5-FU/LV combination, while the HFS was more frequent with capecitabine. The TTP and overall survival was similar in both of the Phase III trials. In situations where previously untreated MCRC patients have documented evidence of disease, or have progressed after a 6 month period following adjuvant therapy, capecitabine would be a reasonable option in patients not able to tolerate the combination therapy of irinotecan/5-FU/LV. Unfortunately, there is no data presently available on the use of capecitabine post irinotecan/5-FU/LV therapy. Data supporting infusional 5-FU post 5-FU/LV bolus is not compelling. There is little confirmatory data to support the efficacy of protracted IV infusions of 5-FU in patients with colorectal cancer that is refractory to 5-FU bolus with or without leucovorin. Trials are underway to evaluate the combination of capecitabine and irinotecan.

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Background

Colorectal cancer (CRC) is the third most common cancer among both men and women in Canada. It is estimated that in 2000, 17,000 new cases of colorectal cancer will be diagnosed in Canada. The incidence and mortality rates have declined steadily over the past decade and a half, the rate of decline being more pronounced amongst women.

The median age at diagnosis of colorectal cancer is approximately 60-65 years old. Curative surgery is possible for patients who present with early stage disease. Up to 30-40% of patients present with metastatic disease. Approximately 50-60% of patients with surgically curable disease will eventually develop metastases. Overall the 5 year survival of colorectal cancer is approximately 50%. The 5 year survival rate is 5% or less for patients with metastatic or advanced disease.

Standard Treatment

For the last 40 years, 5-Fluorouracil (5-FU) has been the mainstay of treatment for advanced and MCRC. Several studies have explored the use of different 5-FU regimens. Additional therapeutic benefit may be obtained from 5-FU regimens which include schedule dependent modulation (i.e. continuous vs bolus) or modulation with another agent. The mode of action of the bolus injection may correspond to high peak drug levels and incorporation of 5-FU metabolites into DNA and RNA. The continuous infusion of 5-FU results in prolonged inhibition of the enzyme, thymidylate synthase which may be the principle anti-neoplastic mechanism of action.

Modulation of 5-FU with folinic acid (leucovorin-LV) has increased the response rate of 5-FU bolus from 11% to approximately 23% without impact on overall survival.

In a recent meta-analysis (Piedbois et al 1998) tumor response rates were significantly higher in patients given 5-FU by continuous infusion compared to 5-FU bolus (22% vs 14%). A marginal, but significant increase in overall survival was also evident in the continuous infusion arm. The median survival times were 12.1 months for the continuous infusion vs 11.3 months for the bolus administration. Some arms of the trial included in this meta-analysis were not considered as they could not be directly compared to any other treatment arm. A subgroup analysis of two small trials comparing infusional versus bolus 5-FU with LV demonstrated no difference in terms of tumor response or survival compared to modulated 5-FU bolus. These were small patient groups.

The on-going question still exists whether continuous infusion of modulated 5-FU is superior to infusional unmodulated 5-FU and to modulated bolus 5-FU. De Gramont et al (1997) found an increased response rate but no difference in survival comparing modulated continuous infusion 5-FU versus the standard "Mayo" bolus 5-FU and LV. A number of European trials have concluded that response rates with modulated infusional 5-FU regimens are higher than modulated bolus 5-FU regimens with no differences in overall survival.

In 1997, a water soluble semisynthetic derivative of camptothecin – irinotecan, (CPT-11) was approved by the Health Protection Branch (HPB) in Canada as a second line agent for use in patients refractory to 5-FU based therapy. The first Phase III trial (Cunningham et al 1999) compared irinotecan to best supportive care and revealed a statistically significant improvement in median survival. The second Phase III (Van Cutsem et al 1999) trial randomized patients to irinotecan versus one of three infusional 5-FU regimens. Patients treated with irinotecan lived significantly longer than patients on 5-FU. Median progression free survival was longer with irinotecan (4.2 vs 2.9 months) versus 5-FU.

