MITOMYCIN C / 5-FLUOROURACIL + RADIOTHERAPY

Indication: Squamous cell carcinoma of the anus
For Peripheral Use as an In-Patient

Drug/Dosage:
- 5-Fluorouracil 1000mg/m²/24hr IV D1 - D4 and D29 – D32
- Mitomycin C 12mg/m² (max 20mg) IV D1 of Week 1 only

Patients aged > 70 years, or those with significant inter-current illness:
- 5-Fluorouracil 750mg/m²/24hr IV D1 – D4 and D29 – D32
- Mitomycin C 10mg/m² (max 20mg) IV D1 of Week 1 only

Radiotherapy:
50.4Gy given over 28 fractions (1.8Gy/fraction) on Mondays to Fridays for 5.6 weeks.
Radiotherapy given in 2 phases. In certain cases a further booster dose may be given.
It is stressed that Week 5 of RT must be accompanied by the second course of 5FU.

Administration:
- Mitomycin C via fast running infusion of 0.9% Sodium Chloride.
- 5 Fluorouracil continuous peripheral IV infusion over 4 days, given in 4 x 1 litre 0.9% Sodium Chloride
- NB. 5FU to be started at least 2 hours prior to first fraction of RT

Frequency:
Week 1 and Week 5 - Chemo - radiotherapy
Weeks 2, 3 and 4 - Radiotherapy only
Clinical review weekly

Main toxicities:
- Myelosuppression (can be delayed with MMC); Mucositis; Diarrhoea; Palmar/Plantar Erythema; Radiation fibrosis / necrosis of perineum; Haemolytic Uraemic Syndrome; Coronary artery spasm (see Comments); Ovarian failure/Infertility; Impotence (males); Urinary frequency/cystitis; vaginal stenosis and dyspareunia

Anti-emetics: Moderately emetogenic

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

Extravasation:
Mitomycin C is a vesicant.
Mitomycin:
Local ulceration and cellulitis may be caused by tissue extravasation during intravenous injection. If extravasation occurs, it is recommended that the area is immediately infiltrated with sodium bicarbonate 8.4% solution, followed by an injection of 4mg dexamethasone. Refer to Trust extravasation guidelines.

Regular investigations:
- FBC Weekly
- LFTs Day 1 of Week 1 & Day 1 of Week 5
- U&Es Day 1 of Week 1 & Day 1 of Week 5

Comments:
Maximum cumulative dose of Mitomycin C = 28mg/m² or 56mg total dose.
Dose Modifications

Haematological Toxicity

WBC < 3.0 x 10^9/l
Or
Neutrophils < 1.5 x 10^9/l
Clinical decision for individual situation.
Or
Platelets < 100 x 10^9/l
5FU infusion completed. If in doubt, discuss with Consultant.

NB. Chemotherapy must not be delayed without Consultant approval

Renal Impairment

<table>
<thead>
<tr>
<th>CrCl (ml/min)</th>
<th>Mitomycin C Dose</th>
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<tbody>
<tr>
<td>&gt; 60</td>
<td>Give 100%</td>
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<tr>
<td>10-60</td>
<td>Give 75%</td>
</tr>
<tr>
<td>&lt; 10</td>
<td>Give 50% or omit, confirm with consultant</td>
</tr>
</tbody>
</table>

Hepatic Impairment

Moderate hepatic impairment Give 75% of 5FU dose
Severe hepatic impairment Give 50% of 5FU dose
Dose can be increased if no toxicity seen. If in doubt, check with the relevant Consultant

No specific guidance for Mitomycin dose reductions in liver impairment exists, monitor carefully. Elevated AST levels may produce a prolonged plasma half-life

Other Toxicities – Fluorouracil non-haematological toxicities

<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 1st appearance</td>
<td>Interrupt until resolved to grade 0-1</td>
<td>100%</td>
</tr>
<tr>
<td>Grade 2 2nd appearance</td>
<td>Interrupt until resolved to grade 0-1</td>
<td>75%</td>
</tr>
<tr>
<td>Grade 2 3rd appearance</td>
<td>Interrupt until resolved to grade 0-1</td>
<td>50%</td>
</tr>
<tr>
<td>Grade 2 4th appearance</td>
<td>Discontinue treatment permanently</td>
<td></td>
</tr>
<tr>
<td>Grade 3 1st appearance</td>
<td>Interrupt until resolved to grade 0-1</td>
<td>75%</td>
</tr>
<tr>
<td>Grade 3 2nd appearance</td>
<td>Interrupt until resolved to grade 0-1</td>
<td>50%</td>
</tr>
<tr>
<td>Grade 3 3rd appearance</td>
<td>Discontinue treatment permanently</td>
<td></td>
</tr>
<tr>
<td>Grade 4 1st appearance</td>
<td>Discontinue or at consultants discretion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Interrupt until resolved to grade 0-1</td>
<td>50%</td>
</tr>
</tbody>
</table>
### Palmar-Plantar Erythema

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<th>Appearance</th>
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<th>Dose next cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>maintain dose</td>
<td>100%</td>
</tr>
<tr>
<td>2 1&lt;sup&gt;st&lt;/sup&gt; appearance</td>
<td></td>
<td>Interrupt until resolved to grade 0-1</td>
<td>75%</td>
</tr>
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<td></td>
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### Haemolytic Uraemic Syndrome

Haemolytic Uraemic Syndrome is a complication of Mitomycin C. HUS is a syndrome characterised by red cell fragmentation, renal impairment and death in severe cases. The risk of developing HUS rises significantly with total cumulative doses of MMC above 56mg. Where suspected blood film examination should be requested for red cell fragmentation. Should HUS develop a course of prednisolone 30mg daily for one week should be prescribed in an attempt to prevent any worsening haemolysis and the patient should be discussed with the renal unit.

### Coronary artery spasm

Coronary artery spasm is a recognised complication of 5FU although the evidence base regarding aetiology, management and prognosis is not particularly strong. The incidence is estimated to be between 2% and 18%. Coronary artery spasm is more common in patients receiving continuous infusions of 5FU, and is usually reversible on discontinuing the infusion. Should a patient receiving 5FU present with chest pains, stop the 5FU. 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, the 5FU should be withdrawn permanently. Refer to Consultant to discuss.

### Congestive heart failure

Congestive heart failure has been reported with Mitomycin.

### 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 of 5FU
- Metronidazole- increased plasma levels and toxicity of 5FU
- Folinic acid- increased toxicity of 5FU
- Allopurinol- reduced efficacy of 5FU
- Antacids- 5FU absorption interference
- Tamoxifen- increased risk of haemolytic uremic syndrome with Mitomycin

### References:

- Slevin, ML et al, Proceedings of ASCO 1998; 17: Abstract 266 p69a
- ACT II study, Cancer Research UK Jan 2002
- COIN Guidelines Oct 2000
- Royal Surrey County Hospital chemotherapy protocols [www.medicines.org.uk](http://www.medicines.org.uk)
- BCCA Protocol Summary; GIFUA. Revised Jan 2007