Guideline Questions

- Does irinotecan in combination with 5-FU/Leucovorin (5-FU/LV) induce response, improve time to tumor progression (TTP) or progression free survival (PFS) and/or overall survival (OS) in patients with previously untreated metastatic colorectal cancer (MCRC)?
- Should irinotecan in combination with 5-FU/LV be offered as first line therapy to all patients with MCRC?
- Does irinotecan as a single agent induce tumour response, prolong survival and provide palliation in patients with MCRC after failure of 5-FU based treatment?
- Should irinotecan (single agent) be offered as second line therapy to all patients progressing on 5-FU based therapy?
- Is there a role for sequential administration of irinotecan after 5-FU treatment progression?
- Does the magnitude of the survival and clinical benefit as monotherapy or in combination outweigh the toxicity in terms of quality of life (QOL)?

Objectives

- To make recommendations regarding the use of irinotecan as a single agent or in combination with 5-FU/LV in MCRC patients.

Outcome Measures

- To review response rates, PFS/ TTP and survival in the MCRC patient.
- Toxicity and QOL are considered.

Quality of Evidence

- Phase I, Phase II and Phase III studies in colorectal cancer have been reported.
  - Phase II non-randomized studies (Rothenberg et al 1996 and 1999;Pitot et al 1997) were the basis for approval in North America for 5-FU refractory colorectal cancer patients (Level III evidence) (Published).
  - Japanese and French Phase II clinical trials (Rouger et al 1997;Shimada et al 1993) which included previously treated patients, have been reported to market the drug in these countries (Level III evidence)(Published).
  - Phase II studies (US, Japanese and French)(Conti et al 1996;Rouger et al 1997;Shimada et al 1993) have been reported in previously untreated colorectal cancer patients (Level III evidence) (Published).
  - Two Phase III randomized studies in patients progressing on 5-FU have been completed in Europe. One Phase III study (Rouger et al 1998) compared irinotecan to infusional 5-FU. The second study (Cunningham et al 1998) compared irinotecan to best supportive care (BSC) (Level II evidence) (Published).
  - Two Phase III randomized trials as first line therapy for MCRC have been reported. The US trial (Saltz et al 2000) compared weekly irinotecan alone, irinotecan/5-FU(bolus)/LV combination to standard “Mayo” (5-FU/LV bolus) regimen. The French trial (Douillard et al 2000) compared two versions of irinotecan plus infusional 5-FU versus infusional 5-FU regimen alone. (Level II evidence) (Published)
  - A combined analysis of the two phase III randomized trials (Saltz et al and Douillard et al) in previously untreated MCRC was reported by Saltz et al (2000) at the American Society of Clinical Oncology (ASCO) meeting. (Level II evidence) (Published in abstract).

Benefit

Metastatic colorectal cancer is currently incurable, and, until recently, treatment options were limited. Data from pooled U.S. pivotal Phase II studies of irinotecan demonstrated an overall response rate of 15% at the starting dose of 125 mg/m² in patients previously treated with 5-FU therapy. Two randomized Phase III European trials that compared irinotecan to best supportive care (BSC) and infusional 5-FU respectively, in MCRC following failure of first line 5-FU therapy, demonstrated a statistically significant survival benefit in favour of irinotecan. The one year survival in the irinotecan treated group was 36.2% compared to 13.8% in the BSC study. In the QOL analysis, all scores were significantly in favor of the irinotecan arm except for the diarrhea score which was lower in the BSC group. Compared to infusional 5-FU, irinotecan demonstrated an improvement in survival at one year from 32% in the 5-FU group to 45% in the irinotecan group. Median survival was 10.8 months in the irinotecan group and 8.5 months in the 5-FU group. Median PFS was 4.2 months vs 2.9 months. QOL was not different in the two groups.

