Systemic Anti Cancer Treatment Protocol

EDP + mitotane

PROCEDURE REF: MPHAHANEDP
(Version No: 1.0)

Approved for use in:

Symptomatic treatment for advanced (unresectable, metastatic or relapsed) adrenocortical carcinoma
ECOG performance status of 0 - 2

All possible tumour tissues should be surgically removed from large metastatic masses before mitotane administration is instituted. This is necessary to minimise the possibility of infarction and haemorrhage in the tumour due to a rapid cytotoxic effect of mitotane

Exclusion criteria: Previous complete cumulative doses of anthracyclines
Decompensated heart failure (ejection fraction <50%)
Unstable angina, uncontrolled cardiac arrhythmias, MI or revascularisation procedure within last 6 months

Dosage:

Drug	Dosage	Route	Frequency
Etoposide	100mg/m^2	IV	Daily on days 2, 3 and 4 of each cycle
Doxorubicin	40mg/m^2	IV	Once only on day 1 of each cycle
Cisplatin	40mg/m^2	IV	Daily on days 3 and 4 of each cycle
Mitotane	Variable, max 6g daily	PO	Continuous, started a week prior to IV chemotherapy if not already taking

With cycles repeated at 28 day intervals until disease progression

Supportive treatments:

Domperidone 10mg oral tablets maximum 3 times a day or as required

Extravasation risk:

Doxorubicin is a vesicant and must be observed during administration.
Follow the procedure for anthracycline extravasation.
Erythematous streaking (a histamine release phenomenon) along the vein proximal to the site of injection has been reported, and must be differentiated from an extravasation event. This reaction usually subsides within 30 minutes.

Cisplatin: Exfoliant
Injection site reactions may occur during the administration of cisplatin. Given the possibility of extravasation, it is recommended to closely monitor the infusion site for possible infiltration during drug administration.
Follow the extravasation procedure for suspected cases, and consider hyaluronidase, topical hydrocortisone cream.

Etoposide: Irritant
Follow the extravasation procedure for suspected cases, and consider cold compress.

Administration:

Mitotane

Mitotane should be started at least 1 week before the initiation of EDP chemotherapy (most patients will already have commenced this ahead of requiring intravenous chemotherapy)

Available as 500mg tablets
It should be taken with a glass of water during a fat rich meal (as this enhances absorption)

Maintenance Mitotane, taken orally, up to 6g daily in divided daily doses (bd to qds)

Dose may be reduced to 1-2 g per day after 2 months of treatment (cumulative dose of 200g) or in case of toxicity

EDP

- **Review patient's fluid intake over the previous 24 hours**
- **Review common toxicity criteria and performance status**
- **Calculate creatinine clearance using Cockroft and Gault equation (see investigation section)**
- **Weigh the patient prior to commencing intravenous fluids**
- **Commence strict fluid balance (input and output)**

Day	Drug	Dose	Route	Diluent and rate
1	Ondansetron	16mg	PO	
	Dexamethasone	8mg	PO	
	Doxorubicin	**40mg/m^2**	**IV**	Via the tubing of a fast running infusion of sodium chloride 0.9%
2	Ondansetron	16mg	PO	
	Dexamethasone	8mg	PO	
	Etoposide	**100mg/m^2**	**IV**	In 1000mL sodium chloride 0.9% over 60 minutes
3	Ondansetron	16mg	PO	
	Dexamethasone	8mg	PO	
	Sodium Chloride 0.9% 500mL		**IV**	Over 30 minutes
	Etoposide	**100mg/m^2**	**IV**	In 1000mL sodium chloride 0.9% over 60 minutes
	Measure urine output volume and record **If urine output averages 100mL/hour over previous 3 hours then proceed with cisplatin infusion** **If urine output is less than 100mL/hour the patient should be assessed and further 500mL sodium chloride 0.9% given IV over 30 minutes** **If urine output still not adequate contact the prescriber**			
	Cisplatin	**40mg/m^2**	**IV**	Sodium Chloride 0.9% 1000mL over 90 minutes
	Sodium Chloride 0.9% 1000mL with 20mmol Potassium Chloride	**1000mL**	**IV**	Over 90 minutes
4	**Ondansetron**	16mg	PO	
	Dexamethasone	12mg	PO	
	Sodium Chloride 0.9% 500mL		**IV**	Over 30 minutes

4	**Etoposide**	**100mg/m^2**	**IV**	Over 60 minutes
	Measure urine output volume and record **If urine output averages 100mL/hour over previous 3 hours then proceed with cisplatin infusion** **If urine output is less than 100mL/hour the patient should be assessed and further 500mL sodium chloride 0.9% given IV over 30 minutes** **If urine output still not adequate contact prescriber**			
	Cisplatin	**40mg/m^2**	**IV**	Sodium Chloride 0.9% 1000mL over 90 minutes
	Sodium Chloride 0.9% 1000mL with 20mmol Potassium Chloride	**1000mL**	**IV**	Over 90 minutes

