Background

Irinotecan in combination with 5-Fluorouracil (5FU) has been shown to be effective in metastatic colon cancer \(^1\) and has been approved for use by the SMC and NICE for this indication. Data by Tournigand, which compared the oxaliplatin and 5FU combination FOLFOX 6 followed by FOLFIRI versus FOLFIRI followed by FOLFOX 6 showed no difference in Disease Free Survival (DFS) \(^2\). It appears that as long as both oxaliplatin and irinotecan combinations are used that survival is prolonged from approximately 17 months to 20 months \(^3\). Although no direct comparison between single agent Irinotecan and combination therapy FOLFIRI has been made the toxicity profile in studies with combination of Irinotecan with 5FU appears to be reduced compared to the toxicity seen with Irinotecan alone and therefore the combination is increasingly being used in clinical trials \(^2,4,5\).

Indication

Metastatic colorectal cancer

Case selection

**CONSIDER ENTRY INTO CLINICAL TRIAL IF AVAILABLE/APPROPRIATE**

**Inclusion**

- Histological or cytological proof of colorectal cancer
- PS 0-2
- Have life expectancy of at least 3 months
- No biological major abnormalities: Absolute neutrophil count $\geq 1.5 \times 10^{9}$/l, Platelets $\geq 100 \times 10^{9}$/l, Creatinine clearance $\geq 30$ml/min
- Written informed consent
- Ideally patients should have measurable disease – but this is not a protocol requirement
- Men and women who are fertile must use a medically acceptable contraceptive throughout the treatment period and for 6 months following cessation of treatment.

**Exclusion**

- Bilirubin $\geq 3$ times upper limit of normal (ULN)
- Pregnant or lactating females
- Evidence of CNS metastases
- Clinically significant cardiac disease – uncontrolled CHF, unstable angina or MI within last 6 months
- Known or suspected DPD deficiency
- Known hypersensitivity to irinotecan based therapeutics
- Other intercurrent serious illness which in the opinion of the treating consultant would render patient at risk of severe toxicity
Pre-treatment evaluation

1. Informed consent
2. Provision of verbal and written information.
3. Assessment of performance status
4. Height, weight and BSA
5. Copy of histopathology reports
6. Copy of CT or MRI reports
7. Baseline FBC, U&Es, LFTS and CEA
8. Medical history and examination

Regimen

Pre-medication: Dexamethasone 8mg + Granisetron 3mg Intravenously 30 minutes prior to chemotherapy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Administration</th>
<th>Infusion fluid</th>
<th>Day to be given</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irinotecan</td>
<td>180mg/m²</td>
<td>I.V</td>
<td>Over 30 min</td>
<td>250ml Glucose 5% or Sodium Chloride 0.9%</td>
<td>Day 1</td>
</tr>
<tr>
<td>Folinic Acid</td>
<td>350mg</td>
<td>I.V</td>
<td>Over 2 hrs</td>
<td>250ml Glucose 5% or Sodium Chloride 0.9%</td>
<td>Day 1</td>
</tr>
<tr>
<td>5fluorouracil</td>
<td>400mg/m²</td>
<td>I.V</td>
<td>Over 10 min</td>
<td>100ml Sodium Chloride 0.9%</td>
<td>Day 1</td>
</tr>
<tr>
<td>5fluorouracil</td>
<td>2400mg/m²</td>
<td>I.V</td>
<td>Over 46 hrs</td>
<td>1000ml Sodium Chloride 0.9% or ambulatory infusion device **</td>
<td>Day 1</td>
</tr>
</tbody>
</table>

** regimen given as day case treatment if patient has PICC/Hickman line in situ

- Repeat every 14 days for 12 cycles
- Cap BSA at 2.0
- Emetogenic Risk: Moderate – refer to local anti-emetic policy for post-med antiemetics
- Loperamide supplied with each cycle of chemotherapy (see ‘Precautions’) – clear verbal and written instructions supplied on how to use loperamide as below:

“If diarrhoea occurs start Loperamide immediately. Take TWO tablets initially then ONE every 2 hours until 12 hours after the last liquid stool up to a maximum of 48 hours. If symptoms persist beyond 48 hours seek medical advice immediately”.