Phase III randomized data from the U.S. compared irinotecan (single agent-125 mg/m²/wk) vs 5-FU/LV alone vs irinotecan/5-FU/LV combination in previously untreated MCRC. The confirmed response rates of 18%, 21% and 39% respectively favoured the irinotecan/5-FU/LV combination with a statistically significant difference in median PFS of 7 months compared to 4.3 months on the 5-FU/LV arm and 4.2 months on the irinotecan only arm. Survival in the irinotecan/5-FU/LV arm was 14.8 months compared to 12.6 months (5-FU/LV) (p=0.042). The median survival in the
Irinotecan Guidelines
MCRC

Irinotecan only arm was 12 months. This study demonstrated no statistically significant difference in QOL in the combination arm over the 5-FU/LV arm. A European randomized Phase III trial compared 5-FU bolus/LV/5-
FU/continuous infusion alone or with irinotecan as first line therapy in MCRC. The confirmed response rate was statistically superior in the combination arm (35% vs 22%). The median TTP favoured the combination arm (6.7 months vs 4.4 months). A survival benefit was demonstrated in the combination arm (17.4 months vs 14.1 months p=0.032).
Again, in this trial QOL did not differ significantly.

Adverse Effects

Neutropenia and diarrhea are dose limiting toxicities which can lead to fatality if not aggressively managed. The diarrhea experienced by the irinotecan may consist of an early cholinergic syndrome, which can be controlled with subcutaneous atropine. Compliance and adherence to a strict anti-diarrheal regimen of oral loperamide is effective for delayed diarrhea. Grade 3 diarrhea was more frequent with combined irinotecan/5-FU/LV than 5-FU/LV. Grade 4 diarrhea was similar in both groups. Grade 3 or 4 mucositis, grade 4 neutropenia, and neutropenic fever was less with the combined therapy regimen (irinotecan/5-FU/LV). It is interesting to note that the grade 3/4 diarrhea in the combined arm in the US trial was actually less than in the single agent irinotecan arm. As a single agent in previously treated patients, grade 3/4 neutropenia developed in 26% of patients treated with the weekly regimen and 22% (grade3) / 14% (grade 4) in the once every three week schedule.

Evidence Based Recommendation

Irinotecan, a water soluble semisynthetic derivative of Camptothecin, has demonstrated significant activity in MCRC. Published, randomized, Phase III trial data has clarified the role of irinotecan as monotherapy in previously treated MCRC. Patients who have disease progression while on or after 5-FU based therapy for metastatic disease with good performance status, willingness to adhere to a stringent anti-diarrheal program and desire for additional treatment, irinotecan is a reasonable therapeutic option.

Results from U.S. and European trials have demonstrated a role for irinotecan in previously untreated MCRC. Irinotecan in combination with 5-FU/LV in this patient group has shown an improvement in response rates and TTF/PFS. A modest yet significant survival benefit was shown in both of the phase III trials. The use of combined irinotecan/5-FU/LV as first line therapy may be considered as a reasonable treatment option in those previously untreated MCRC patients with good performance status. Patient education concerning toxicities, appropriate patient compliance, strict nursing assessments and frequent blood work review are essential to ensure patient safety. There is currently, lack of evidence to clearly determine whether combined irinotecan or sequential irinotecan is superior in terms of overall survival. Trials are underway including new agents and/or new combinations.
**Guidelines for the Use of Irinotecan in Metastatic Colorectal Cancer**

Queen Elizabeth Health Sciences Centre/Cancer Care Nova Scotia

**Background**

Colorectal cancer is a leading cause of cancer death in industrialized countries and the second leading cause of death from cancer in the U.S. In 2000 estimates, 17,000 new cases of colorectal cancer will present. Sex distribution for new cases and deaths is almost equal. In 1995 for males and females there were 316 and 285 new cases, respectively, in Nova Scotia.

The median age of diagnosis of colorectal cancer is approximately 60-65 years old. Overall, the 5 year survival of colorectal cancer is approximately 50%\(^1\). Disseminated disease has an expectancy of less than 5% 5 year survival. Colon carcinomas account for approximately 70-75% of all cancers in the large bowel with the right side of the proximal colon the most common site. The remaining cases arise in the rectum.

Among the suspected risk factors, diets rich in fat and cholesterol have been linked to an increased risk. Lower rates of colorectal cancer are observed in Asia, Africa and South America. Other risk factors include environmental exposures, genetic predisposition and pre-existing colonic diseases.