Cisplatin:

Infusion bag should be protected from light
Store at room temperature

Etoposide:

Check storage conditions on infusion bag label as this will depend on the concentration

Main Toxicities:

Cisplatin
Haematological: leukopenia, thrombocytopenia and anaemia Gastrointestinal: anorexia, nausea, vomiting and diarrhoea Nephrotoxicity: urine output of 100 ml/hour or greater will help minimise cisplatin nephrotoxicity. Neuropathies Ototoxicity
Etoposide
Nausea and vomiting, myelosuppression (thrombocytopenia, anaemia and neutropenia), Mucositis, oesophagitis and stomatitis occur infrequently. Alopecia, Anaphylactoid reactions Hypotension may occur following an excessively rapid infusion of etoposide and may be reversed by slowing the infusion rate. Hypertension and/or flushing have also been reported. Blood pressure usually returns to normal within a few hours after cessation of the infusion. Bronchospasm. Peripheral neuropathy. Fatigue. Fever.
Doxorubicin
High cumulative doses are associated with cardiomyopathy and it is usual to limit total cumulative doses to 450mg/m^2 Myelosuppression Red colouration to urine Alopecia Nausea and vomiting
Mitotane
Elevated liver enzymes, increased plasma cholesterol and triglyceride levels Immunosuppression and prolonged bleeding time GI toxicity – nausea, vomiting, diarrhoea, mucositis Sleepiness, vertigo, headache, dizziness, mental confusion Rash, gynaecomastia Adrenal insufficiency Patients should be counselled not to drive

Investigations:

- FBC prior to each cycle
- U&Es & LFTs prior to each cycle, including magnesium
- Calculate creatinine clearance using the Cockroft and Gault Formula
- Consultant review prior to each cycle

Cockroft and Gault formula

Male patients $\frac{1.23 \times (140 - \text{age}) \times \text{weight (kg)}}{\text{Serum Creatinine (micromol/L)}}$

Female patients $\frac{1.04 \times (140 - \text{age}) \times \text{weight (kg)}}{\text{Serum Creatinine (micromol/L)}}$

Dose Modifications and Toxicity Management:

Haematological toxicity

Proceed on day 1 if:-

WCC ≥ 3.0 x 10^9/L	Platelets ≥ 100 x 10^9/L	ANC ≥ 1.0 x 10^9/L

Delay 1 week on day 1 if:-

WCC ≤ 2.9 x 10^9/L	Platelets ≤ 99 x 10^9/L	ANC ≤ 0.9 x 10^9/L

- If WCC, platelets or ANC still below required levels for treatment at week 2, delay treatment again and refer back to oncologist for review considering dose reduction
- If severe neutropenia or thrombocytopenia between cycles, consider dose reduction to 80%for doxorubicin and etoposide.

Non-haematological toxicity

Renal

Cisplatin:
Review toxicity of previous dose of cisplatin and take account of previous renal impairment when making decision about subsequent doses.

GFR (mL/min)	Dose
>60	100%
45-59	75%
<45	Consider carboplatin, but caution regarding potential for myelosuppression

Etoposide:

GFR (mL/min)	Dose
>50	100%
15-50	75%
<15	50%

Avoid doxorubicin in severe renal failure, e.g.CrCl < 20mL/min
Mitotane dose reduction should be considered when < 60mL/min

Hepatic

Bilirubin (µmol/L)		AST/ALT (units)	Etoposide Dose	Doxorubicin Dose
26-51	or	60-180	50%	50%
>51	or	>180	Clinical decision	25%

Neurotoxicity

CTC grade	Cisplatin	Doxorubicin	Etoposide	Mitotane
0-1	100% dose	100% dose	100% dose	100% dose
2	50% dose	100% dose	50% dose	Delay then restart at 100%
3	Delay	Delay	Delay	Delay then restart at 50 – 70% dose
4	Stop	Stop	Stop	Stop

Drug Interactions

Mitotane is a cytochrome P450 enzyme inducer (anticonvulsants, rifabutin, rifampicin, St.johns wort)

Mitotane has been shown to increase plasma hormone binding protein: this should be taken into account when interpreting the results of hormonal assays.

Spironolactone blocks the action of mitotane
Warfarin: accelerated metabolism of warfarin
Anti-epileptics: reduced absorption of phenytoin with cisplatin and doxorubicin
Nephrotoxic drugs: avoid concomitant use with cisplatin
Ototoxic drugs: avoid concomitant use with cisplatin
Grape fruit juice: reduced etoposide levels

References:

London Cancer Alliance protocol 2008
Combination chemotherapy in advanced adrenocortial carcinoma: NEJM 2012; 366: 2189-97.
Fassnacht M et al