Gemcitabine – Capecitabine for Palliative Pancreatic Cancer

Indication: First line palliative therapy for locally advanced or metastatic or relapsed disease.

Regimen details: Gemcitabine 1000mg/m² IV Day 1, 8 and 15
Capecitabine 830 mg/m² PO Twice Daily, Day 1-21 followed by a 7 day rest

Administration: Gemcitabine in 250-500ml Sodium Chloride 0.9% IV infusion over 30 minutes
Capecitabine tablets orally twice daily, swallow whole with water within 30 minutes after a meal and approximately 12 hours apart. Capecitabine is available as 500mg and 150mg tablets.

Frequency: 28 day cycle until disease progression

Pre-medications: Not routinely given

Anti-emetics: Low emetogenicity
Follow Local Anti-emetic Policy

Supportive medication: Diarrhoea can be managed with loperamide
Mouthcare as per local policy

Extravasation: Non-vesicant

Regular investigations: Prior to Day 1 Cycle 1:
FBC Day 1 (within 14 days)
U&Es Day 1 (within 14 days)
LFTs Day 1 (within 14 days)
CT scan Baseline

Prior to Day 8 and Day 15 (all cycles):
FBC Day 8 and 15 (within 48 hours)

Prior to Day 1 (all cycles)
FBC Day 1 (within 72 hours)
U&Es Day 1 (within 72 hours)
LFTs Day 1 (within 72 hours)
CT scan After 3 cycles
Toxicities: Diarrhoea, nausea, vomiting, stomatitis, skin reactions and hand and foot syndrome (palmar-plantar erythrodysesthesia), myelosuppression, proteinuria and haematuria, flu-like syndrome, elevation of transaminases, peripheral oedema, dyspnoea, allergic skin rash often associated with pruritus, alopecia (mild).

Cardiotoxicity: Cardiac arrhythmias, angina pectoris, myocardial infarction, heart failure and cardiomyopathy have been reported in patients receiving capecitabine. Caution must be exercised in patients with history of significant cardiac disease, arrhythmias and angina pectoris

DOSE MODIFICATIONS

Haematological Toxicity

Prior to Day 1

<table>
<thead>
<tr>
<th>Neutrophils (x 10^9/L)</th>
<th>Platelets (x 10^9/L)</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1.0 &amp; ≥ 100</td>
<td></td>
<td>100%</td>
</tr>
<tr>
<td>&lt;1.0 or &lt;100</td>
<td></td>
<td>Delay 1 week. Repeat FBC, if recovered to about these levels, give 100% dose.</td>
</tr>
</tbody>
</table>

If neutrophils < 0.5 x 10^9/L for more than 5 days or < 1.0 x 10^9/L for more than 3 days, or platelets < 25 x 10^9/L, or febrile neutropenia is diagnosed, or toxicity related delay is > 1 week - gemcitabine dose should be reduced to 75% from previous dose (do not escalate for subsequent cycles).

Prior to Day 8 and 15

<table>
<thead>
<tr>
<th>Neutrophils (x 10^9/L)</th>
<th>Platelets (x 10^9/L)</th>
<th>Gemcitabine Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1.0 &amp; ≥ 100</td>
<td></td>
<td>100% dose</td>
</tr>
<tr>
<td>0.5 – 0.9 or 50 - 99</td>
<td></td>
<td>Give 75% dose</td>
</tr>
<tr>
<td>&lt; 0.5 or &lt; 50</td>
<td></td>
<td>Dose can be re-escalated providing the FBC has returned to normal limits.</td>
</tr>
</tbody>
</table>

Non-haematological Toxicities

Renal Impairment Before every course, calculate CrCl using Cockcroft and Gault. If borderline, an EDTA should be requested
<table>
<thead>
<tr>
<th>CrCl (ml/min)</th>
<th>Gemcitabine</th>
<th>Capecitabine</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 50</td>
<td>Give 100% dose</td>
<td>Give 100% dose</td>
</tr>
<tr>
<td>30 - 50</td>
<td>Give 100% dose</td>
<td>Give 75% dose</td>
</tr>
<tr>
<td>&lt; 30</td>
<td>Use with caution, no specific dosing recommendations available</td>
<td>Omit</td>
</tr>
</tbody>
</table>

**Hepatic Impairment**

In the absence of safety and efficacy data in patients with hepatic impairment, capecitabine use should be carefully monitored in patients with mild to moderate liver dysfunction, regardless of the presence or absence of liver metastasis.

