MCF: Mitomycin C / Cisplatin / PVI Fluorouracil for Advanced Oesophageal or Gastric Cancer

Indication: Second line palliative therapy for locally advanced or Metastatic Oesophageal or Gastric Cancer, especially in patients who are unsuitable for anthracycline treatment or who have previously been treated with ECF

Regimen details:
- **Mitomycin C** 7mg/m² (max. 14mg) IV D1 (alternate cycles only)
- **Cisplatin** 60mg/m² IV D1
- **5-Fluorouracil (5-FU)** 300mg/m²/24hrs (♦) IV D1 – D21 (see Administration)

Administration:
- Furosemide 40mg orally
- 1 litre 0.9% Sodium Chloride + 20 mmol KCl + 1g MgSO₄ IV infusion over 60 minutes
- **Mitomycin C** IV Bolus injection via a fast-running Sodium Chloride 0.9% infusion (alternate cycles)
- **Cisplatin** in 1 litre Sodium Chloride 0.9% IV over 2 hours
- Then either 500ml Sodium Chloride 0.9% IV infusion over 60 minutes or 500ml drinking water

*Follow guidance protocol for Hydration schedules & fluid balance monitoring for outpatient Cisplatin regimens*

Any device containing aluminium that may come in contact with Cisplatin must be avoided

(♦) Frail patients – continuous infusion 5-FU

The dose of 5-FU in this regimen is quite high, particularly since it is used in combination. Especially in frail patients, it may be prudent to start at 200mg/m²/day (which most patients tolerate) and increase the dose stepwise (250, 275 then 300mg/m²/day) on successive cycles, if it is well tolerated

5-FU infusion, via central venous catheter and ambulatory infusion device

The Protracted Venous Infused (PVI) 5-FU is continued for a total of 18 weeks, if given for 6 cycles or 24 weeks if 8 cycles

Frequency: Advanced / Metastatic use: 21 days, for 6 – 8 cycles

Extravasation: Mitomycin: Vesicant
Cisplatin and 5-FU: Non-vesicants

Anti-emetics: Highly emetogenic. Follow Local Antiemetic 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)
If warfarin is used as thromboprophylaxis, it should be dosed to a target INR of 1.5

Regular investigations:
- FBC D1
- LFTs & U&Es D1
- Mg²⁺ and Ca²⁺ D1
- EDTA Prior to 1st cycle
- CT scan / OGD After cycles 3, 6 and 8
- CA 19-9 / CEA Prior to 1st and subsequent cycles

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Reason for Update: Network Protocol Development

Version: 1 Approved by Upper GI Consultant: Peter Harper
Supersedes: All other versions Date: 21.05.09
Prepared by: Maria Teresa Pacheca-Palomar July’08 Checked by (Network Pharmacist): Jacky Turner
Approved by SELCN DTAC Chair: Nic Ketley Date: 23.07.09
Comments:
Hemolytic-uremic syndrome – Mitomycin C
A syndrome of renal failure and microangiopathic haemolytic anaemia with hypertension and neurological symptoms (haemolytic-uremic syndrome) has been reported in 10% patients. This syndrome usually appears after 6 months of therapy of Mitomycin C, and may be exacerbated with blood transfusions. Patients should be monitored for development of renal failure or haemolysis.

Hydration - Cisplatin
Encourage oral hydration during treatment; for instance, drink a glass of water every hour during treatment, and at least a further 2 litres over the 24 hours following treatment. Weight should be recorded prior to and at the end of cisplatin treatment, and a strict fluid balance chart should be maintained. An average urine output of at least 100ml/hr must be maintained throughout treatment, and cisplatin infusion should not be commenced unless this urine output is achieved. For low urine output, consider increasing the pre-hydration and diuretic regimen. Consider adding diuretics in weight-gain of 1.5 kg, or symptoms of fluid overload.

Allergy – Cisplatin
Anaphylactic-like reactions to Cisplatin have been reported. Facial edema, bronchoconstriction, tachycardia and hypotension may occur within minutes of Cisplatin administration. Adrenaline, corticosteroids and antihistamines have been effectively employed to alleviate symptoms. No further Cisplatin should be given unless within a “desensitising” protocol.

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.

Coronary artery spasm is more common in patients receiving continuous infusions of 5-FU and is usually reversible on discontinuing the infusion. Should a patient receiving 5-FU present with chest pains, stop the 5-FU. Standard investigation and treatment of angina may be required. If rechallenge is necessary, this can be performed under Consultant supervision, but should symptoms redevelop, the 5-FU should be withdrawn permanently.

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.

Fertility
Both male and female patients must use contraceptive methods to prevent conception and/or reproduction during and for at least 6 months after chemotherapy.
DOSE MODIFICATIONS

Haematological Toxicity

WBC < 3.0 x 10^9/L
or
Neutrophils < 1.5 x 10^9/L
or
Platelets < 100 x 10^9/L
Delay Mitomycin C and Cisplatin for 1 week. Continue with 5-FU, only if Neutrophils ≥ 1.0 x 10^9/L and Platelets ≥ 75 x 10^9/L.