**Standard Treatment**

The majority of large bowel cancers are adenocarcinomas accounting for 90-95% of cases. Other histologies arising in colon or rectum include squamous, carcinoid, adenosquamous and undifferentiated carcinomas. Non-epithelial tumours such as sarcomas and lymphomas are rare. Colorectal carcinomas have a tendency to invade locally and spread to regional lymph nodes. The degree of spread may correlate to the depth of invasion and tumour grades. Liver and lungs are the most common sites of distant metastases. Other sites may include peritoneum, bones, kidneys, adrenal glands and brain.

Tumour node metastasis (TNM) stage is the most important prognostic factor for large bowel cancers. This staging system is based on the depth of tumour invasion through the intestinal wall, regional lymph node involvement and presence or absence of distant metastases. At diagnosis approximately 8% of patients present with Stage I, 39% Stage II, 28% Stage III and 25% Stage IV disease. Surgery is the only curative treatment modality for disease Stages I-III. Unfortunately, despite potentially curative surgical treatment, approximately 50% of all patients will die of metastatic disease. Approximately 70% of recurrences will occur within 2 years and 90% within 5 years of diagnosis. Patients with advanced disease rarely survive 5 years after diagnosis of metastases, with median duration of survival from 6-12 months without treatment.

Treatment strategies after curative intent surgery may include adjuvant systemic therapy for Stage III and possibly some Stage II colon tumours. A definitive role for radiation therapy combined with systemic chemotherapy as adjuvant therapy in rectal cancer has been established for Stage II and III diseases.

Adjuvant therapy for colon cancer will not be discussed in detail in this document as the main focus is advanced disease.

Since the 1950’s, 5-fluorouracil (5-FU) has been the most effective agent in advanced colorectal cancer. A meta-analysis (Piedbois P et al; Advanced Colorectal Cancer Meta-Analysis Project, 30% for QEII 1992 & 1993, GI Outcomes Project)

August, 2001
Irinotecan Guidelines
MCRC

1992) of nine clinical studies delivering 5-FU as a bolus infusion in metastatic disease, demonstrated an overall response rate of 11% and median survival of 11 months. The combination of 5-FU/folinic acid increased response rates to approximately 23%. This combination has been standard treatment for advanced disease. A variety of schedules have been used to improve the efficacy of this regimen. Despite improvements in response rates no difference in overall survival has been demonstrated compared to 5-FU alone. With no second-line option of proven value, many patients who progress on first line treatment, however, still have a good performance status and second line therapy would be an option.

Camptothecin (CPT), a plant alkaloid obtained from Camptotheca Acuminata showed significant antitumor activity in preclinical studies of metastatic colon cancer. In the 1970's early trials led to severe toxicities and further trials were abandoned. In 1983, a new water soluble semisynthetic derivative of CPT was synthesized (irinotecan;CPT-11). In vivo, irinotecan is converted to SN-38 which is an active metabolite. The mechanism of action is characteristic of a topoisomerase I inhibitor leading to lethal accumulation of single-strand DNA breaks in the cell. Irinotecan (Camptosar®) was approved by the Food and Drug Administration (FDA) in the U.S. for 5-FU refractory colorectal cancer in 1996. The Health Protection Branch (HPB) in Canada approved a similar submission for irinotecan in 1997. Irinotecan, presently has Health Canada, Therapeutics Products Program (TPP) approval for those patients whose disease has recurred or progressed following 5-FU based therapy. Both The U.S. (weekly) and European (once every three week) dosing schedules have been approved based on data in this document. In the U.S. the first line combination irinotecan/5-FU/LV regimen was approved in 2000 with TPP approval in Canada (2001).

Clinical Studies

Phase I studies of irinotecan conducted in Europe showed promising results in a variety of malignancies including colorectal cancer. Studies conducted in the U.S. and Japan utilized different study designs and endpoints. In Europe, Phase II studies employed irinotecan at a dose of 350 mg/m2 once every three weeks while the doses of 100-150 mg/m2 weekly were tested in the U.S. and Japan.

