**WEEKLY 5-FLUOROURACIL AND FOLINIC ACID**

**Indication:** Adjuvant use in stage II/III colorectal cancer

**Drugs / Dosage:**
- Calcium Folinate (Folinic acid) 40mg IV once weekly
- (Calcium Folinate 50mg is equivalent to L-Folinic Acid 25mg quoted in Quasar Trial)
- 5-Fluorouracil 370mg/m² IV once weekly

**Administration:**
- Bolus injections.
- Calcium Folinate should be administered first.

**Frequency:**
- Weekly for 30 cycles
- Clinical review every 4 weeks as below:

**Main Toxicities:**
- Mucositis; Diarrhoea; Palmar/Plantar Erythema; Myelosuppression; Coronary artery spasm (see Comments); Ovarian failure/Infertility;

**Anti-emetics:**
- Mildly emetogenic

**Supportive medication:**
- Loperamide tablets 4mg stat, then 2mg prn for diarrhoea
- Pyridoxine tablets 50mg tds, if required for palmar-plantar erythema (PPE)

**Extravasation:**
- Non-vesicants

**Regular investigations:**
- FBC Every 4 weeks
- LFTs Every 4 weeks
- U&Es Every 4 weeks
- CEA Every 4 weeks

**Toxicities and Dose Modifications**

**Haematological Toxicity**

- WBC < 2.0 x 10⁹/l
  - or
- Neutrophils < 1.0 x 10⁹/l
  - or
- Platelets < 75 x 10⁹/l
  - Delay treatment for 1 week

Haematological toxicity is unusual. If it occurs appropriate dose modification should be discussed with consultant.
Renal Impairment
Before every course, calculate CrCl using Cockcroft and Gault. If borderline, an EDTA should be requested.

Creatinine Clearance (ml/min) 5FU Dose
> 50 Give 100% dose
30 – 50 Give 100% dose
< 30 Give 80% dose

Hepatic Impairment

Bilirubin > 3 x ULN
or
ALT/AST > 2.5 ULN
Omit fluorouracil until liver function recovers

Non-Haematological Toxicities
*Note that severe diarrhoea and/or severe mucositis early in the first treatment cycle can be the first presenting toxicity due to DPD enzyme deficiency, in which case potentially fatal neutropenia can quickly follow.*

Toxicity due to fluorouracil administration may be managed symptomatically and/or modification of the dose (treatment interruption or dose reduction). Once the dose has been reduced, it should not be increased at a later time. Doses of fluorouracil omitted for toxicity are not replaced or restored. Instead the patient should resume the planned treatment cycle.

<table>
<thead>
<tr>
<th>Diarrhoea, abdo pain, N&amp;V, Stomatitis</th>
<th>Immediate action</th>
<th>Dose next cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>maintain dose</td>
<td>100%</td>
</tr>
<tr>
<td>Grade 2 1&lt;sup&gt;st&lt;/sup&gt; appearance</td>
<td>Interrupt until resolved to grade 0-1</td>
<td>100%</td>
</tr>
<tr>
<td>Grade 2 2&lt;sup&gt;nd&lt;/sup&gt; appearance</td>
<td>Interrupt until resolved to grade 0-1</td>
<td>75%</td>
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<tr>
<td>Grade 2 3&lt;sup&gt;rd&lt;/sup&gt; appearance</td>
<td>Interrupt until resolved to grade 0-1</td>
<td>50%</td>
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<tr>
<td>Grade 2 4&lt;sup&gt;th&lt;/sup&gt; appearance</td>
<td>Discontinue treatment permanently</td>
<td></td>
</tr>
<tr>
<td>Grade 3 1&lt;sup&gt;st&lt;/sup&gt; appearance</td>
<td>Interrupt until resolved to grade 0-1</td>
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<tr>
<td>Grade 3 3&lt;sup&gt;rd&lt;/sup&gt; appearance</td>
<td>Discontinue treatment permanently</td>
<td></td>
</tr>
<tr>
<td>Grade 4 1&lt;sup&gt;st&lt;/sup&gt; appearance</td>
<td>Discontinue or at consultants discretion</td>
<td></td>
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<tr>
<td></td>
<td>Interrupt until resolved to grade 0-1</td>
<td>50%</td>
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<tr>
<th>Palmar-Plantar Erythema</th>
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<th>Dose next cycle</th>
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</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>maintain dose</td>
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Cardiotoxicity

Coronary artery spasm is a recognised complication of fluorouracil although the evidence base regarding aetiology, management & prognosis is not particularly strong. The incidence is estimated to be between 2% and 18%. Coronary artery spasm is usually reversible on discontinuing the treatment. Should a patient receiving fluorouracil present with chest pains, stop the treatment. Standard investigation and treatment of angina may be required. If re-challenge is deemed necessary, this can be performed under close supervision, but should symptoms redevelop, fluorouracil should be withdrawn permanently. Refer to Consultant to discuss.

**Neurotoxicity**

Caution must be exercised in patients with central or peripheral nervous system disease e.g. cerebral metastasis or neuropathy

**Drug interactions:**

- Coumarin anticoagulants-monitor INR
- Phenytoin- altered plasma levels
- Metronidazole- increased plasma levels and toxicity
- Folinic acid- increased toxicity
- Allopurinol- reduced efficacy
- Antacids- absorption interference

**References**

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Annals of Oncology 2000 (Aug); 11 (8): 947 - 955
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www.medicines.org.uk,
Micromedex review, Fluorouracil. Sept2007