DOXORUBICIN CISPLATIN ETOPOSIDE MITOTANE (Lysodren) (EDP-Mitotane)

INDICATION (ICD10) C74

1. Metastatic adrenal cancer. PS 0, 1, 2

REGIMEN

Day 1 DOXORUBICIN 40mg/m^2 IV bolus
Day 2 ETOPOSIDE 100mg/m^2 in #ml sodium chloride 0.9% IV infusion over 60 minutes
Days 3 and 4 Prehydration
ETOPOSIDE 100mg/m^2 in #ml sodium chloride 0.9% IV infusion over 60 minutes
CISPLATIN 40mg/m^2 in 1000ml sodium chloride 0.9% IV infusion over 60 minutes
Post hydration
Days 1-28 MITOTANE start at 2-6g per day (maximum 6g/day) in 2 or 3 divided doses

diluent volume for dose prescribed as per national standardised product specification

CYCLE FREQUENCY AND NUMBER OF CYCLES

Every 28 days for 6 cycles
If after 3 months at the maximum tolerated mitotane dose no clinical benefits are observed, the case would generally be considered a clinical failure

ANTI-EMETICS

High emetic risk day 1
Low emetic risk day 2
High emetic risk days 3 and 4
Minimal emetic risk days 5 to 28

CONCURRENT MEDICATION REQUIRED

Cisplatin	Ensure adequate pre and post hydration. If urine output is <100ml/hour or if patient gains >2kg in weight during IV administration post cisplatin give 20-40mg furosemide PO/IV.
Mitotane	Hydrocortisone 20-30mg daily in divided doses

ADMINISTRATION

Available as 500mg tablets
Swallowed whole with water with fat-rich meal

EXTRAVASATION AND TYPE OF LINE / FILTERS

Cisplatin – exfoliant
Doxorubicin - vesicant
Etoposide - irritant

Peripheral line

INVESTIGATIONS

Blood results required before SACT administration
FBC, U&E including Mg^{++} and LFTs every cycle
Neutrophils x 10^9/L ≥1.5
Platelets x 10^9/L ≥100
Ideally EDTA GFR should be used
Creatinine clearance (GFR) calculated, at the Consultant's discretion
Serum creatinine - each cycle,
Baseline weight and every cycle

MAIN TOXICITES AND ADVERSE REACTIONS

Cisplatin	Nephrotoxicity – ensure adequate pre and post hydration is prescribed. Ototoxicity – assess patient for tinnitus or hearing abnormalities.
Doxorubicin	Cardiotoxicity – monitor cardiac function. Doxorubicin may be stopped in future cycles if signs of cardiotoxicity e.g. cardiac arrhythmias, pericardial effusion, tachycardia with fatigue.
Mitotane	Gastrointestinal disturbances - anorexia, nausea or vomiting, diarrhoea. Central Nervous System – depression, lethargy and somnolence, dizziness or vertigo. Skin toxicity - transient skin rashes this side effect subsided while the patients were maintained on the drug without a change of dose. Visual blurring, diplopia, lens opacity, toxic retinopathy). Haematuria, hemorrhagic cystitis, and albuminuria Hhypertension, orthostatic hypotention, and flushing

INTERACTIONS WHICH MAY REQUIRE DOSE MODIFICATIONS
(not exhaustive list check SPC/BNF/Stockleys)

Cisplatin	Aminoglycosides increased risk of nephrotoxicity and ototoxicity. Renal function should be well monitored and audiometric tests as required. Cisplatin can cause a decrease in phenytoin serum levels. This may lead to reappearance of seizures and may require an increase of phenytoin dosages.
Mitotane	Many interactions check carefully

DOSE MODIFICATIONS

Doxorubicin maximum lifetime dose
= 400mg/m^2 (in patients with cardiac dysfunction or exposed to mediastinal irradiation)
= 450-550mg/m^2 (with normal cardiac function)

Mitotane
If severe side effects appear, the dose should be reduced until the maximum tolerated dose is achieved.
If the patient can tolerate higher doses and improved clinical response appears possible, the dose should be increased until adverse reactions interfere. Experience has shown that the maximum tolerated dose will vary from 2 to 16g per day, but has usually been 9 to 10g per day. The highest doses used in the studies to date were 18 to 19g per day.

Non-haematological

If patient complains of tinnitus, tingling of fingers and/or toes, discuss with SpR or Consultant before administration.

Hepatic impairment

Doxorubicin

Bilirubin 20-50micromol/L	give 50% dose
Bilirubin 51-86micromol/L	give 25% dose
Bilirubin >86micromol/L or Child-Pugh C	not recommended

Etoposide

Bilirubin ≥50micromol/L or decreased albumin	give 50% dose

Renal impairment

Cisplatin

CrCl >60ml/min	give 100% dose
CrCl 50-59ml/min	give 75% dose
CrCl 40-49ml/min	give 50% dose (curative intent) not recommended (palliative intent)
CrCl <40ml/min	not recommended

Etoposide

CrCl >50ml/min	give 100% dose
CrCl 15-50ml/min	give 75% dose
CrCl <15ml/min	further dose reduction

REFERENCES