Cisplatin / 5-Fluorouracil (+ Trastuzumab) in Gastric Cancer

Indication: Confirmed HER2-positive (3+ or FISH+) metastatic adenocarcinoma of the stomach or gastro-oesophageal junction.

For Trastuzumab doses and scheduling see protocol “Trastuzumab in gastric cancer”

Regimen details: Cisplatin 80mg/m\(^2\) IV D1
5-Fluorouracil (5-FU) 800mg/m\(^2\)/24 hours IV D1–D5

Administration: Furosemide 40mg orally
1 litre Sodium Chloride 0.9% + 20mmol KCl + 1g Mg SO\(_4\) IV infusion over 60 minutes
Cisplatin in 1000ml Sodium Chloride 0.9% over 2 hours
1 litre Sodium Chloride 0.9% + 40mmol KCl + 1g Mg SO\(_4\) IV infusion 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

5-FU infusion either via central venous catheter and ambulatory infusion device (this may be attached on the afternoon of Day 1, after the Cisplatin and post-hydration have been completed)

OR
Continuous peripheral IV infusion over 120 hours (5 days) (this administration method requires an inpatient admission for the duration of the infusion), given in 5 x 1 litre Sodium Chloride 0.9%, each 1 litre bag being infused over 24 hours.
(Cisplatin, hydration and any other IV drugs to be administered via a second peripheral cannula)

Frequency: 3 weekly, for 6 cycles

Extravasation: Cisplatin and 5FU: 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)
Mouthwashes, when required- refer to local mouthcare guidelines

Regular investigations: FBC D1
LFTs & U&Es D1
Mg\(^{2+}\) and Ca\(^{2+}\) D1
EDTA Prior to 1st cycle (if necessary)
Audiogram Prior to 1st cycle, when clinically indicated
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.

Electrolyte disturbances – Cisplatin
Disturbances in electrolytes can be a long term manifestation due to the Cisplatin induced renal tubular dysfunction. Check electrolytes- additional supplementation of magnesium, calcium or potassium may be required.

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 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 rechallenge is necessary, this can be performed under Consultant supervision, but should symptoms redevelop, the 5FU 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

<table>
<thead>
<tr>
<th>WBC &lt; 3.0 x 10^9/L</th>
<th>Delay for 1 week or until the myelosuppression is resolved.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophils &lt; 1.5 x 10^9/L</td>
<td>- If there is a 2-week delay, give all drugs at 75% doses</td>
</tr>
<tr>
<td>Platelets &lt; 100 x 10^9/L</td>
<td>- If &gt; 2 week delay, give all drugs at 50% doses</td>
</tr>
</tbody>
</table>

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.

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

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>
</tbody>
</table>

Hepatic Impairment

Cisplatin: No dose reduction necessary.

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 or &gt; 180</td>
<td></td>
<td>Contraindicated</td>
</tr>
</tbody>
</table>

DOSE MODIFICATIONS FOR OTHER TOXICITIES AS APPROPRIATE

NEUROPATHY/ OTOTOXICITY – CISPLATIN

If patient develops symptoms indicative of 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.
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</td>
<td>Life-threatening consequences</td>
<td>Give 25%</td>
</tr>
</tbody>
</table>

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

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

Drug interactions:

Cisplatin
- Allopurinol, colchicine, probenecid, sulfinpyrazone : increase in serum uric acid concentration
- Cephalosporins, aminoglycosides, amphotericin B : increase nephrototoxic 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

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
www.micromedex.com
NICE TA208, Nov 2010
Bang et al.(2010) Lancet; 376: 687-697