5FU AND RADIOTHERAPY

**Indications:**
1. For pre-operative use in rectal cancer.
2. For post-operative use in selected patients with rectal cancer
3. Post-operative use in gastric cancer
4. Pre / Post-operative use in pancreatic cancer

**Drug/Dosage:**
5 Fluorouracil 200 mg/m² per day as a continuous infusion administered through a PICC or Hickman line
In elderly or frail patients consider 150 mg/m²/day
*In selected gastric cancer patients 300 mg/m² day can be used in the weeks before and after radiotherapy (see below).*

**Radiotherapy:**
45 Gy – 54 Gy in 25 - 30 fractions (1.8 Gy/#) on weekdays only over the same 5 – 6 week period. Gastric/Pancreatic 45Gy in 25 fractions

**Frequency:**
Administered 7 days per week continuously for 5 - 6 weeks
In gastric cancer can be given for up to 12 weeks
Review weekly.

**Main Toxicities:**
Myelosuppression; Diarrhoea; Palmar-Plantar Erythema (PPE); Mucositis; Cardiotoxicity (uncommon); Ovarian failure/Infertility; Impotence (males); Urinary frequency/cystitis; coronary artery spasm

**Anti- emetics:**
Mildly emetogenic

**Regular Investigations:**
- FBC Every week
- U&Es* Day 1 and during Week 3 (*renal function should be closely monitored)
- LFTs Day 1 and during Week 3
- ECG If previous history of angina, MI or rhythm disturbances

**Comments:**
If 5FU is omitted due to toxicity, radiotherapy should continue. Once RT completed, 5FU treatment should not continue, even if patient has not taken the full course.

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

**Dose Modifications**

**Haematological Toxicity**

- Neutrophils ≤ 1.0 x 10⁹/l  Delay for 1 week, or until recovered.
  - Or  Continue with radiotherapy.
- Platelets ≤ 75 x 10⁹/l  If in doubt, discuss with Consultant or Specialist Registrar
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 75% dose
< 30     Give 50% dose (consider Omitting)

Hepatic Impairment

Moderate hepatic impairment: Bilirubin > 3xULN but < 5xULN Reduce initial Fluorouracil dose to 75%

Severe hepatic impairment: Bilirubin > 5xULN Reduce initial Fluorouracil dose to 50%

Non-Haematological Toxicities

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

Toxicity due to 5FU 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 5FU omitted for toxicity are not replaced or restored. Instead the patient should resume the planned treatment cycle.

Diarrhoea, abdo pain, N&V, Stomatitis

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<thead>
<tr>
<th>Grade</th>
<th>Immediate action</th>
<th>Dose next cycle</th>
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<tbody>
<tr>
<td>Grade 1</td>
<td>maintain dose</td>
<td>100%</td>
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<tr>
<td>Grade 2</td>
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<td>Interrupt until resolved to grade 0-1</td>
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<tr>
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<td>Interrupt until resolved to grade 0-1</td>
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<tr>
<td>Grade 2</td>
<td>4th appearance</td>
<td>Discontinue treatment permanently</td>
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<tr>
<td>Grade 3</td>
<td>1st appearance</td>
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<tr>
<td>Grade 3</td>
<td>2nd appearance</td>
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<tr>
<td>Grade 3</td>
<td>3rd appearance</td>
<td>Discontinue treatment permanently</td>
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<tr>
<td>Grade 4</td>
<td>1st appearance</td>
<td>Discontinue or at consultants discretion</td>
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<td></td>
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<td>Interrupt until resolved to grade 0-1</td>
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Palmar-Plantar Erythema

<table>
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<th>Grade</th>
<th>Appearance</th>
<th>Immediate action</th>
<th>Dose next cycle</th>
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<td>3rd</td>
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</tr>
<tr>
<td>3</td>
<td>1st</td>
<td>Interrupt until resolved to grade 0-1</td>
<td>50%</td>
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<tr>
<td>3</td>
<td>2nd</td>
<td>Discontinue or at consultant’s discretion</td>
<td>50%</td>
</tr>
<tr>
<td>3</td>
<td>3rd</td>
<td>Discontinue treatment permanently</td>
<td></td>
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</tbody>
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Cardiotoxicity: Has been associated with fluoropyrimidine therapy (including myocardial infarction, angina, arrhythmias, cardiogenic shock, sudden death and ECG changes). Therefore, exercise caution in patients with prior history of coronary heart disease, arrhythmias and angina pectoris. Coronary artery spasm is a recognised complication of 5FU 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, 5FU 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:

Ngan, S et al, Proceedings ASCO 2001; 20; 591
Royal Surrey County Hospital chemotherapy protocols
www.medicines.org.uk,
Micromedex review, Fluorouracil. Sept2007
BCCA Protocol Summary, GIFUR. Revised Oct2006