<table>
<thead>
<tr>
<th>Bilirubin (μmol/L)</th>
<th>ALT or ALP</th>
<th>Capecitabine</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 3 x ULN or &gt; 2.5 x ULN</td>
<td>Give 100% dose</td>
<td></td>
</tr>
</tbody>
</table>

Use gemcitabine with caution in the presence of hepatic dysfunction.

In clinical trials, gemcitabine was associated with transient elevations of serum transaminases in approximately 70% of patients. However, there is no evidence that longer duration of gemcitabine exposure or greater total cumulative gemcitabine dose increases hepatic toxicity. Administration of gemcitabine in patients with concurrent liver metastases or a pre-existing medical history of hepatitis, alcoholism, or liver cirrhosis may lead to exacerbation of the underlying hepatic insufficiency.

**Dose modifications for other toxicities**

**Gemcitabine Dose adjustment guidelines for non-haematological toxicities**

For any Grade 3 – 4 toxicity, treatment should be deferred until recovery, and then restarted with an appropriate dose reduction - discuss with Consultant

**Capecitabine Dose adjustment guidelines for non-haematological toxicities**

<table>
<thead>
<tr>
<th>CTC Grade</th>
<th>1st Appearance Dose</th>
<th>2nd Appearance Dose</th>
<th>3rd Appearance Dose</th>
<th>4th Appearance Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>2</td>
<td>delay* then 100%</td>
<td>delay* then 75%</td>
<td>delay* then 50%</td>
<td>discontinue</td>
</tr>
<tr>
<td>3</td>
<td>delay* then 75%</td>
<td>delay* then 50%</td>
<td>discontinue</td>
<td>discontinue</td>
</tr>
<tr>
<td>4</td>
<td>discontinue or delay* then 50%</td>
<td>discontinue</td>
<td>discontinue</td>
<td>discontinue</td>
</tr>
</tbody>
</table>
Location of regimen: Out-patient setting

Capecitabine to be supplied to the patient for oral self-administration.
Ensure that the patient has an information pack and the treatment plan.

Comments:

**Haemolytic anaemia**

Gemcitabine should be discontinued at the first signs of any evidence of micro-angiopathic haemolytic anaemia, such as rapidly falling haemoglobin with concomitant thrombocytopenia, elevation of serum bilirubin, serum creatinine, blood urea nitrogen, or LDH, which may indicate development of haemolytic uraemic syndrome. Renal failure may not be reversible, even with discontinuation of therapy, and dialysis may be required.

Women of childbearing potential must use effective contraception during treatment.
Sexually mature males are advised not to father a child during the treatment, and up to 6 months thereafter. If appropriate, male patients should be advised to seek counselling on sperm storage before starting treatment.

Severe skin reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported during treatment with capecitabine. Some cases were fatal. Capecitabine should be discontinued if a serious skin reaction occurs, and the reaction should be treated promptly.

Capecitabine contains anhydrous lactose, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Drug interactions:

- Gemcitabine is a radiosensitiser
- Warfarin - increased anticoagulant effect of warfarin

Significant interactions below. For full details consult product literature/reference texts.

- Allopurinol: avoid concomitant use (reduced efficacy of capecitabine)
- Folinate: avoid concomitant use (enhanced capecitabine toxicity)
- Phenytoin: monitor plasma phenytoin levels (increase phenytoin level)
- Warfarin/coumarin anticoagulants: switched to low molecular weight heparin (altered coagulation parameters and/or bleeding including death)

References:

[www.medicines.org.uk](http://www.medicines.org.uk)


[www.macmillan.org.uk](http://www.macmillan.org.uk)