Adverse effects – for both Irinotecan and Fluorouracil

<table>
<thead>
<tr>
<th>Very Common</th>
<th>Common</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal: severe diarrhoea, nausea and vomiting Blood disorders: neutropenia, anaemia General Disorders &amp; infusion site reactions: Acute cholinergic syndrome* Skin &amp; subcutaneous tissue disorders: alopecia (reversible), thrombophlebitis/vein tracking</td>
<td>Gastrointestinal: dehydration as a result of diarrhoea/vomiting, constipation as a result of loperamide use with Irinotecan Blood disorders: febrile neutropenia, thrombocytopenia Infection &amp; Infestation: infrequent cases of renal insufficiency, hypotension or cardio-circulatory failure observed in patients who experienced sepsis Respiratory disorders: dyspnoea* Laboratory tests: mild to moderate increases in AST, ALT, Bilirubin or Creatinine Skin &amp; subcutaneous tissue disorders: dermatitis, pigmentation, changes in the nails, palmer-plantar erythrodysesthesia Cardiovascular: chest pain, tachycardia* Other: increased lacrimation, dacroyostenosis, visual changes &amp; photophobia,</td>
</tr>
</tbody>
</table>
*see ‘Precautions’

**Uncommon**

For more detailed information regarding Irinotecan and 5fluorouracil please refer to the full current summary of product characteristics (SPC) 6,7.

**Extravasation Risk Category**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Group</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irinotecan</td>
<td>3</td>
<td>Irritant</td>
</tr>
<tr>
<td>5fluorouracil</td>
<td>4</td>
<td>Inflammatory Agent</td>
</tr>
</tbody>
</table>

In the event of an extravasation occurring refer to local extravasation policy

**Contraindications**

- Known history of severe hypersensitivity reactions to Irinotecan +/- 5fluorouracil or to one of the products excipients
- Chronic Inflammatory bowel disease and/or bowel obstruction
- Pregnancy and lactation
- Severe bone marrow failure
- Severe hepatic impairment, Bilirubin > 3 times ULN
- Concomitant use of St Johns Wort
- WHO performance status > 2

**Precautions**

- *Delayed diarrhoea* - patients should be made aware of the risk of delayed diarrhoea more than 24 hours after administration of Irinotecan and at any time within each chemotherapy cycle. Patients should be advised on initiation of antidiarrhoeal therapy (see ‘Regimen’) and the need to drink large quantities of electrolyte containing beverages as soon as the first liquid stool occurs.

  - patients with a higher risk of suffering delayed diarrhoea include: females, those with pelvic tumours and/or those receiving pelvic radiotherapy.

  - there is an increased risk of infections and haematological toxicity in patients with severe diarrhoea. FBC should always be performed in patients with severe diarrhoea.

- *Acute cholinergic syndrome* - defined as early diarrhoea, sweating, abdominal cramping, lacrimation, myosis and salivation.

  - Atropine Sulphate 0.25mg should be administered subcutaneously unless contraindicated (caution in those with asthma. Prophylactic atropine should be given in subsequent cycles of Irinotecan in those who experience an acute and severe cholinergic syndrome.

- *Interstitial pulmonary disease* - presenting as pulmonary infiltrates is uncommon during irinotecan therapy however it can be potentially fatal

  - patients with risk factors which include those receiving pneumotoxic drugs, radiation therapy and/or colony stimulating factors should be closely monitored for respiratory symptoms before and during treatment.
Chest pain, tachycardia, breathlessness and ECG changes may occur with 5fluorouracil therefore careful monitoring should be performed in those patients with a history of heart disease or those who develop chest pain during treatment.