The Phase II studies conducted in the U.S. (Rothenberg et al 1996;1999;Pitot et al 1997) enrolled patients who had previously been treated with 5-FU, while one study at Memorial Sloan Kettering Cancer Centre (Conti et al 1996) included only previously untreated patients. In all the U.S. trials, the regimen consisted of repeated 6 week courses (once a week for 4 weeks followed by a 2 week rest period). The doses used were 100, 125 and 150 mg/m2. A previously untreated population of patients was enrolled in the trial by Conti et al. (1996). The group was fairly small in sample size but reported a partial response rate of 32%, median duration of response of 8.1 months and median survival of 12.1 months. Another study by Pitot et al. (1997) of the North Central Cancer Treatment Group (NC CTG) enrolled previously untreated patients demonstrating a partial response rate of 25.8% and median survival of 11.8 months.

Pooled data from U.S. pivotal clinical trials (Protocol 001 – Rothenberg et al. (1996); Protocol 003 – Pitot et al. (1997) and Protocol 006 – Rothenberg et al (1999)), of previously treated patients involving over 300 patients, demonstrated an overall response rate of 15% and overall time to tumour progression (TTP) of 4 months. Disease stabilization was seen in approximately 49% of patients. Median survival was 9 months. The initial starting dose of 150 mg/m2 was found to be too toxic and thereafter, 125 mg/m2 was used.

Japanese studies incorporated the same dosage regimen as that used in the U.S. Data from these trials included patients who had received prior 5-FU based therapy. A partial response rate of 27% and median overall duration of response was 208 days was reported in a Phase II trial by Shimada et al. (1993).

The largest Phase II studies of irinotecan were conducted in Europe. Response rates were similar in the pre-treated and chemotherapy naive groups. In the study by Rougier et al. (1997),
the response rate was 17.7% in the pre-treated group and 18.8% in the chemotherapy naïve group. There was no statistically significant difference in median survival between chemotherapy naïve (12 months) and pre-treated (10 months) patients.

It was apparent due to the similar response rates in previously treated and untreated patients, that there was lack of cross resistance between 5-FU and irinotecan. This provided support for use of irinotecan after 5-FU progression.

Phase III European trials which enrolled patients that failed first line 5-FU have been conducted and completed. These trials were reported by Rougier et al (1998) and Cunningham et al (1998). Endpoints for these trials included: survival, performance status, weight, tumour related symptoms and quality of life (QOL).

The first study compared irinotecan (350 mg/m² q3 wk) to best supportive care (BSC). With a median follow-up of 13 months, the median survival was significantly better in the irinotecan arm (p=0.0001). Median survival in the irinotecan group was 9.2 months compared to 6.5 months in the BSC group. One year survival was 36.2% and 13.8% in the irinotecan and BSC group, respectively. Clinical benefit, survival without performance status deterioration, weight loss of >5% and pain free survival were significantly improved in the irinotecan arm. A prospective QOL analysis was analysed in this trial. The scores were significantly different in favour of irinotecan except diarrhea which was better in the supportive care group.

The second phase III trial randomized patients to irinotecan 350 mg/m² q3weeks vs one of three possible infusional 5-FU regimens. With a median follow-up of 15 months, the median survival in the irinotecan group was 10.8 months versus 8.5 months for the 5-FU treated group. Survival at one year was 45% vs 32% in favour of the irinotecan group. PFS was significantly improved in the irinotecan group with a median of 4.2 months vs 2.9 months in the 5-FU group. Trends in favour of irinotecan were also seen in the median time to deterioration of performance status. QOL analysis was similar in both groups, however diarrhea and vomiting were less frequent in the 5-FU group.

The role of irinotecan as first line therapy for MCRC has been reported by two authors (Saltz et al 2000-U.S. and Douillard et al 2000-France). The U.S. trial randomized 683 previously untreated chemotherapy patients (except for patients who received 5-FU adjuvant therapy and remained disease free for 12 months—approximately 10% of the study population) to one of three treatment arms. Patients received weekly irinotecan/5-FU/LV, 5-FU/LV (as per Mayo regimen) or irinotecan as a single agent. The results reported improved PFS (median 7.0 vs 4.3 months p=0.004), higher confirmed response rate (39% vs 21% p<0.001) and longer OS (median 14.8 months vs 12.6 months p=0.042) in the combined irinotecan/5-FU/LV arm compared to the 5-FU/LV arm. The results for the irinotecan only arm were similar to 5-FU/LV. Analyses of the QOL showed that there were no significant differences between the group given the irinotecan/5-FU/LV and the group given the 5-FU/LV.

