

## Gemcitabine and Dacarbazine

### 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

Day	Drug	Dose	Route
1 and 15	Gemcitabine	1800mg/m <sup>2</sup>	IV infusion
1 and 15	Dacarbazine	500mg/m <sup>2</sup>	IV infusion

### 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

Antiemetics 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

Investigation	Validity period
FBC	14 days
U+E (including creatinine)	14 days
LFT	14 days

### Investigations – pre subsequent cycles\*

Investigation	Validity period
FBC	96 hours
U+E (including creatinine)	7 days
LFT	7 days

\*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

Investigation	Limit
Neutrophils	$\geq 1.0 \times 10^9/L$
Platelets	$\geq 100 \times 10^9/L$
Creatinine clearance	$\geq 60$ ml/min
Bilirubin	$\leq 1.5 \times$ ULN
ALT/AST	$\leq 2.5 \times$ ULN

### Dose modifications

Dose reduction	Full	Dose level -1	Dose level -2
Gemcitabine	1800 mg/m <sup>2</sup>	1500mg/m <sup>2</sup>	1200mg/m <sup>2</sup>
Dacarbazine	500mg/m <sup>2</sup>	400mg/m <sup>2</sup>	350mg/m <sup>2</sup>

#### • Haematological toxicity

Neutrophils (x 10 <sup>9</sup> /L)		Platelets (x 10 <sup>9</sup> /L)	Gemcitabine dose	Dacarbazine dose
$\geq 1.0$	and	$\geq 100$	100%	100%
0.5 – 0.99	and/or	50 – 99	Delay 1 week or until recovery (or omit dose) and resume at 100%	Delay 1 week or until recovery (or omit dose) and resume at 100%
< 0.5	and/or	< 50	Omit dose then resume at next dose level reduction	Omit dose then resume at next dose level reduction

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

CrCl (mL/min)	Dacarbazine dose
30-60mL/min	400mg/m <sup>2</sup>
<30mL/min	300mg/m <sup>2</sup>

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<sup>2</sup> and maintain dacarbazine at 400mg/m<sup>2</sup>

- Other toxicities**

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

**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

1. Garcia-del-Muro X et al. Randomised Phase II Study Comparing Gemcitabine Plus Dacarbazine Versus Dacarbazine alone in Patients With Previously Treated Soft Tissue Sarcoma: A Spanish Group for Research on Sarcomas Study. *J Clin Oncol* 2011; 29:2528-2533
2. Gemcitabine and Dacarbazine Royal Marsden NHS Trust Protocol
3. Gemcitabine SPC, Electronic Medicines Compendium, via <https://www.medicines.org.uk/emc>
4. Dacarbazine SPC, Electronic Medicines Compendium, via <https://www.medicines.org.uk/emc>
5. Gemcitabine (pancreas), South West Strategic Clinical Network chemotherapy protocol, via <http://www.swscn.org.uk>

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