With the introduction of a new second line agent in the treatment of advanced colorectal cancer, trials explored the benefits of irinotecan as a component of initial therapy. Saltz et al (2000) recently reported the results of a large colorectal trial which enrolled 683 patients and randomly assigned them to one of three arms. The assignments included a combination of irinotecan, 5-FU and LV weekly for four weeks every six weeks; 5-FU and LV daily for five consecutive days every four weeks; or irinotecan alone weekly for four weeks every six weeks. The trial concluded that weekly treatment with irinotecan plus 5-FU and LV was superior to standard 5-FU and LV for metastatic colorectal cancer in terms of progression-free and overall survival.
survival. A second trial reported by Douillard et al (2000) confirmed the beneficial results of irinotecan combined with 5-FU and LV.

The goals of systemic treatment for patients with advanced colorectal cancer are palliative. Trials involving the use of oral 5-FU agents or prodrugs have demonstrated activity which “mimics” a prolonged continuous infusion of 5-FU. As previously described, continuous infusions of 5-FU have lead to a modest but significant increase in overall survival. 5-FU/LV regimens were previously considered to be standard therapy for patients with advanced colorectal cancer. Trials compared a standard 5-FU/LV regimen to a novel oral agent, capecitabine. It is a new prodrug in the fluouropyrimidine class. 5-FU is not suitable for oral administration due to variations in absorption, metabolism and inactivation. Capecitabine was rationally designed to be rapidly and extensively absorbed as an intact molecule which is metabolized to 5-FU in three steps; to 5-DFCR by hepatic carboxylesterase, (primarily in the liver) to 5-DFUR by cytidine deaminase (in tumor cells and liver) and to 5-FU by thymidine phosphorylase which is concentrated in tumor cells.

Capecitabine does not contain dehydropyrimidine dehydrogenase (DPD) inhibitory activity. The need for thymidine phosphorylase for activation may lead to enhanced tumor selectivity as a higher level of this enzyme is evident in tumors compared to normal tissues. Capecitabine (Xeloda®) was approved originally for breast cancer by the Therapeutic Products Programme (TPP) (Health Canada) in 1998. The approval for the indication of first line treatment of patients with MCRC was granted in July 2000.

**Clinical Studies**

On-going interest in continuous infusion 5-FU has dominated the colorectal cancer field for many years. The results of the meta-analysis in 1998 suggesting benefits for infusional 5-FU has sparked renewed interest in this regimen. Due to the short half-life of 5-FU, optimal anti-tumor response rates are only achieved by continuous infusions which can be difficult to deliver in many settings. The need for ambulatory pump programs, intravenous access devices, risk for infection, venous thrombosis, and appropriateness for individual patients has lead to restricted use of such a regimen. Strategies have led to the development of agents to selectively deliver anticancer drugs to tumors. Prodrug activation by enzymes located in tumor tissues has been used as the major target for drug development. Capecitabine, a prodrug which is not cytotoxic becomes effective only after conversion to the active drug, 5-FU. This process occurs selectively in tumors through a cascade of three enzymes. In the case of human colon cancer and breast cancer xerograft models, capecitabine produced higher levels of 5-FU in tumors and was found to be more effective than 5-FU and other fluoropyrimidines. The advantages of capecitabine may translate into improving the therapeutic index, greater anti-tumor activity with reduced drug levels in normal tissues, thereby reducing systemic toxicity.

Phase I clinical trials of capecitabine have been performed with a variety of dosing schedules with and without LV. A continuous dosing schedule as well as intermittent dosing were determined to be feasible. Anti-tumor activity was observed with the regimens studied.

A Phase II trial evaluated three capecitabine dosing schedules in a randomized fashion. One hundred and nine patients were randomized to one of three possible arms. The three schedules included a 1331 mg/m²/day (Arm A) twice a day continuous dosing, 2510 mg/m²/day (Arm B) twice a day intermittent (2 weeks on/one week off) dosing and a dose of 1657 mg/m²/day (Arm C) plus oral LV as an intermittent schedule. Tumor responses were 21%, 24% and 23% respectively. The median time to progression was 127 days (Arm A), 230 days (Arm B) and 165 days (Arm C). Approximately 30% of patients in each arm had previous adjuvant chemotherapy. The toxicity profile, particularly diarrhea and HFS, was worse in Arm C (capecitabine and LV). The addition of LV to the intermittent regimen required a reduction in the capecitabine dose intensity without improvement in response rates compared to bolus 5-FU/LV. From this data, the intermittent single agent regimen moved forward to Phase III clinical trials.