The second Phase III randomized study compared infusional 5-FU plus irinotecan versus infusional 5-FU alone as first line therapy in MCRC (adjuvant chemotherapy completed more than 6 months before randomization). Patients were randomized to one of two infusional 5-FU regimens—“De Gramont or AIO” with irinotecan in one arm versus no irinotecan. The overall response rate was significantly higher in the patients receiving irinotecan. (35% vs 22% p<0.005). The TTP was significantly longer in the irinotecan group (6.7 months vs 4.4 months) and OS was higher (median 17.4 months vs 14.1 months p=0.031). The median duration of treatment was longer in the irinotecan group, irrespective of the 5-FU regimen. QOL did not differ significantly between groups.

Phase I/II data has confirmed that dose limiting toxicities are neutropenia and delayed diarrhea. The incidence of these toxicities are non-cumulative and must be treated aggressively.
In one study (Rothenberg et al, 1996), Grade 4 diarrhea occurred early in patients at a dose level of 150 mg/m² requiring an amendment to reduce the dose to 125 mg/m². Pooled data from three clinical trials (n=304) evaluated the weekly regime (Appendix I). Grade 3-4 late diarrhea occurred in 30.6% of patients. The median time to onset of late diarrhea was 11 days following administration of irinotecan. The median duration of any grade of diarrhea was 3 days. For those patients treated at 125 mg/m² and who experienced grade 3 or 4 diarrhea, the median duration of the entire episode of diarrhea was 7 days. The frequency of grade 3 or 4 late diarrhea was somewhat greater in patients starting treatment at 125 mg/m² than in those starting at 100 mg/m² (34% vs 24%). Adherence to a strict antidiarrheal regimen has helped to reduce this toxicity.

Early onset diarrhea can occur during or within 24 hours of administration of irinotecan. This diarrhea is cholinergic in nature and can be severe but is usually transient. It may be preceded by complaints of diaphoresis and abdominal cramping. Administration of 0.25 mg to 1 mg subcutaneous (s.c.) of atropine has been effective treatment. Neutropenia is a second dose limiting toxicity. Data from the pooled analysis reports Grade 3-4 neutropenia occurred in 26.3% and neutropenic fever in 3% of patients. Deaths due to sepsis during severe myelosuppression have been reported. The frequency of grade 3 and 4 neutropenia was significantly higher in patients who received previous pelvic/abdominal irradiation than in those who had not received irradiation (48.1% vs 24.1%). No significant differences in the frequency of grade 3 and 4 neutropenia by age or gender were observed.

In the Phase III irinotecan vs BSC and 5-FU infusional protocols, grade 3 and 4 late diarrhea occurred in 22% of the patients in the irinotecan arm compared to 11% in the 5-FU arm. Other Grade 3-4 adverse effects included neutropenia at 14%. The median time to the onset of late diarrhea was 5 days after the irinotecan infusion. These trials used the recommended starting dose of 350 mg/m² once every three weeks.

Unfortunately, at this time there has been no head to head comparison of the weekly North American regimen and the European every three week regimen.

Toxicity profiles in the Phase III combination (irinotecan/5-FU/LV) randomized trials are interesting (Appendix II and III). The evidence of grade 3 diarrhea in both studies was greater with irinotecan-based combination therapy. However, the rates of grade 4 diarrhea were similar (<8%) when comparing irinotecan/5-FU/LV and 5-FU/LV treated patients. In the U.S. study, grade 4 neutropenia, neutropenic fever, and Grade 3 - 4 mucositis were observed less often with weekly irinotecan/5-FU/LV than with the 5-FU/LV (Mayo regimen). The toxic death rate for the irinotecan/5-FU/LV was 0.9% compared to 1.4% for the 5-FU/LV regimen. The incidence of Grade 3-4 neutropenia on the combination arm appears to be lower in the European trial which utilized infusional 5-FU.
Approved Use

Irinotecan, as a single agent, in patients who have documented evidence of metastatic colorectal cancer, with an ECOG performance status of 0-2 who have:

- Progressed while on 5-FU-based (or raltitrexed) therapy,

OR

- Disease progression less than 6 months after completion of 5-FU-based (or raltitrexed) therapy.

