5-Fluorouracil & Folinic Acid in Adjuvant Colorectal Cancer (Mayo Regimen)

Indication:
1) Adjuvant therapy for patients with resected Liver metastases from Colorectal Cancer
2) Adjuvant therapy for Stage III Colorectal Cancer
   Treatment should begin within 5 weeks of surgery

Regimen details:
Folinic Acid (Leucovorin)  40mg  IV  D1 – D5
5-Fluorouracil (5-FU)  425mg/m²  IV  D1 – D5

Administration:
Folinic Acid and 5-FU are given as IV Bolus injection via a fast-running Sodium Chloride 0.9% infusion
Folinic Acid must not be mixed with 5-FU in the same IV injection

Frequency:
Every 28 days, for a maximum of 6 cycles

Extravasation:
5-FU: Non-vesicant

Anti-emetics:
Low emetogenic. Follow local Anti-emetic Policy

Supportive medication:
Loperamide tablet/caps 4mg stat, then 2mg PRN for diarrhoea
Pyridoxine tablets 50mg po tds, if required for palmar-plantar erythema (PPE)

Advice on mouthcare and use of prophylactic mouthwashes should be given. If significant mucositis, consider use of ice chips (ice sucked by patient, starting 5 minutes before chemotherapy given and continued during administration) as an adjunct to dose reduction specified by Consultant

Regular investigations:
FBC  D1
LFTs  D1
U&Es  D1
Ca²⁺  D1
Clinical toxicity assessment (stomatitis, diarrhoea)  D1
CEA  D1

Comments:
Cardiotoxicity – 5-Fluorouracil
Cardiotoxicity has been associated with fluoropyrimidine therapy, including myocardial infarction, angina, dysrhythmias, cardiogenic shock, sudden death and electrocardiographic changes. These adverse events may be more common in patients with a prior history of coronary artery disease. Caution must be exercised in patients with history of significant cardiac disease, arrhythmias and angina pectoris.
DPD deficiency - 5-Fluorouracil
Dihydropyrimidine dehydrogenase (DPD) deficiency can result in severe toxicity secondary to reduced metabolism of fluorouracil, usually manifest as severe toxicity within days of administration. If patients complain of toxicity very soon after administration, it is important to ensure supportive measures are implemented as soon as possible and Consultant consulted before further doses prescribed.

Gastrointestinal toxicity (GI) – Folinic Acid/5-FU
Because diarrhoea may be a sign of GI toxicity, patients presenting with diarrhoea must be carefully monitored until the symptoms have disappeared completely, since a rapid clinical deterioration leading to death can occur. If diarrhoea and/or stomatitis occur, it is advisable to reduce the dose of 5-FU until symptoms have fully disappeared (see Dose modifications for other toxicities as appropriate).

Calcium imbalance – Folinic Acid/5-FU
Calcium levels should be monitored in patients receiving combined 5-FU/Folinic Acid therapy and Calcium supplementation should be provided if Calcium levels are low.

DOSE MODIFICATIONS

Haematological Toxicity

<table>
<thead>
<tr>
<th>Neutrophils</th>
<th>Platelets</th>
<th>5-FU Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1.0 x 10⁹/L AND ≥ 100 x 10⁹/L</td>
<td>Give 100%</td>
<td></td>
</tr>
<tr>
<td>&lt; 1.0 x 10⁹/L OR &lt; 100 x 10⁹/L</td>
<td>Delay therapy for 1 week and resume 5-FU at 75% dose</td>
<td></td>
</tr>
</tbody>
</table>

The dose of Folinic Acid is not modified for chemotherapy toxicity.

