**Indication**
- Treatment of patients with advanced soft tissue sarcoma who have failed, are unsuitable for or are intolerant of treatment with an anthracycline or ifosfamide.
- Usually consider after failure of trabectedin.
- Performance status 0-2

**ICD-10 codes**
C49

**Regimen details**

<table>
<thead>
<tr>
<th>Day</th>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 and 15</td>
<td>Gemcitabine</td>
<td>1800mg/m²</td>
<td>IV infusion</td>
</tr>
<tr>
<td>1 and 15</td>
<td>Dacarbazine</td>
<td>500mg/m²</td>
<td>IV infusion</td>
</tr>
</tbody>
</table>

**Cycle frequency**
28 days

**Number of cycles**
Up to 6 cycles

**Administration**
Gemcitabine is administered as an IV infusion in 250-500mL sodium chloride 0.9% over 180 minutes prior to the dacarbazine.

Following the Gemcitabine, Dacarbazine is administered as an IV infusion in 500ml sodium chloride 0.9% over 60 minutes. Dacarbazine is sensitive to light exposure. All reconstituted solutions should be suitably protected from light during administration, using a light-resistant giving set.

**Pre-medication**
Anti-emetics as per local policy or as below.
Metoclopramide 10mg IV bolus 10 minutes prior to gemcitabine.
Ondansetron 8mg PO and Dexamethasone 8mg IV bolus 30 minutes prior to dacarbazine

**Emetogenicity**
This regimen has high emetic potential

**Additional supportive medication**
Anti-emetics as per local policy.
Dexamethasone 4mg BD for 2 days after day 1 and 15 of chemotherapy
PPI whilst on dexamethasone, and additionally if required
Mouthwash as required

**Extravasation**
Gemcitabine is neutral (Group 1)
Dacarbazine is a vesicant (Group 5)
Investigations – pre first cycle

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Validity period</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBC</td>
<td>14 days</td>
</tr>
<tr>
<td>U+E (including creatinine)</td>
<td>14 days</td>
</tr>
<tr>
<td>LFT</td>
<td>14 days</td>
</tr>
</tbody>
</table>

Investigations – pre subsequent cycles*

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Validity period</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBC</td>
<td>96 hours</td>
</tr>
<tr>
<td>U+E (including creatinine)</td>
<td>7 days</td>
</tr>
<tr>
<td>LFT</td>
<td>7 days</td>
</tr>
</tbody>
</table>

*Note: all bloods are required pre D1 and D15.

Standard limits for administration to go ahead
If blood results not within range, authorisation to administer must be given by prescriber/consultant

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophils</td>
<td>≥1.0 x 10⁹/L</td>
</tr>
<tr>
<td>Platelets</td>
<td>≥100 x 10⁹/L</td>
</tr>
<tr>
<td>Creatinine clearance</td>
<td>≥60 ml/min</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>≤1.5 x ULN</td>
</tr>
<tr>
<td>ALT/AST</td>
<td>≤2.5 x ULN</td>
</tr>
</tbody>
</table>

Dose modifications

<table>
<thead>
<tr>
<th>Dose reduction</th>
<th>Full</th>
<th>Dose level -1</th>
<th>Dose level -2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemcitabine</td>
<td>1800 mg/m²</td>
<td>1500mg/m²</td>
<td>1200mg/m²</td>
</tr>
<tr>
<td>Dacarbazine</td>
<td>500mg/m²</td>
<td>400mg/m²</td>
<td>350mg/m²</td>
</tr>
</tbody>
</table>

- Haematological toxicity

<table>
<thead>
<tr>
<th>Neutrophils (x 10⁹/L)</th>
<th>Platelets (x 10⁹/L)</th>
<th>Gemcitabine dose</th>
<th>Dacarbazine dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1.0 and/or 0.5 – 0.99 and/or 50 – 99</td>
<td>100% and 100%</td>
<td>Delay 1 week or until recovery (or omit dose) and resume at 100%</td>
<td>Delay 1 week or until recovery (or omit dose) and resume at 100%</td>
</tr>
<tr>
<td>&lt; 0.5 and/or &lt; 50</td>
<td>Omit dose then resume at next dose level reduction</td>
<td>Omit dose then resume at next dose level reduction</td>
<td></td>
</tr>
</tbody>
</table>

If any episode of febrile neutropenia, reduce both drugs by one dose level.
Consider prophylactic G-CSF for grade 3 or 4 neutropenia with previous cycles. Doses may be maintained if isolated neutropenia without pancytopenia.
Once dose levels have been reduced do not escalate for future cycles
If recurrent delays despite reducing gemcitabine two dose levels, consider extending to 21 day interval between doses for both drugs to allow for count recovery.

