

CODE: CISPAE-MITOTANE

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A		REGIMEN NAME	CISPLATIN-DOXORUBICIN-ETOPOSIDE-MITOTANE Chemotherapy
Cancer		Adrenocortical Carcinoma	Palliative intent
Regimen Category		Local: A regimen not widely used by Regional Cancer Centres in this disease site.	
Rationale and Uses		Treatment of patients with metastatic or locally advanced unresectable adrenocortical carcinoma, who have no prior radiation or chemotherapy treatment (except adjuvant mitotane) and have no brain metastases	

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B				DRUG REGIMEN
<u>DOXORUBICIN</u> (Round to nearest 1 mg)	20 mg/m ²	IV		Days 1 and 8
<u>CISPLATIN</u> (Round to nearest 1 mg)	40 mg/m ²	IV		Days 2 and 9
<u>ETOPOSIDE</u> (Round to nearest 10 mg)	100 mg/m ²	IV		Days 5 to 7
<u>MITOTANE</u> (Outpatient prescription in multiples of 500 mg tablets)	1000 – 4000 mg	PO		Daily as tolerated

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C**CYCLE FREQUENCY****REPEAT EVERY 28 DAYS***Cisplatin-Doxorubicin-Etoposide:**For a maximum of 6 Cycles unless disease progression or unacceptable toxicity occurs**Mitotane:**Until disease progression or unacceptable toxicity occurs*▲ [Back to Top](#)**D****PREMEDICATION AND SUPPORTIVE MEASURES**

ANTIEMETIC REGIMENS:

MODERATE*Supplement with replacement cortisone (glucocorticoid) and fludrocortisone (mineralocorticoid) (see [Mitotane](#) drug monograph)*

Mitotane:

Adjust according to symptoms

Use standard regimens for cisplatin pre-medication and hydration. (See [Cisplatin](#) drug monograph)▲ [Back to Top](#)

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DOSE MODIFICATION

Doses should be modified according to the protocol by which the patient is being treated. The following recommendations are in use at some centres.

Hematologic Toxicities

See [Appendix 6](#) for general recommendations.

Do not retreat until platelets $\geq 100 \times 10^9/L$ and ANC $\geq 1.5 \times 10^9/L$ and non-hematologic toxicity is \leq grade 2.

Toxicity and Grade	Dose Reduction
Grade 4 ANC	↓ by 25%
Grade 3 or 4 platelets	↓ by 25%
Grade 3 or 4 non-hematologic toxicity	↓ by 25%

Renal Impairment

Creatinine clearance (mL/min)	Cisplatin % previous dose)	Doxorubicin	Etoposide (% previous dose)	Mitotane* (% previous dose)
> 30 - 50	75%	No dose adjustment required	75%	75%
15 – 30	50%-75%		75%	75%
< 15	50% or OMIT		50%	50% or discontinue

* suggested – no specific recommendations found

Hepatic Impairment

Bilirubin	Cisplatin	Doxorubicin (% previous dose)	Etoposide (% previous dose)	Mitotane^ (% previous dose)
1-2 x ULN	No dose adjustment required	50%	50%	50%
>2 – 4 x ULN		25%*	25%	25%
> 4 x ULN		Discontinue*	Discontinue	Discontinue

* Consider 75% dose reduction or OMIT dose for severe increases in LFTs (i.e. > 5 x ULN)

^ suggested – no specific recommendations found

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F**ADVERSE EFFECTS**

Refer to Cisplatin, Doxorubicin, Etoposide and Mitotane drug monographs for full details of adverse effects.

Most Frequently Occurring Adverse Effects

- Myelosuppression ± infection or bleeding (may be severe)
- Nausea/vomiting
- Mucositis
- Diarrhea
- Fatigue and anorexia
- Myalgia
- Alopecia
- Neurotoxicity, ototoxicity
- Nephrotoxicity (may be severe)
- Electrolyte imbalances
- Adrenocortical insufficiency
- Somnolence and other CNS effects
- Infertility

Less Common but may be Severe or Life-Threatening

- Hematuria, hemorrhagic cystitis
- Cardiotoxicity
- Secondary leukemia
- Thrombotic microangiopathy

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G**INTERACTIONS**

Refer to Cisplatin, Doxorubicin, Etoposide and Mitotane drug monographs for full details.

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DRUG ADMINISTRATION AND SPECIAL PRECAUTIONS

Refer to Cisplatin, Doxorubicin, Etoposide and Mitotane drug monograph for full details.

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CLINICAL MONITORING

- Clinical toxicity assessment (including nausea and vomiting, local toxicity, mucositis, infection, neurotoxicity, ototoxicity, adrenal insufficiency). Grade toxicity using the current [NCI Common Toxicity Criteria Version](#).
- CBC before each cycle.
- Cardiac examination especially with risk factors (including prior therapy with Epirubicin, Mitoxantrone or other cardiac drug), or a cumulative Doxorubicin dose of > 450mg/m²
- Baseline & periodic serum cortisol levels
- Baseline and regular hepatic function tests.
- Baseline and regular renal function tests and electrolytes (including magnesium).

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ADMINISTRATIVE INFORMATION

Patient visit	Days 1 and 8: Approximately 1 hour Days 2 and 9: Approximately 2 hours Days 5-7: Approximately 1.5 hours
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KEY REFERENCE(S)

Berruti A, Terzolo M, Sperone P, et al. Etoposide, doxorubicin and cisplatin plus mitotane in the treatment of advanced adrenocortical carcinoma: a large prospective phase II trial. *Endocrine-Related Cancer* 2005; 12: 657–66.

Berruti A, Terzolo M, Pia A, et al. Mitotane Associated with Etoposide, Doxorubicin, and Cisplatin in the Treatment of Advanced Adrenocortical Carcinoma. *Cancer* 1998; 83: 2194–200.

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OTHER NOTES

Mitotane causes adrenal suppression; it is important to maintain adequate replacement of both the glucocorticoid and mineralocorticoid steroids throughout Mitotane treatment, and possibly after Mitotane is discontinued.

Mitotane is not listed in the Ontario Drug Benefit Formulary.

Prescription costs may be covered by other third party prescription plans.

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June 2010: Modified sections A and D