SACT PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

Cyclophosphamide , Vincristine an Dacarbazine (CVD) Malignant Phaeochromocytoma

PROTOCOL REF: MPHACVDMP
(Version No.1.0)

Approved for use in:

Advanced or metastatic malignant phaeochromocytoma.

ECOG Performance Score (PS) ≥ 2.

Dosage:

Drug	Dosage	Route	Frequency
Vincristine	1.4mg/m^2 (max 2mg) Day 1	IV Infusion	Every 21 days
Dacarbazine	600mg/m^2 Days 1 and 2	IV infusion	Every 21 days
Cyclophosphamide	750mg/m^2 Day 1	Slow IV Bolus	Every 21 days

For 6 to 8 cycles but can be continued beyond this depending on the efficacy and tolerability in individual patients.

Counselling Points

Women of childbearing potential should use effective contraception throughout treatment and for at least 12 months following discontinuation of treatment. Sexually mature males are advised to use effective contraceptive measures during the treatment and up to 6 months thereafter.

Cyclophosphamide can irritate the bladder, maintaining a good fluid intake is recommended.

Please contact the triage line if any of the following symptoms occur:

- Easy bruising or bleeding.
- Uncontrolled nausea, vomiting, constipation or diarrhoea.
- New or worsening cough, chest pain or shortness of breath
- Signs of infection such as fever, chills, cough, pain or burning on passing urine.
- Redness, swelling, pain or sores where the needle was place or along the arm.
- Redness, swelling, pain or sores on your lips, tongue, mouth or throat.
- Allergic reaction such as dizziness, fast heart rate, facial swelling, shortness of breath, skin rash or itching.
- Numbness or tingling in feet or hands or painful leg cramps.
- Signs of anaemia such as unusual tiredness, dizziness, shortness of breath or weakness.

Emetogenic risk:

Highly emetogenic.

Supportive treatments:

- Dexamethasone 4mg twice daily for 3 days.
- Metoclopramide10mg tablets, to be taken up to three times a day as required (total 5 days' supply).
- Cyclizine 50mg orally up to three times a day when required (2nd line anti-emetic).

Extravasation risk:

Cyclophosphamide- IRRITANT

Vincristine- VESICANT

Dacarbazine- VESICANT

Refer to the CCC policy for '[Prevention and Management of Extravasation Injuries]'

Dosing in renal and hepatic impairment:

<table>
<tr><td rowspan="3">Renal</td><td>Cyclophosphamide</td><td><table>
<tr><th>CrCl (mL/min)</th><th>Dose</th></tr>
<tr><td>≥ 30</td><td>100%</td></tr>
<tr><td>10-29</td><td>75%</td></tr>
<tr><td>< 10
Or
Haemodialysis (HDx)</td><td>Not recommended. If unavoidable consider 50% of the original dose</td></tr>
</table></td></tr>
<tr><td>Vincristine</td><td>No dose adjustment required.</td></tr>
<tr><td>Dacarbazine</td><td>CrCl ≥30 ml/min without hepatic impairment: no dose adjustment is needed
CrCl <30 ml/min: 70% of the original dose may be considered. Discuss with clinical team.
CrCl ≤ 15ml/min or on haemodialysis – not recommended.</td></tr>
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<table>
<tr><td>Hepatic</td><td>Cyclophosphamide</td><td><table>
<tr><th>LFTs</th><th>Dose</th></tr>
<tr><td>Bil 21 to 51 µmol/L
Or
AST 2-4 x ULN</td><td>100%</td></tr>
<tr><td>Bil 52 to 85 µmol/L
Or
AST > 4 x ULN</td><td>75%</td></tr>
<tr><td>Bil > 85 µmol/L
Or
Child-Pugh C</td><td>OMIT</td></tr>
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	Vincristine	Bilirubin > 51 µmol/l: administer 50% of original dose
	Dacarbazine	Dacarbazine is activated and metabolised in the liver. It can be hepatotoxic. Mild (bilirubin >1.0-1.5 x ULN and any AST/ALT OR bilirubin ≤ULN and AST/ALT >ULN) and moderate (bilirubin 1.5-3 x ULN, with any AST/ALT) without renal impairment (CrCl ≥ 30ml/min): no dose adjustment is needed **Severe (bilirubin >3.0-10 x ULN, with any AST): contra-indicated.**

Interactions:

Refer to SmPC for full list of interactions.