- Renal impairment

<table>
<thead>
<tr>
<th>CrCl (mL/min)</th>
<th>Dacarbazine dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-60mL/min</td>
<td>400mg/m²</td>
</tr>
<tr>
<td>&lt;30mL/min</td>
<td>300mg/m²</td>
</tr>
</tbody>
</table>

If creatinine clearance <30mL/min consider dose reduction to gemcitabine - discuss with consultant
• **Hepatic impairment**
  If bilirubin >1.5 ULN or ALT > 3x ULN consider reducing gemcitabine one dose level – discuss with consultant

  Grade 4 hepatotoxicity: Delay at least 1 week then dose reduce both drugs by one dose level
  
  If further occurrences, reduce gemcitabine to 1200mg/m\(^2\) and maintain dacarbazine at 400mg/m\(^2\)

• **Other toxicities**

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade</th>
<th>Dose adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin rash</td>
<td>2 or 3</td>
<td>Omit until ≤ grade 1 then restart with gemcitabine reduced one dose level</td>
</tr>
<tr>
<td>Emesis</td>
<td>3</td>
<td>Optimise anti-emetics or stop dacarbazine – consultant decision</td>
</tr>
<tr>
<td>Other non-haematological toxicities</td>
<td>3</td>
<td>Omit until ≤ grade 1 then reduce by one dose level</td>
</tr>
</tbody>
</table>

**Adverse effects** - for full details consult product literature/ reference texts

• **Rare or serious side effects**
  - Myelosuppression
  - Infertility
  - Haemolytic uraemic anaemia*
  - Interstitial pneumonitis, ARDS
  - Cardiotoxicity
  - Hepatotoxicity
  - Impaired renal function
  - Anaphylaxis
  - Extravasation/irritation at application site

  *Gemcitabine should be discontinued at the first sign of microangiopathic haemolytic anaemia (such as rapidly falling haemoglobin with concomitant thrombocytopenia, elevated bilirubin, creatinine, blood urea nitrogen or LDH. Renal failure may not be reversible with discontinuation of therapy, dialysis may be required.

• **Frequently occurring side effects**
  - Nausea and vomiting
  - Myelosuppression
  - Mucositis, stomatitis
  - Diarrhoea, constipation
  - Raised transaminases
  - Peripheral neuropathy
  - Oedema
  - Haematuria
  - Influenza like symptoms
  - Rash
  - Peripheral neuropathy
  - Bone pain

• **Other side effects**
  - Headache
  - Alopecia
  - Fatigue
  - Hyperpigmentation
  - Photosensitivity
  - Anorexia
  - Confusion
**Significant drug interactions** – for full details consult product literature/ reference texts

**Methoxypsoralen:** Dacarbazine can enhance the effect of methoxypsoralen due to photosensitization

**Phenytoin:** Dacarbazine may cause reduced absorption of Phenytoin from the GI tract

**Fotemustine:** Dacarbazine used concomitantly with Fotemustine may cause acute pulmonary toxicity (ARDS)

**Warfarin/coumarin anticoagulants:** increased or fluctuating anticoagulant effects. Avoid if possible or increase monitoring of INR and adjust dose accordingly.

**Ciclosporin:** increased risk of immunosuppression.

**CYP1A2 and 2E1 inhibitors:** may enhance toxicity of dacarbazine

**CYP1A2 inducers:** may reduce effect of dacarbazine

Gemcitabine is a radiosensitiser.

**Additional comments**

Nil

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**References**

2. Gemcitabine and Dacarbazine Royal Marsden NHS Trust Protocol
5. Gemcitabine (pancreas), South West Strategic Clinical Network chemotherapy protocol, via [http://www.swscn.org.uk](http://www.swscn.org.uk)

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