EAP & MITOTANE

Advanced (unresectable, metastatic or relapsed) adrenal cortical cancer

Drugs/Dosage:	Mitotane	1 –3 g/day start dose*	po	to be initiated gradually, see table on page 3 below for suggested initial dosing schedule, plus dosing adjustment advice according to plasma levels and side effects. Mitotane to ideally start up to 2 weeks before IV chemotherapy starts.

***** Mitotane dose should be adjusted to achieve a therapeutic plasma level of 14 – 20mg/l.
The dose may be reduced to 1 – 2 g/day after cumulative dose of 200g or if toxicity occurs.

Doxorubicin	40 mg/m^2	IV	Day 1 of each cycle
Etoposide	100 mg/m^2	IV	Day 2, Day 3 and Day 4 of each cycle
Cisplatin	40 mg/m^2	IV	Day 3 and Day 4 of each cycle

Other drugs:	Hydrocortisone	20 – 30 mg	po	daily throughout mitotane treatment - usual starting dose is 10mg am, 5mg at midday, 5mg at 5pm
	Fludrocortisone	100 mcg	po	od **only if patient has symptoms of postural hypotension**

Also refer to endocrinologist (see Comments)
N.B. In the event of shock / trauma, stop mitotane and give full steroid replacement.

Administration: Mitotane available as 500mg tablets. The total daily dose may be divided into 2 or 3 doses according to patient convenience. They should be taken with a glass of water during meals containing fat-rich food.

Doxorubicin via fast-running infusion of 0.9% sodium chloride
Etoposide in 1000ml 0.9% sodium chloride and infused over minimum of 1 hour

Cisplatin:
1 litre 0.9% sodium chloride + 20mmol KCl + 10mmol $MgSO_4$ IV over 2 hours
Mannitol 20% 100mls over 15 minutes
Cisplatin in 1 litre 0.9% sodium chloride IV over 2 hours
1 litre 0.9% sodium chloride + 20mmol KCl + 10mmol $MgSO_4$ IV over 2 hours
500mls – 1 litre water orally over 1 hour

Frequency: Repeat 4 weekly for 6 cycles of EAP chemotherapy, with clinic review before Day 1 of each cycle. Mitotane should be given without any interruption unless severe toxicity, and should continue until progressive disease.
Supplementation with hydrocortisone +/- fludrocortisone to continue after mitotane discontinued, as mitotane induces a state of potentially permanent adrenal insufficiency.

Main Toxicities: myelosuppression; alopecia; mucositis; nephrotoxicity; neurotoxicity/ototoxicity; ovarian failure/infertility

mitotane side effects: CNS toxicity (lethargy, dizziness, headache, mental impairment); adrenal insufficiency; peripheral neuropathy; nausea; skin rash; lipid disorders; prolonged bleeding times; leucopenia.

Patients should be advised to avoid driving or operating machinery, unless their Consultant advises otherwise.

Reason for Update: major review: EAP dosing schedule reviewed; extra information on mitotane dosing and monitoring; funding statement removed; updated reference	Approved by Consultant: Dr S Cummin
Version: 4	Approved by Lead Chemotherapy Nurse: V Mumford
Supersedes: Version 3	Date: 9.4.14
Prepared by: S Taylor	Checked by: C Tucker

Anti-emetics:	Day 1, 3 & 4: highly emetogenic, including aprepitant starting on Day 3 Day 2: moderately emetogenic	
Extravasation:	Doxorubicin is a vesicant	
Regular Investigations:	FBC	}
	U&Es	} Day 1 of each chemotherapy cycle
	LFTs	}
	Mg^{2+} and Ca^{2+}	}
	Serum cholesterol/triglycerides	baseline, then every 1 – 2 months
	Mitotane levels	2 weeks from start of treatment, 2 weeks after any dose change, and at least 4 weekly once stable dose achieved, with bloods ideally taken just before a dose is due. levelling kit provided by HRA Pharma
	EDTA	prior to Cycle 1
	MUGA scan	see Comm**e**nts
	Behavioural and neurological assessments (especially if mitotane levels > 20mg/l)	
	Signs and symptoms of adrenal insufficiency, hypothyroidism, hypogonadism	

Comments: Ensure that the patient is referred to an endocrinologist to allow for regular monitoring of adrenal function, and to optimise dosing of steroid substitution.

Patients should be told to carry with them the Lysodren Patient Card provided with the mitotane PIL.

Scalp cooling can be offered, which should be used for doxorubicin **and** etoposide

Maximum cumulative dose of doxorubicin = 450 - 550mg/m^2
A baseline MUGA scan should be performed where the patient is considered at risk of having significantly impaired cardiac contractility. If the ejection fraction is less than 50%, an alternative regimen should be given. MUGA scan should be repeated if there is suspicion of cardiac toxicity at any point during treatment.