Cyclophosphamide
Increase Cyclophosphamide Active Metabolites Cytochrome P450 enzyme inducers such as rifampicin, carbamazepine, phenytoin, St John's Wort, corticosteroids Allopurinol, cimetidine and protease inhibitors. Altered Effectiveness of Cyclophosphamide Aprepitant, ciprofloxacin, fluconazole, itraconazole, grapefruit juice.
Vincristine
Increased risk of neurotoxicity when co-administered with other neurotoxic rugs e.g. isoniazid. Reduced anti-convulsant effect when administered with phenytoin (increased seizure activity). Monitoring of phenytoin plasma levels recommended. Concurrent administration of vincristine sulfate with itraconazole or fluconazole (known inhibitor of the P450 metabolic pathway) have been reported to cause an earlier onset and/or an increased severity of neuromuscular side-effects, inducers like St. John's Wort

should be given cautiously. This interaction is presumed to be related to inhibition of the metabolism of vincristine.

Dacarbazine

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.

Administration of **live vaccines** to patients who are immunocompromised as a result of treatment with chemotherapeutics such as dacarbazine can cause serious and potentially fatal infections.

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.

Treatment schedule:

Day	Drug	Dose	Route	Diluent and rate
1	**Ondansetron**	**24mg**	**PO**	30 minutes before chemotherapy
	Dexamethasone	**12mg**	**PO**	30 minutes before chemotherapy
	Vincristine	**1.4mg/m^2 (Max 2mg)**	**IV**	In 50mL sodium chloride 0.9% over 10 minutes
	Dacarbazine	**600mg/m2**	**IV**	In 500mL sodium chloride 0.9% over 15 to 30 minutes

				via an opaque non-pyrogenic line – store in a fridge and protect from light (especially direct sunlight)
	Cyclophosphamide	**750mg/m2**	**IV**	Over 30 minutes
2	**Ondansetron**	**24mg**	**PO**	30 minutes before chemotherapy
	Dexamethasone	**12mg**	**PO**	30 minutes before chemotherapy
	Dacarbazine*	**600mg/m2**	**IV**	In 500mL sodium chloride 0.9% over 15 to 30 minutes via an opaque non-pyrogenic line – store in a fridge and protect from light (especially direct sunlight)

For 6 to 8 cycles but can be continued beyond this depending on the efficacy and tolerability in individual patients.

***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 is observed.**

Patients may experience allergic reaction during administration. Please refer to the CCC Hypersensitivity; Management Prevention Policy.

For severe reactions, discuss with Consultant before continuing with treatment. It should be strongly noted that patients who have severe reactions should not be re-challenged.

Main toxicities:

Thrombocytopenia, neutropenia, anaemia, nausea, vomiting, diarrhoea

Gastrointestinal	Anorexia, nausea, vomiting, diarrhoea, constipation, mucositis
Cardiac	**Episodes of hypotension-** in clinical trials these most often occurred following the 1st cycle, 3-5 days after SACT administration. These resolved quickly with appropriate administration of fluids and reducing dose of anti-hypertensives. **Cyclophosphamide-** high dose over prolonged period can cause transient ECG changes, asymptomatic increase in cardiac enzymes to severe myocarditis. Clinical signs include SOB, raised RR, peripheral oedema.
Haematological- Cyclophosphamide and dacarbazine	Myelosuppression –fever, neutropenia, anaemia, thrombocytopena may be more severe and required dose reductions
Respiratory	Interstitial lung disease (ILD) - high dose over prolonged period. Risk factors include exposure to other drugs with pulmonary toxicity and RT to the lungs.
Hepatobillary	Dacarbazine can cause hepatotoxicity with hepatocellular necrosis and/or hepatic vascular occlusion.
Renal/Genitourinary (GU)-	**Cyclophosphamide**

	Non-haemorrhagic cystitis- increased frequency, urgency, nocturia and dysuria (pain/burning/stinging on urination). Haemorrhagic cystitis- risk factors are high dose, prolonged duration of treatment, rate of infusion, impaired metabolism, hydrations status, urine output and exposure to other nephrotoxic drugs of GU RT. Non-specific symptoms such as haematuria, dysuria, urgency and increased frequency of urination and can be confirmed using cystoscopy Severe hemorrhagic cystitis can be life-threatening. **Dacarbazine** Phototoxicity can occur in up to 10% of cases. Typically, occurs hours after treatment and lasts 1-4 days. It is self-limiting and does not require drug discontinuation.
Dermatological reactions	Cyclophosphamide- alopecia, hyperpigmentation of nails and skin, rash hives or itching. Facial flushing can occur in up to 10% of cases,
Nervous system- vincristine	Involves peripheral, autonomic and central neuropathy. It is the principal dose-limiting toxicity of vincristine. Most side effects are dose-related and reversible, but neurotoxicity can persist for months after

