Regimen Monograph

A - Regimen Name

MTTN Regimen

Mitotane (Adjuvant)

Disease Site
Endocrine
Adrenal

Intent
Adjuvant

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
For patients with adrenal carcinoma who have undergone complete resection, and who have no prior chemotherapy or radiotherapy and no distant metastases.

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

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B - Drug Regimen

mitotane	1 to 3 g	PO	*Daily, adjust as tolerated

(*may give the daily dose in divided doses. Up to 5000 mg daily used in some clinical trials; Outpatient prescription in multiples of 500mg tablets)

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C - Cycle Frequency

CONTINUOUS TREATMENT

Until disease progression or unacceptable toxicity

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D - Premedication and Supportive Measures

Antiemetic Regimen: Moderate – Consider prophylaxis daily

Febrile Neutropenia Risk: Low

Other Supportive Care:

- Antiemetics: Adjust according to symptoms
- Supplement with replacement cortisone (glucocorticoid) and fludrocortisone (mineralocorticoid) (see mitotane drug monograph)

Also refer to CCO Antiemetic Recommendations.

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E - Dose Modifications

Refer to protocol by which patient is being treated.

Dosage with toxicity

Mitotane has a long half life an accumulates in fat. Dose adjustments may not result in immediate improvement in drug related effects.

Toxicity / Event	Dose
Severe trauma, stress or infection	Interrupt; start steroids
Myelosuppression	No dose adjustment required
Adrenal insufficiency	Use corticosteroid supplementation
Mild to moderate GI, skin or CNS toxicity	Decrease dose* or hold, depending on severity
Mitotane levels > 20 mg/L	Hold and monitor levels; restart when levels within therapeutic range
Toxicty / Event (Continued)	**Dose**
Grade 3 related non-hematologic toxicity	Hold, consider dose reduction* * reduce to maximum dose tolerated by patient
Grade 4 related non-hematologic toxicity	Discontinue

Hepatic Impairment

No specific dose adjustments found. Exercise caution in mild to moderate hepatic impairment (unless due to metastatic disease), as mitotane is mainly metabolized by the liver. Not recommended for use in patients with severe hepatic impairment.

Renal Impairment

No specific dose adjustments found. Exercise caution in mild to moderate renal impairment. Not recommended for use in patients with severe renal impairment. Mitotane is unlikely to be dialyzable in the case of an overdose.

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F - Adverse Effects

Refer to mitotane drug monograph(s) for additional details of adverse effects

Most Common Side Effects	Less Common Side Effects, but may be Severe or Life-Threatening
• Adrenocortical insufficiency • Fatigue • Anorexia • Somnolence and other CNS effects (may be severe) • Nausea and vomiting • Diarrhea • Rash • ↑ LFTs (may be severe) • Hyperlipidemia • Myelosuppression (± infection/bleeding - may be severe)	• Hematuria, hemorrhagic cystitis • Toxic retinopathy, maculopathy • Prolonged bleeding time

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G - Interactions

Refer to mitotane drug monograph(s) for additional details

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H - Drug Administration and Special Precautions

Refer to mitotane drug monograph(s) for additional details. Patients should use medical alert tag or bracelet warning of adrenal suppression.

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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

- Observe for adrenal insufficiency
- Clinical CNS evaluation especially with long-term usage
- Regular clinical assessment of GI and skin toxicity, adrenal insufficiency, ophthalmic and CNS effects

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

Suggested Clinical Monitoring

- Neurological assessments; baseline and regular
- Serum cortisol levels; baseline and periodic
- Urine test; periodic
- CBC; baseline and regular
- Liver function tests; baseline and as clinically indicated
- If mitotane plasma level testing is available and clinically necessary, consider levels q2 weeks after starting treatment, after each dose adjustment, in hepatic/renal impairment, obese patients or recent weight loss; every 1 week monitoring if a high starting dose has been used. Monitor levels regularly (e.g. monthly) after reaching maintenance dose especially with toxicity and in obese patients. If treatment is interrupted, monitor levels q2 months.

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J - Administrative Information

Outpatient prescription for home administration

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K - References

Baudin E, Pellegriti G, Bonnay M, et al. Impact of monitoring plasma 1,1-dichlorodiphenildichloroethane (o,p'-DDD) levels on the treatment of patients with adrenocortical carcinoma. Cancer 2001;92:1385–92.

Haak HR, Hermans J, van de Velde CJ, et al. Optimal treatment of adrenocortical carcinoma with mitotane: results in a consecutive series of 96 patients. Br J Cancer. 1994;69(5):947-51.

Mitotane drug monograph, Cancer Care Ontario.

Terzolo M, Angeli A, Fassnacht M, et al. Adjuvant mitotane treatment for adrenocortical carcinoma. N Engl J Med 2007; 356: 2372-80.

Terzolo M, Pia A, Berruti A, et al. Low-dose monitored mitotane treatment achieves the therapeutic range with manageable side effects in patients with adrenocortical cancer. J Clin Endocrinol Metab 2000;85:2234–38

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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