Irinotecan, in combination with 5-FU/LV, in patients who have documented evidence of metastatic colorectal cancer, with an ECOG performance status of 0-2 who have:

- Disease progression 6 months after completion of 5-FU-based (or raltitrexed) therapy,

OR

- Never received any previous chemotherapy.

NOTE: Special approval of irinotecan as a single agent or in combination 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

### Appendix I

**Single agent – post 5-FU based therapy.**

This information is based on medical events which occurred in a combination of three Phase II studies of a total of 304 patients using the **weekly** (i.e. 6 week regimen)

<table>
<thead>
<tr>
<th>Infusion-related Toxicities</th>
<th>Cholinergic type reaction – diaphoresis, abdominal cramps or early onset diarrhea (&lt; 24 hours after administration) Grade 3 / 4 approx. 7.9%</th>
<th>Recommend: Atropine 0.25 mg to 1 mg IV or subcutaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extravasation</td>
<td>Flush infusion site and/or apply ice</td>
<td></td>
</tr>
<tr>
<td><strong>Nausea/Vomiting</strong></td>
<td>All grades = 86%/67% Grade 3 / 4 = 17%/13%</td>
<td>Recommend: Antiemetics</td>
</tr>
<tr>
<td><strong>Hematologic</strong></td>
<td>Grade 3 neutropenia = 14.8% Grade 4 neutropenia = 11.5% Grade 3 / 4 anemia = 6.9% Severe thrombocytopenia = uncommon</td>
<td></td>
</tr>
<tr>
<td><strong>Diarrhea</strong></td>
<td>Delayed diarrhea occurring &gt; 24 hours after irinotecan Grade 3 / 4 = 30.6%</td>
<td>Recommend: Intensive Loperamide regimen</td>
</tr>
</tbody>
</table>
## Appendix II

### Combination – Irinotecan / 5-FU / LV

This information is based on experience reported by Saltz et al (2000)

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Grade 3 / 4</th>
<th>Combination Vs 5-FU/LV Vs Irinotecan</th>
<th>Grade 4</th>
<th>Combination Vs 5-FU/LV Vs Irinotecan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vomiting</td>
<td>Combination</td>
<td>10%</td>
<td>Grade 4</td>
<td>Combination Vs 5-FU/LV Vs Irinotecan</td>
</tr>
<tr>
<td></td>
<td>5-FU / LV</td>
<td>4%</td>
<td></td>
<td>1.4%</td>
</tr>
<tr>
<td></td>
<td>Vs Irinotecan</td>
<td>12%</td>
<td></td>
<td>6.3%</td>
</tr>
<tr>
<td>Mucositis</td>
<td>Grade 3 / 4</td>
<td>Combination</td>
<td>Grade 4</td>
<td>Combination Vs 5-FU/LV Vs Irinotecan</td>
</tr>
<tr>
<td></td>
<td>5-FU / LV</td>
<td>2.2%</td>
<td></td>
<td>2.3%</td>
</tr>
<tr>
<td></td>
<td>Vs Irinotecan</td>
<td>17%</td>
<td></td>
<td>0.4%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Grade 3 / 4</td>
<td>Combination</td>
<td>Grade 4</td>
<td>Combination Vs 5-FU/LV Vs Irinotecan</td>
</tr>
<tr>
<td></td>
<td>5-FU / LV</td>
<td>23%</td>
<td></td>
<td>7.6%</td>
</tr>
<tr>
<td></td>
<td>Vs Irinotecan</td>
<td>13%</td>
<td></td>
<td>7.3%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>31%</td>
<td></td>
<td>12.6%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>Grade 3 / 4</td>
<td>Combination</td>
<td>Grade 4</td>
<td>Combination Vs 5-FU/LV Vs Irinotecan</td>
</tr>
<tr>
<td></td>
<td>5-FU / LV</td>
<td>54%</td>
<td></td>
<td>24%</td>
</tr>
<tr>
<td></td>
<td>Vs Irinotecan</td>
<td>67%</td>
<td></td>
<td>43%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>31%</td>
<td></td>
<td>12%</td>
</tr>
</tbody>
</table>