	discontinuation of therapy in some patients, and in rare cases may be disabling. **Peripheral neuropathy-** most common form. Manifests as loss of deep tendon reflexes, peripheral paraesthesias, pain and tingling can occur. If therapy is prolonged or high doses are administered, wrist and foot drop, ataxia, a slapping gait and difficulty in walking can occur. Cranial nerve toxicities may lead to vocal cord paresis or paralysis (hoarseness, weak voice), ocular motor nerve dysfunction (ptosis, strabismus), bilateral facial nerve palsies, or jaw pain **Autonomic neuropathy-** causes constipation (which can be severe), abdominal pain, urinary retention and paralytic ileus. Constipation may be associated with impaction of stool in the upper colon. This condition is responsive to high enemas and stimulant laxatives. Stool softeners and laxatives can be given prophylactically to prevent constipation. **Central neuropathy**- includes headache, malaise, dizziness, seizures, mental depression, psychosis and SIADH.
Radiation recall reactions	In rare cases cyclophosphamide can potentiate radiation injury to tissues. This may occur with RT given prior, concurrent or even after cyclophosphamide treatment.

Investigations and treatment plan:

	Pre	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Ongoing
Informed Consent	X					
Clinical Assessment	X		X			Prior to cycle 2 then every three cycles
SACT Assessment (to include PS and toxicities)*	X	X	X	X	X	Every cycle
FBC	X	X	X	X	X	Every cycle
U&E & LFTs & Magnesium	X	X	X	X	X	Every Cycle
Bone profile	X	X	X	X	X	Every cycle
Check CrCl using Cockroft and Gault (C&G) formula	X	X	X	X	X	Every cycle
CT scan	X				X	Every three months
ECG						If clinically indicated
Full set of observations (*BP, heart rate, temperature, respiratory rate and O_2 sats*)		X				At baseline then as clinically indicated
Weight recorded	X	X	X	X	X	Every cycle
Height recorded	X					

* **Episodes of hypotension-** in clinical trials these most often occurred following the 1st cycle, 3-5 days after SACT administration. These resolved quickly with appropriate administration of fluids and reducing dose of anti-hypertensives.

Dose Modifications and Toxicity Management:

Haematological toxicity:

These haematological guidelines assume that patients are well with good performance status, that other acute toxicities have resolved and the patient has not had a previous episode of neutropenic sepsis.

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 of platelets 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:

Grading and Management of Toxicity

Toxicity should be grading according to the CTCAEv5 criteria. Following assessment treatment should be withheld for any toxicity until resolved to grade 0/1.

For dose modification, based on renal or hepatic toxicity refer to 'Dosing in renal and hepatic impairment' section above.

For any other:

- **Persistent/un-resolving G2 (despite treatment breaks and supportive measures)** hold treatment until resolved to G1 or less and consider dose reduction by 20%. Discuss with clinical team.

- **G3 toxicities-** hold treatment until resolved to G1 or less and refer to clinical team for review ahead of next cycle.

References:

1. Averbuch, S.D., Steakley, C.S., Young, R.C., Gelmann, E.P., Goldstein, D.S., Stull, R. and Keiser, H.R., 1988. Malignant pheochromocytoma: effective treatment with a combination of cyclophosphamide, vincristine, and dacarbazine. Annals of internal medicine, 109(4), pp.267-273.
2. Cyclophosphamide 500mg powder for solution for injection SmPC, Baxter Healthcare Ltd. Available from www.medicines.org.uk/emc/medicine. Last updated 29th June 2016.
3. Dacarbazine medac 500 mg, powder for solution for infusion SmPC, Medac GmbH. Available from www.medicines.org.uk/emc/medicine. Last updated 20th November 2020.
4. Huang, H., Abraham, J., Hung, E., Averbuch, S., Merino, M., Steinberg, S.M., Pacak, K. and Fojo, T., 2008. Treatment of malignant pheochromocytoma/paraganglioma with cyclophosphamide, vincristine, and dacarbazine: recommendation from a 22-year follow-up of 18 patients. Cancer, 113(8), pp.2020-2028.
5. 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.
6. Vincristine Sulphate 1 mg/ml Injection SmPC, Hospira UK Ltd. Available from www.medicines.org.uk/emc/medicine. Last updated 14th March 2023.

Circulation/Dissemination

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Date document posted on the Intranet	N/A

Version History

		Author name and designation	Summary of main changes
		Hala Ghoz **Lead Protocols Pharmacist**	V1.0 New regimen protocol