After 1 week, repeat FBC and, if normal, resume treatment at full dose.
If there is a 2 – week delay, give Mitomycin C at 75% dose
If > 2 week delay, give Mitomycin C at 50% dose

Renal Impairment:
GFR should be calculated using the Cockcroft & Gault equation in all patients; if the calculated GFR < 60 or > 120ml/min, measure EDTA clearance or creatinine clearance before prescribing. Monitor trends in serum creatinine between treatments: if 25% from baseline value, re-calculate GFR using the Cockcroft & Gault equation

Fluorouracil: Consider dose reduction in severe renal impairment (GFR < 10ml/min) only

Mitomycin C: Severe renal toxicity has occasionally been reported after treatment and renal function should be monitored before each course

GFR (ml/min) Mitomycin C Dose
> 10 Give 100%
< 10 Give 75%

Cisplatin induces nephrotoxicity, which is cumulative. It is therefore contraindicated in patients with renal impairment. Consider dose reduction following the table below:

<table>
<thead>
<tr>
<th>CrCl (ml/min)</th>
<th>Cisplatin Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 60</td>
<td>Give 100%</td>
</tr>
<tr>
<td>51– 60</td>
<td>Give 75%</td>
</tr>
<tr>
<td>40 – 50</td>
<td>Give 50%</td>
</tr>
<tr>
<td>&lt; 40</td>
<td>Contraindicated</td>
</tr>
<tr>
<td></td>
<td>Consider Carboplatin-Discuss with Consultant</td>
</tr>
<tr>
<td>Dialysis</td>
<td>Give 50%</td>
</tr>
</tbody>
</table>

Hepatic Impairment
Mitomycin C: Dose reductions, probably not necessary. Discuss with Consultant when AST levels > 2 x ULN

Cisplatin: No dose reduction necessary

5-FU 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>5-FU Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 85</td>
<td>&lt; 180</td>
<td>Give 100%</td>
</tr>
<tr>
<td>&gt; 85 or &gt; 180</td>
<td></td>
<td>Contraindicated</td>
</tr>
</tbody>
</table>

Reason for Update: Network Protocol Development

Version: 1
Supersedes: All other versions
Prepared by: Maria Teresa Pacheca-Palomar July’08
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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, PVI 5FU should be discontinued until healing has occurred, and then recommence with dose reduction 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 Life-threatening consequences</td>
<td></td>
<td>Give 25% Discuss with Consultant</td>
</tr>
</tbody>
</table>

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

NEUROPATHY/ OTOTOXICITY – CISPLATIN

If patient develops symptoms indicative Grade 2 Neuropathy (paresthesia interfering with function, but not interfering with activities of daily living) or Ototoxicity (tinnitus not interfering with activities of daily living), seek Consultant advice and consider changing Cisplatin to Carboplatin.

Toxicities: Myelosuppression; alopecia; diarrhoea; mucositis; stomatitis; nausea; vomiting; nephrotoxicity; neuropathy/ ototoxicity; cardiomyopathy; coronary artery spasm; fatigue; fever; palmar-plantar erythema (PPE); ovarian failure; infertility; urine discoloration

Drug interactions: Mitomycin C
- Clozapine: increased risk of agranulocytosis, avoid concomitant use
- Tamoxifen: haemolytic anaemia, thrombocytopenia, renal impairment
- Vinca alkaloids: shortness of breath and bronchospasm
Cisplatin

- Allopurinol, colchicine, probenecid, sulfinpyrazone: increase in serum uric acid concentration
- Cephalosporins, aminoglycosides, amphotericin B: increase nephrotoxic and ototoxic effects of Cisplatin in these organs
- Ciclosporine: excessive immunosuppression, with risk of lymphoproliferation
- Cyclizine, phenothiazines: may mask ototoxicity symptoms
- Furosemide (high doses), hydralazine, diazoxide and propranolol: intensify nephrotoxicity
- Oral anticoagulants: require an increased frequency of the INR monitoring
- Penicillamine: may diminish the effectiveness of Cisplatin
- Phenytoin: reduced epilepsy control

5-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

References:

www.medicines.org.uk
COIN Guidelines. October 2000
UCLH- Dosage Adjustment for Cytotoxics in Renal Impairment. November 2003
UCLH- Dosage Adjustment for Cytotoxics in Hepatic Impairment. November 2003
GSTT guidelines for treating nausea and vomiting in adult patients. September 2007
GSTT Hydration schedules & fluid balance monitoring for outpatient Cisplatin regimens. March 2006
Stockley’s Drug Interactions. Interactions search: Mitomycin, Cisplatin & Fluorouracil. July 08
CTCAE v3.0. August 2006