**Drug Interactions - Irinotecan**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Interaction</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>ST JOHNS WORT</td>
<td>SIGNIFICANTLY DECREASES THE ACTIVE METABOLITE OF IRINOTECAN</td>
<td>AVOID CONCOMITANT USE - CONTRAINDICATED</td>
</tr>
<tr>
<td>CYP3A4-inducing (e.g rifampicin, carbamazepine, Phenobarbital, phenytoin) or inhibiting (e.g ketoconazole) drugs</td>
<td>Metabolism of Irinotecan altered</td>
<td>Avoid concomitant use where possible</td>
</tr>
<tr>
<td>Neuromuscular blocking agents e.g suxamethonium and the neuromuscular blockade of non-depolarising drugs</td>
<td>Prolongation of neuromuscular blocking effects due to anticholinesterase activity of irinotecan may occur – theoretical interaction</td>
<td>Risk versus benefit assessment</td>
</tr>
</tbody>
</table>

Various agents have been reported to biochemically modulate the antitumour efficacy or toxicity of 5FU, common drugs include Methotrexate, Metronidazole, Leucovorin as well as Allopurinol and Cimetidine which can affect the availability of the active drug – obtain advice from pharmacy.

**Investigations prior to subsequent cycles**

**Day 1 of each cycle**

- FBC, U&E’s, LFT’s & CEA
- Monitor patients weight
- Toxicity assessment to be performed prior to each cycle of chemotherapy (see dose modification chart for actions to be taken).

**Dose modifications**

**Haematological** - (from CRystal study)

- Treatment **MUST** be delayed until Neutrophils ≥ 1.5 x 10^9/L and platelets ≥ 75 x 10^9/L
- Treatment delayed greater than one week should lead to a 20 % dose reduction

Given in the table as a % of the original standard dose

<table>
<thead>
<tr>
<th>Toxic haematological effect in previous cycle</th>
<th>Grade (CTC version 3)</th>
<th>Dose modification for subsequent cycles</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Bolus 5-FU</td>
</tr>
<tr>
<td>Neutropaenia</td>
<td>0-3</td>
<td>100%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>0-2</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>80%</td>
</tr>
</tbody>
</table>

**Dose Modifications for grade 4 neutropenia, febrile neutropenia and/or grade 4 thrombocytopenia should be made at the discretion of the responsible consultant.**
Non-haematological - (from CRYSTAL study)

- Treatment MUST be delayed until toxicity resolved to grade 0 or 1
- In the event of a grade 4 toxicity occurring the patient should be referred to the consultant
- Treatment delayed greater than one week should lead to a 20% dose reduction

Given in the table as a % of the original standard dose

<table>
<thead>
<tr>
<th>Toxic Non-haematological effect in previous cycle</th>
<th>Grade (CTC version 3)</th>
<th>Dose modification for subsequent cycles</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Bolus 5-FU</td>
</tr>
<tr>
<td>Delayed diarrhoea*</td>
<td>1 or 2</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>80%</td>
</tr>
<tr>
<td>Stomatitis, oral</td>
<td>1 or 2</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>80%</td>
</tr>
<tr>
<td>Skin (Hand Foot syndrome)</td>
<td>3</td>
<td>80%</td>
</tr>
<tr>
<td>Other events**</td>
<td>3</td>
<td>80%</td>
</tr>
</tbody>
</table>

*only if this occurs despite loperamide
** Except nausea and alopecia

Renal Function

Irinotecan - studies in renally impaired patients have not been performed therefore Irinotecan should be used with caution in this setting.

5FU - SPC advises to use fluorouracil with caution in patients with renal impairment. If CrCl is < 30ml/min discuss with responsible consultant.

Hepatic Function

Irinotecan - No data is available for dose modification of irinotecan in combination with 5FU. However, consideration should be given to dose reduction if bilirubin > 1.5 x ULN and < 3 x ULN. Irinotecan is contra-indicated if bilirubin is 3 x ULN.

5FU - SPC advises to use fluorouracil with caution in patients with hepatic impairment.

Evaluation of response to treatment

- CEA should be assessed with every cycle of chemotherapy.
- Review by Consultant team before 1st cycle and after cycles 3, 6, 9 and 12 if given as an outpatient. Those patients receiving in-patient FOLFIRI will be reviewed by the consultant team before each cycle of treatment.
- Review by consultant following CT scan of chest, abdomen and pelvis at least every 6 cycles – it may be more frequent in patients with suspected early progression. Only those patients who have formal evidence of stable or responding disease should continue on therapy beyond 6 cycles.
On progression ‘fit’ patients should be considered for a Phase I trial.

References


