Regimen Monograph

Regimen Name | Drug Regimen | Cycle Frequency | Premedication and Supportive Measures | Dose Modifications | Adverse Effects | Interactions | Drug Administration and Special Precautions | Recommended Clinical Monitoring | Administrative Information | References | Other Notes | Disclaimer

A - Regimen Name

CISPDOXOETOPMTTN Regimen

CISplatin-DOXOrubicin-Etoposide-Mitotane

Disease Site
Endocrine
Adrenal

Intent
Palliative

Regimen Category
Evidence-Informed :

Regimen is considered appropriate as part of the standard care of patients; meaningfully improves outcomes (survival, quality of life), tolerability or costs compared to alternatives (recommended by the Disease Site Team and national consensus body e.g. pan-Canadian Oncology Drug Review, pCODR). Recommendation is based on an appropriately conducted phase III clinical trial relevant to the Canadian context OR (where phase III trials are not feasible) an appropriately sized phase II trial. Regimens where one or more drugs are not approved by Health Canada for any indication will be identified under Rationale and Use.

Rationale and Uses
Treatment of patients with metastatic or locally advanced unresectable adrenocortical carcinoma, who have good performance status, no prior radiation or chemotherapy treatment (except adjuvant mitotane) and have no brain metastases. A phase III clinical trial has shown significantly higher response rate and progression-free survival, but similar overall survival and toxicity compared to streptozocin-mitotane.

Supplementary Public Funding
mitotane
ODB - General Benefit (mitotane) (ODB Formulary)

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B - Drug Regimen

DOXOrubicin	40 mg /m²	IV	Day 1
etoposide	100 mg /m²	IV	Days 2, 3, and 4
CISplatin	40 mg /m²	IV	Days 3 and 4
mitotane	1 to 4 g	PO	Daily as tolerated, start 1 week before chemotherapy *

*(Outpatient prescription in multiples of 500 mg tablets; to reach mitotane blood level of 14-20 mg/L)

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C - Cycle Frequency

REPEAT EVERY 28 DAYS

• Cisplatin-Doxorubicin-Etoposide: For a usual maximum of 6 cycles, or until disease progression in the absence of unacceptable toxicity

• Mitotane: Until disease progression or unacceptable toxicity occurs

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D - Premedication and Supportive Measures

Antiemetic Regimen: Moderate (Mitotane: Adjust according to symptoms)

Other Supportive Care:

- Supplement with replacement cortisone (glucocorticoid) and fludrocortisone (mineralocorticoid) (See mitotane drug monograph.)
- Standard regimens for Cisplatin premedication and hydration should be followed. Refer to Cisplatin monograph.

Also refer to CCO Antiemetic Summary

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E - Dose Modifications

Doses should be modified according to the protocol by which the patient is being treated. The following recommendations have been adapted from clinical trials or product monographs and could be considered.

Dosage with toxicity

Worst Toxicity / Counts (x 10^9/L) in previous cycle		**Worst Toxicity / Counts (x 10^9/L) in previous cycle**	**DOXOrubicin (% previous dose)**	**CISplatin (% previous dose)**	**etoposide (% previous dose)**	**Mitotane (% previous dose)**
Febrile Neutropenia Or ANC < 0.5 for ≥ 5-7 d	Or	Thrombocytopenic bleeding Or Platelets < 25	Hold *, then 75%			No change
Cardiotoxicity**			Discontinue	No change		
Grade 2 neurotoxicity /ototoxicity			No change	75%	No change	Caution
Grade 3 or 4 neurotoxicity/ototoxicity			No change	Discontinue	No change	Hold* or discontinue
Grade 3 related organ / non-hematologic			*75% for suspect drug(s)			
Grade 4 related organ / non-hematologic Hemolysis, optic neuritis, arterial thromboembolism, severe hypersensitivity reactions			Discontinue			

*Do not start new cycle until toxicities have recovered to ≤ grade 2, platelets ≥ 100 x 10^9/L, creatinine ≤ grade 1 and ANC ≥ 1.5 x 10^9/L.
**including any signs and symptoms of heart failure, greater than 10% decline in LVEF to below the lower limit of normal, a greater than 20% decline in LVEF from any level, or LVEF ≤ 45%.