Two randomized, multicentre, open label Phase III trials were undertaken to compare capecitabine to 5-FU/LV as first line treatment for MCRC. One trial was conducted in the Americas while the second enrolled patients in Europe, Australia, New Zealand, Israel and Taiwan. The two trials were identical in design and compared capecitabine (1250 mg/m² bid x 2 weeks followed by 1 week rest) vs the Mayo regimen (5-FU 425 mg/m²/LV 20 mg/m² IV bolus day 1-5 every 4 weeks). Each of the trials reported results separately in abstract form at the American Society of Clinical Oncology (ASCO) meeting in 1999 (see Figure 1).
An integrated analysis was performed and reported in abstract form. The demographic characteristics of patients in the two treatment groups were well balanced. The predominant metastatic site was the liver in almost three-quarters of patients in both treatment groups and the lungs in approximately one-third of each group. The primary end point was to assess equivalency of these two treatments. An independent review committee confirmed a statistically significant response rate in favour of capecitabine (21% vs 13% combined data) respectively. In patients who had received prior adjuvant treatment, the response to capecitabine was 15.3% and 14.5% versus 5.5% and 4.4% in the 5-FU/LV group (Study 1 and 2, respectively). Capecitabine was found to be more responsive than 5-FU/LV in patients with liver metastases (25.2% vs 17.1%) and lung metastases (29.7% vs 8%). The median TTP (4.6 months vs 4.7 months) was equivalent and median OS (12.9 months) the same.

The most common side effects including stomatitis, diarrhea, nausea and alopecia were significantly less with capecitabine. Only HFS was more common in patients receiving capecitabine and this cutaneous effect was managed with treatment interruption and dose reduction. Vomiting and fatigue was similar in the two groups. Grade 3 / 4 neutropenia was significantly more common with 5-FU/LV than with capecitabine (21.1% vs 2.2%). This resulted in a higher incidence of neutropenic fever, sepsis and associated hospitalizations. Hyperbilirubinaemia occurred more frequently in the capecitabine arm.

The only data available on the use of capecitabine post 5-FU based therapy was reported in an abstract by (Hoff et al 2000) at a recent ASCO meeting. Capecitabine was administered to twenty two MCRC patients who failed initial intravenous bolus 5-FU. No objective responses were observed. Of the 19 patients eligible and evaluable, six patients (32%) experienced disease stabilization for greater than 6 cycles of capecitabine therapy.

There is currently no data available on the use of capecitabine in place of protracted infusion of 5-FU after failure of irinotecan/5-FU/LV based therapy.
Approved Use

As a single agent in patients who have documented evidence of metastatic colorectal cancer, with an ECOG performance status of 0-2, who choose not to receive combination chemotherapy (5-FU/LV / irinotecan) and/or are unable to tolerate first line therapy. This includes:

- Patients who are chemotherapy naïve and are candidates for therapy.

Or

- Patients who have progressed 6 months after completion of adjuvant 5-FU/LV therapy and are candidates for treatment of metastatic disease.

Note: Special approval of capecitabine as a single agent for patients outside the approved use can be sought through the Request for Non-Formulary or Restricted Drug Process. Requests should be submitted in writing with specific references included. Guidelines will be updated and modifications made on the basis of published studies only.

Side Effects

The side effect profile is based on pooled data from Phase III colorectal cancer trials where patients were treated with 2500 mg/m²/day of capecitabine.

<table>
<thead>
<tr>
<th>Side Effects</th>
<th>CAPECITABINE</th>
<th>5-FU / Leucovorin</th>
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<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>49%</td>
<td>12%</td>
</tr>
<tr>
<td>Hand-Foot Syndrome</td>
<td>53%</td>
<td>17%</td>
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<tr>
<td>Nausea</td>
<td>38%</td>
<td>3%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>23%</td>
<td>3%</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>25%</td>
<td>2%</td>
</tr>
<tr>
<td>Haematologic Neutropenia</td>
<td>21%</td>
<td>0.7%</td>
</tr>
<tr>
<td>Haematologic Thrombocytopenia</td>
<td>20%</td>
<td>0.5%</td>
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<tr>
<td>Alopecia</td>
<td>6%</td>
<td>-</td>
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Dosing:

Hepatic Insufficiency – In patients with mild to moderate hepatic dysfunction, there were no clinically significant influences on the pharmacokinetic parameters of capecitabine and its metabolites. Patients with severe hepatic dysfunction have not been studied.

