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^2	IV infusion
1 and 15	Dacarbazine	500mg/m^2	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 PO or 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	≥1.0 x 10^9/L
Platelets	≥100 x 10^9/L
Creatinine clearance	≥60 ml/min
Bilirubin	≤1.5 x ULN
ALT/AST	≤2.5 x ULN

Dose modifications

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

- **Haematological toxicity**

Neutrophils (x 10^9/L)		Platelets (x 10^9/L)	Gemcitabine dose	Dacarbazine dose
≥ 1.0	and	≥ 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^2
<30mL/min	300mg/m^2

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**

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

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

---

Written/reviewed by: Dr Tim Spencer (Clinical Oncology SpR, UHBW NHS Trust), Dr Gareth Ayre (Consultant Clinical Oncologist, UHBW NHS Trust) and Dr Adam Dangoor (Consultant Medical Oncologist, UHBW NHS Trust)

Checked by: Kate Gregory (Lead Pharmacist for SACT protocols, SWAG Cancer Alliance)

Authorised by: Dr J Braybrooke (Consultant Oncologist, UHBW NHS Trust , SWAG Cancer Alliance)

Date: February 2021