**Caution:** An excess rate of early deaths has been reported in two separate unpublished cooperative group clinical trials sponsored by the National Cancer Institute (NCI) using the “Saltz” regimen. Common characteristics include dehydration, neutropenia, sepsis, pulmonary emboli, aspiration, myocardial infarction, cerebrovascular accident and bowel ischemia.
### Appendix III

This information is based on the data reported by Douillard et al (2000):

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Grade 3 / 4</th>
<th>Comparison</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vomiting</td>
<td>Combination</td>
<td>Vs 5-FU/LV</td>
<td>6%</td>
</tr>
<tr>
<td>Mucositis</td>
<td>Combination</td>
<td>Vs 5-FU/LV</td>
<td>3%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Combination</td>
<td>Vs 5-FU/LV</td>
<td>2.7%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>Combination</td>
<td>Vs 5-FU/LV</td>
<td>42%</td>
</tr>
</tbody>
</table>

August, 2001
**Expected Patient Numbers**

**Cost**
Estimated cost/cycle for treatment of MCRC with irinotecan based on a BSA of 1.7 m² is approximately:

Single agent - $4,100/cycle – weekly x 4 q6 weeks; $2,875/cycle – q3 weeks
Combination therapy with 5-FU/LV - $4,125/cycle – weekly x 4 q6 weeks.

Irinotecan (single agent) 10 patients/year will be treated.
Irinotecan (combination therapy) 40 patients/year will be treated.

Estimated number of cycles/patient = 5.5 cycles. Average cost/patient $15,000 (assuming dose reductions)

Approximate Drug costs/year:

**Irinotecan = $750,000**
Summary
For the last 40 years, 5-FU has been the only viable option of systemic chemotherapy for patients with MCRC. As a single agent, irinotecan, a semisynthetic derivative of camptothecin, has demonstrated significant activity in MCRC. Response rates are similar to 5-FU/LV combination and appear to be similar in both chemotherapy naïve and pretreated patients with metastatic disease. Many patients who have relapsed or progressed on typical 5-FU regimens who have an adequate performance status are requesting additional treatment. With the survival data that has been reported by the European Phase III clinical trials, irinotecan has been found to be a better option than no specific treatment after 5-FU failure. Patients treated with irinotecan lived significantly longer than those receiving infusional 5-FU. Statistically significant progression free survival advantage was also observed with the irinotecan treated group. The QOL evaluation (using the QLQ – C30 questionnaire) revealed that survival without deterioration of QOL was significantly improved with irinotecan compared to BSC and was not different compared to 5-FU therapy. The second line use of irinotecan was adopted at the QEII Health Sciences Centre in 1998.

What is the role of irinotecan as first line therapy for MCRC? The results of two large, randomized Phase III trials have shown that the combination of irinotecan to 5-FU/LV benefits patients with MCRC by significantly improving tumor shrinkage, prolonging tumor control and lengthening survival. The two trials have demonstrated that the combination of irinotecan/5-FU/LV can be given safely in patients with a good performance status, extending life without causing a negative impact to QOL.

Restriction for Use
Restricted to medical oncologists for the treatment of MCRC as per eligibility criteria as defined in the approved use indications.

Treatment Location
Patients will be treated on an out-patient basis for intravenous infusion unless clinically unstable and hospitalization required.

Original Dates: August, 1998
February, 2000 (Revised)
November, 2000 (Revised)

Review Date: August, 2001

Prepared by: Dr. B. Colwell, Medical Oncologist, GI Cancer Site Team Chair
Marlene Sellon, Pharmacist, Managed Systemic Therapy Program

Reviewed by: GI Cancer Site Team
Oncology Therapy Subcommittee
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