Coumadin Anticoagulants – Patients taking coumarin – derivative anticoagulants and capecitabine should be monitored for alterations in their coagulation parameters.

Dosing:

Renal Insufficiency – United States manufacturer warning:

Severe Renal Dysfunction (Cr Cl <30)
- Capecitabine is contraindicated. These patients had a high rate of Grade 3-4 adverse events and should not be treated.

Moderate Renal Dysfunction (Cr Cl 30-50ml/min)
- Dose reduction is required. These patients also had a high grade of 3-4 adverse events and should be given 75% doses.

Mild Renal Dysfunction (CrCl >50ml/min)
- Full doses can be used. These patients had slightly more adverse events and withdrawals but can be given 100% doses.
**Expected Patient Numbers**

**Cost**
Estimated cost/cycle for treatment of MCRC, with capecitabine based on a BSA of 1.7 m$^2$ is approximately $742.00.

Capecitabine _______ 30 _______ patients/year will be treated.

Drug          Estimated number of cycles/patient ____6____          Average cost/patient ____4500.00______

(according to pooled colorectal data the median duration of treatment was 139 days – approximately 6-7 cycles of therapy)

Approximate Drug Cost/year
Capecitabine = $135,000.00________

Current estimates from the Department of Health (DOH) suggest that 40% of the Nova Scotia population is covered by private drug insurance, 40% by public insurance and 20% non-insured. Based on these estimates, the approximate drug cost to the QEII Health Sciences Centre would be in the order of $27,000.00.

**Summary**

Capecitabine, a novel oral fluoropyrimidine, may mimic a continuous infusion of 5-FU. It is activated by thymidine phosphorylase which is present at significantly higher levels in tumor tissues than in healthy tissue, leading to a preferential conversion to 5-FU at the tumor site. The two Phase III trials reported a 21% response rate with capecitabine vs 13% OR with 5-FU/LV which is currently one of the standard regimens offered to patients with advanced MCRC. Approximately 50% of patients achieved tumor control with capecitabine. An interesting point to note is the response in patients who received prior adjuvant chemotherapy. The objective response rates were very different for the two regimens (15.3% and 14.5% for capecitabine and 5.5% and 4.4%, Study 1 and 2 respectively for 5-FU/LV). In these two studies, the primary endpoints included response rates which have determined that capecitabine is at least as good as the 5-FU/LV regimen. The safety profile reveals a statistically significant benefit in terms of stomatitis, diarrhea, nausea and alopecia with less frequent events with capecitabine. The HFS which was normally seen in the past with continuous infusions of 5-FU were more common with capecitabine but managed with treatment interruption and dose reduction.

As the area of systemic therapy is dramatically changing in MCRC, the availability of an oral agent demonstrating a higher response rate with no difference in TTP or OR in a selected group of patients, offers a convenient and acceptable therapy in this palliative setting. Patients are not willing to sacrifice response for convenience but the benefits of this agent have translated into a reasonable option. Unfortunately, the theoretical advantages of this agent in terms of survival have not yet been manifested. The direct comparison in two clinical trials confirms clinical response in terms of response and disease stabilization.

As there is no data available on the use of capecitabine post irinotecan/5-FU/LV combination, there is not a strong recommendation to move in such a direction. Theoretically the action of capecitabine would suggest its value, but no trials have yet demonstrated this benefit.
Capecitabine MCRC

**Restrictions for Use**

Restricted to Medical Oncologist for the first-line treatment of patients with advanced or metastatic colorectal cancer.

**Treatment Location**

Patients will be treated on an out-patient basis at home. The convenience of an oral agent allows patients to be treated in their more familiar setting. Patients hospitalized while on treatment will be instructed to bring their own medications with them. A small portion of patients may initiate therapy as hospital in patients.

**Date Prepared:** February, 2001

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Oncology Therapy Subcommittee
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