Weight should be recorded prior to and at the end of cisplatin treatment, and a strict fluid balance chart should be maintained. An average urine output of at least 100ml/hr must be maintained throughout treatment, and cisplatin infusion should not be commenced unless this urine output is achieved. If the urine output is inadequate, the patient should be assessed and urine output increased by administering 500ml sodium chloride 0.9% IV +/- furosemide 20 - 40mg. Furosemide 20 – 40mg po may also be given if there is a positive fluid balance of 1.5 litres, a weight gain of 1.5kg or symptoms of fluid overload. The patient should be asked to drink 2 litres of fluid in the 24hrs following treatment, and to contact the hospital if this is impossible because of problems e.g. nausea and vomiting.

Check electrolytes – additional supplementation of potassium, Mg^{2+} or Ca^{2+} may be required.

For patients on Cycle 1 whose EDTA is not yet available, Cockcroft & Gault may be used to predict GFR. Doses of cisplatin and etoposide should be adjusted if necessary once EDTA available. EDTA should only be repeated if the result is borderline at the start of treatment or if there is a 30% change in serum creatinine.

Dose Modifications

Haematological Toxicity:

WBC < 3.0 x 10^9/l
or
Neutrophils < 1.5 x 10^9/l
or
Platelets < 100 x 10^9/l

Delay chemotherapy for 1 week (continue mitotane). Repeat FBC and, if within normal limits, proceed with treatment. If platelets < 50 x 10^9/l or neutrophils < 0.5 x 10^9/l, further doses of chemotherapy should be given with 25% dose reduction.

Mitotane:

Mitotane dose should be adjusted to achieve a therapeutic plasma level of 14 – 20mg/l.
Mitotane has a long half-life (18 – 159 days) so dose adjustments will not result in immediate changes in levels. Levels can continue to rise on maintenance doses and after dose reductions. So mitotane plasma levels should be checked at least every 4 weeks throughout.
It may take 3 – 5 months to achieve therapeutic levels.

See table below[1] for suggested initial dosing schedule and dose adjustment advice:

Mitotane dosing, Weeks 1 - 2						
Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
1.0 g	1.0 g	1.5 g	1.5 g	1.5 g	2.0 g	2.0 g
Week 2						
Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14
2.0 g	2.5 g	2.5 g	2.5 g	3.0 g	3.0 g	3.0 g

Mitotane dosing, Week 3 onwards

Review dose every 2 weeks initially, according to CNS/GI side effects and plasma mitotane level, then at least every 4 weeks once stable dose achieved

Plasma mitotane level	**CNS (Grade2) / GI side effects (Grade 3/4)**		**Grade 3/4 CNS side effects**
	Absent	Present	Present
< 14 mg/l	Increase daily dose by 1g*	Reduce daily dose by 1g	Stop Mitotane#
14 – 20 mg/l	Maintain dose	Reduce daily dose by 1.5 g	Stop Mitotane#
> 20 mg/l	Reduce daily dose to 50-80% of the most recent dose	Stop Mitotane#	Stop Mitotane#

* Maximum daily mitotane dose permitted is 12 g
# until recovery of side effects and restart with a lower dose (50 - 80% of the most recent dose).

Renal Impairment:

NB. Cisplatin is both eliminated primarily (> 90%) in the urine and is itself nephrotoxic.

GFR (ml/min)	**Cisplatin Dose**
≥ 60	Give 100%
45 – 59	Give 75%
< 45	CI (consider carboplatin)

CrCl (ml/min)	Etoposide Dose
> 50	Give 100%
15 – 50	Give 75%
< 15	Give 50%

There is insufficient data for mitotane dosing advice in renal impairment. Use with caution, and carry out frequent monitoring of mitotane plasma levels.

Hepatic Impairment: Mitotane should be used with caution in mild to moderate hepatic impairment, and avoided in severe impairment. (mitotane is mainly metabolised via the liver)

ALT / AST	Bilirubin (µmol/l)	Doxorubicin Dose
2 – 3 x ULN	-	Give 75%
> 3 x ULN or	20 – 50	Give 50%
-	51 – 85	Give 25%
-	> 85	Omit

There is conflicting evidence for etoposide dose reduction in hepatic impairment. If in doubt, discuss with Consultant:

Bilirubin (µmol/l)	AST (units/l)	Etoposide Dose
26 – 51 **or**	60 - 180	Give 50% dose
> 51 **or**	> 180	Clinical decision

Neurotoxicity: Seek further advice if the patient reports symptoms indicative of cisplatin-related neurotoxicity or ototoxicity.
See mitotane table above, for advice on mitotane dosing in the event of any Grade 2 + neurotoxicity.

Reference:
Fassnacht, M et al ; NEJM 2012 ; 366 (23) : 2189 – 2197
[1]as used by South East London Cancer Network