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Hepatic Impairment

Bilirubin	Cisplatin	Doxorubicin (% previous dose)	Etoposide (% previous dose)	Mitotane^ (% previous dose)
1-2 x ULN	No change	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				

Renal Impairment

Creatinine clearance	Doxorubicin	Cisplatin (% previous dose)	Etoposide (% previous dose)	Mitotane*
>45-60	No adjustment required	75%	100%	75-100%
>30-45		50%	75%	75%
15-30		Discontinue	75%	75%
<15		Discontinue	Discontinue	50% or discontinue

*suggested - no specific recommendations found

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F - Adverse Effects

Refer to DOXOrubicin, CISplatin, etoposide, mitotane drug monograph(s) for additional details of adverse effects

Most common side effects	Less common but may be severe or life-threatening
• Nausea, vomiting • Anorexia • Diarrhea • Alopecia • Nephrotoxicity (may be severe) • Neurotoxicity/ototoxicity (may be severe) • Myelosuppression +/- infection, bleeding (may be severe) • Fatigue • Somnolence • Increased LFTs (may be severe) • Abnormal electrolyte(s) • Adrenal insufficiency • Rash (may be severe) .	• Arterial thromboembolism • Cardiotoxicity, arrhythmia • Hemolytic uremic syndrome, vasculitis • Secondary malignancies • Hypersensitivity • Raynaud's • Hemolysis • Vesicant • Venous thromboembolism • Pneumonitis

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G - Interactions

Refer to DOXOrubicin, CISplatin, etoposide, mitotane drug monograph(s) for additional details

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H - Drug Administration and Special Precautions

Refer to DOXOrubicin, CISplatin, etoposide, mitotane drug monograph(s) for additional details

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Recommended Clinical Monitoring

- CBC; baseline and regular
- Liver function tests; baseline and regular
- Renal function tests; baseline and regular
- Electrolytes, including magnesium, phosphate and calcium; baseline and regular
- Cardiac tests for all patients with cardiac risk factors (including prior trastuzumab or patients at or above the threshold dose levels (doxorubicin 400mg/m^2 for q21 day schedules and 550mg/m^2 for weekly schedules); baseline and periodic
- Clinical toxicity assessment (infection, bleeding, mucositis, adrenal insufficiency, cardiotoxicity, thromboembolism, GI, nausea/vomiting, local toxicity, infusion reactions, neurotoxicity, ototoxicity); at each visit

- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

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J - Administrative Information

Approximate Patient Visit	Day 1: 0.5 to 1 hour; Day 2: 1-2 hours; Day 3-4: 3-4 hours
Pharmacy Workload (average time per visit)	13.384 minutes
Nursing Workload (average time per visit)	47.917 minutes

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K - References

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.

Cisplatin, doxorubicin, etoposide and mitotane drug monographs, Cancer Care Ontario.

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Fassnacht M, Terzolo M, Allolio B, et al. Combination chemotherapy in advanced adrenocortical carcinoma. N Engl J Med 2012;366(23):2189-97.

November 2021 Added mitotane public funding info

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L - 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.

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M - Disclaimer

Regimen Abstracts

A Regimen Abstract is an abbreviated version of a Regimen Monograph and contains only top level information on usage, dosing, schedule, cycle length and special notes (if available). It is intended for healthcare providers and is to be used for informational purposes only. It is not intended to constitute or be a substitute for medical advice, and all uses of the Regimen Abstract are subject to clinical judgment. Such information is provided on an "as-is" basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the information's quality, accuracy, currency, completeness, or reliability, and Cancer Care Ontario disclaims all liability for the use of this information, and for any claims, actions, demands or suits that arise from such use.

Information in regimen abstracts is accurate to the extent of the ST-QBP regimen master listings, and has not undergone the full review process of a regimen monograph. Full regimen monographs will be published for each ST-QBP regimen as they are developed.

Regimen Monographs

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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last revision will be visible on each page of the monograph and regimen. Since standards of usage are constantly evolving, it is advised that the Formulary not be used as the sole source of information. It is strongly recommended that original references or product monograph be consulted prior to using a chemotherapy regimen for the first time.

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