Renal Impairment: 5FU: Consider dose reduction in severe renal impairment (GFR < 10ml/min) only

Hepatic Impairment
Fluorouracil should be used with caution in patients with reduced liver function or jaundice:

<table>
<thead>
<tr>
<th>Bilirubin (µmol/L)</th>
<th>AST</th>
<th>5FU Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 85</td>
<td>&lt; 180</td>
<td>Give 100%</td>
</tr>
<tr>
<td>&gt; 85</td>
<td>or &gt; 180</td>
<td>Contraindicated</td>
</tr>
</tbody>
</table>
DOSE MODIFICATIONS FOR OTHER TOXICITIES AS APPROPRIATE

PALMAR/PLANTAR ERYTHEMA (PPE)/ MUCOSITIS/ DIARRHOEA – FLUOROURACIL

Patients with any grade PPE should receive Pyridoxine 50mg po tds throughout remainder of treatment. For Grade 2 and above toxicities, 5-FU should be discontinued until healing has occurred, and then recommence according to toxicity grading:

<table>
<thead>
<tr>
<th>Grade</th>
<th>Palmar-plantar Erythema</th>
<th>Mucositis</th>
<th>Diarrhoea</th>
<th>5FU Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Minimal skin changes (erythema) without pain</td>
<td>Erythema of the mucosa but normal diet</td>
<td>&lt; 4 stools / day</td>
<td>Give 100%</td>
</tr>
<tr>
<td>2</td>
<td>Skin changes (peeling, blisters, edema) or pain, not interfering with function</td>
<td>Patchy ulcerations, can eat and swallow modified diet</td>
<td>4 – 6 stools / day</td>
<td>Give 75%</td>
</tr>
<tr>
<td>3</td>
<td>Ulcerative dermatitis or skin changes with pain interfering with function</td>
<td>Confluent ulcerations; bleeding with minor trauma. Unable to adequately eat or hydrate orally</td>
<td>≥ 7 stools / day</td>
<td>Give 50%</td>
</tr>
<tr>
<td>4</td>
<td>-----------------</td>
<td>Tissue necrosis; significant spontaneous bleeding</td>
<td>Life-threatening consequences</td>
<td>Discuss with Consultant</td>
</tr>
</tbody>
</table>

Once dose reduction has been made, all subsequent treatment should remain at reduced dose.

Toxicities: Myelosuppression; alopecia (reversible); diarrhoea; mucositis; stomatitis; nausea; vomiting; palmar-plantar erythema (PPE); amenorrhoea

Drug interactions: 5-Fluorouracil is a known radiation-sensitizer. Patients should be carefully monitored for gastrointestinal toxicity when they are receiving concurrent 5-FU & Radiation therapy

Fluorouracil
- Allopurinol : avoid concomitant use
- Clozapine : increased risk of agranulocytosis, avoid concomitant use
- Coumarins : enhanced anticoagulant effect
- Digoxin tablets : reduced absorption (resolved by giving the digoxin in liquid)
- Leucovorin : increased cytotoxic and toxic effects of Fluorouracil
- Metronidazole ; Cimetidine : inhibit metabolism of fluorouracil (increased toxicity)
- Phenytoin : reduced absorption of the antiepileptic
- Sorivudine : marked and rapidly fatal fluorouracil toxicity

Reason for Update: Network Protocol Development
Version: 1  Approved by Colorectal Consultant: Nick Maisey
Supersedes: All other versions  Date: 16/12/09
Prepared by: Maria Teresa Pacheca-Palomar  March’09  Checked by (Network Pharmacist): Jacky Turner
Approved by SELCN DTAC Chair: Dr Nic Ketley  Date:29/01/2010
Page 3 of 4
Folinic Acid

- Antiepileptic drugs (phenobarbital, primidone, phenytoin): may increase the frequency of seizures
- Folic Acid Antagonists (co-trimoxazole, pyrimethamine): efficacy may be reduced or completely neutralized by concomitant use of Leucovorin

References:
www.medicines.org.uk
NLCN- Dosage Adjustment for Cytotoxics in Renal Impairment. November 2003
NLCN- Dosage Adjustment for Cytotoxics in Hepatic Impairment. November 2003
GSTT guidelines for treating nausea and vomiting in adult patients. September 2007
Stockley’s Drug Interactions. Interactions search: Fluorouracil. March’09
CTCAE v3.0. August 2006