SACT PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

Dacarbazine Melanoma

PROTOCOL REF: MPHAMMEDAC
(Version No. 2.0)

Approved for use in:

- Malignant melanoma
- ECOG performance status score must be 0 or 2.

Dosage:

Drug	Dose	Route	Frequency
Dacarbazine	**850mg/m^2**	IV infusion	Day 1 only of a 21 day cycle

The duration of treatment depends on the efficacy and tolerability in the individual patient. Maximum of 8 cycles will be set in Meditech.

Administration (+/- Counselling Points):

Dacarbazine is light sensitive. The infusion should be protected from light during administration. Do not use if the solution has a pink or red discolouration.

Hepatotoxic medicinal products and alcohol should be avoided during chemotherapy.

Women of child-bearing potential have to use effective contraception during treatment and breast-feeding should be avoided.

Men are advised to take contraceptive measures during and for 6 months after cessation of therapy.

Dacarbazine may influence the ability to drive or operate machines because of its central nervous side effects or because of nausea and vomiting.

Emetogenic risk:

Severely emetogenic.

Supportive treatments:

Dexamethasone 4mg oral tablets twice daily for 3 days
Domperidone 10mg oral tablets maximum 3 times a day or as required

Extravasation risk:

Vesicant.
Refer to the CCC policy for the 'Prevention and Management of Extravasation Injuries'

Dosing in renal and hepatic impairment:

	Creatinine Clearance (ml/min)	Dose (% of original dose)
Renal	≥ 30 (without hepatic impairment)	No dose adjustment
	< 30	70% of the original dose
	Haemodialysis	70% of the original dose

Hepatic	Dacarbazine is activated and metabolised in the liver. It can be hepatotoxic. If there is mild to moderate hepatic impairment without renal impairment, a dose reduction is not usually required. Dacarbazine is contraindicated in severe liver disease. Consider a dose reduction in patients with combined renal and hepatic impairment.

Interactions:

Dacarbazine is metabolised by cytochrome P450 (CYP1A1, CYP1A2, and CYP2E1). This has to be taken into account if other medicinal products are co-administered which are metabolised by the same hepatic enzymes.

Dacarbazine can enhance the effects of methoxypsoralen because of photosensitization.

Concomitant use with phenytoin should be avoided because reduced absorption of phenytoin from the gastrointestinal tract may predispose the patient to convulsions.

Concomitant use of cyclosporine (and in some cases tacrolimus) must be considered carefully because these agents may cause excessive immunosuppression and lymphoproliferation.

Concomitant use of fotemustine can cause acute pulmonary toxicity (adult respiratory distress syndrome). Fotemustine and dacarbazine should not be used concomitantly.

In case of previous or concomitant treatment having adverse effects on the bone marrow (particularly cytostatic agents, irradiation) myelotoxic interactions are possible.

Treatment schedule:

Day	Drug	Dose	Route	Diluent and rate
1	**Ondansetron** 30mins before chemotherapy	24mg	oral	
	Dexamethasone 30mins before chemotherapy	12mg	Oral	
1	**Dacarbazine**	850mg/m²	IV Infusion	500ml sodium chloride 0.9% Over 15 to 30 minutes in an opaque non-pyrogenic line – store in a fridge and protect from light (especially direct sunlight)

Main toxicities:

Dacarbazine	
Infections and infestations	Uncommon Infections
Blood and lymphatic system disorders	Common Anaemia, leukopenia, thrombocytopenia Rare) Pancytopenia, agranulocytosis
Immune system disorders	Rare Anaphylactic reactions
Nervous system disorders	Rare Headaches, impaired vision, confusion, lethargy, convulsions, facial paraesthesia
Vascular disorders	Rare Facial flushing
Gastrointestinal disorders	Common Anorexia, nausea, vomiting Rare Diarrhoea
Hepatobiliary disorders	Rare Hepatic necrosis due to veno-occlusive disease (VOD) of the liver, Budd-Chiari syndrome (with potentially fatal outcome)
Renal and urinary disorders	Rare Impaired renal function

Skin and subcutaneous tissue disorders	Uncommon Alopecia, hyperpigmentation, photosensitivity Rare Erythema, maculopapular exanthema, urticaria
General disorders and administration site conditions	Uncommon Flu-like symptoms Rare Application site irritation
Investigations	Rare Hepatic enzymes increased (e.g. alkaline phosphatase, ASAT, ALAT), blood lactate dehydrogenase (LDH) increased, blood creatinine increased, blood urea increased

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

Investigations and treatment plan:

	Pre	Cycle 1	Cycle 2	Cycle 3	Ongoing
Informed Consent	x				
Clinical Assessment	x			x	Every 3 months and as clinically indicated
SACT Assessment (to include PS and toxicities)	x	x	x	x	Every cycle
FBC	x	x	x	x	Every cycle
U&E & LFTs & LDH	x	x	x	x	Every cycle
CT scan	x			x	Every 9 - 12 weeks/if clinically indicated

Pregnancy test if applicable.

Dose Modifications and Toxicity Management:

Dacarbazine dose reduction	
First dose reduction	20%
Second dose reduction	Review by oncologist

Haematological toxicity:

Proceed on day 1 if-

ANC ≥ 1.0 x 10^9/L	Plt ≥ 100 x 10^9/L

Delay 1 week on day 1 if-

ANC ≤ 0.9 x 10^9/L	Plt ≤ 99 x 10^9/L

If treatment is delayed for a second week, as a result ofplatelets or neutrophils remaining below the required levels, the patient must be assessed by an oncologist for a review of the treatment plan.

Non- Haematological toxicity:

	Creatinine Clearance (ml/min)	Dose (% of original dose)
Renal	≥ 30 (without hepatic impairment)	No dose adjustment
	< 30	70% of the original dose
	Haemodialysis	70% of the original dose

Hepatic	Dacarbazine is activated and metabolised in the liver. It can be hepatotoxic. If there is mild to moderate hepatic impairment without renal impairment, a dose reduction is not usually required. Dacarbazine is contraindicated in severe liver disease. Consider a dose reduction in patients with combined renal and hepatic impairment or if the baseline liver function tests double during therapy.

References:

1. https://www.medicines.org.uk/emc. Dacarbazine 100mg, 200mg, 500mg, 1000mg. Summary of Product Characteristics. medac GmbH 28/11/1997. Available from https://www.medicines.org.uk/emc/product/7748/smpc. Last updated 20/11/20.
2. BNF available via: https://bnf.nice.org.uk/

3. NICE: NG14 Melanoma: assessment and management. Published date: July 2015. Last updated: July 2022.
4. Krens S D, Lassche, Jansman G F G A, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. Lancet Oncol 2019; 20: e201–08.

Circulation/Dissemination

Date added into Q-Pulse	17th August 2023
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Version History

		Author name and designation	Summary of main changes
10th of June 2016	1.0	Jo Upton / Gareth Hunt Pharmacist	New protocol
April 2023	2.0	Hugh O'Neill Skin SRG Pharmacist	Updated to new template Updated indication Updated dose modification and toxicity management to align with standard IO protocol