Systemic Anti-Cancer Treatment Protocol

Mitotane

PROTOCOL REF: MPHAMITMIS
(Version No: 1.0)

Approved for use in:

Symptomatic treatment of advanced adrenal cortical carcinoma (ACC)

Dosage:

Drug	Dosage	Route	Frequency
Mitotane	2-3g*	PO	Daily

- 6 weekly cycle
- Max dose: Up to 12g OD but few patients will tolerate more than 6g a day
- Recommended starting dose is 500mg THREE times a day and dose should be increased by 1g/day every 1-2 weeks depending on tolerability and plasma levels
- To achieve more rapid levels of mitotane an accelerated dosing regimen can be used starting at 1.5g/day on day 1 increasing by 1.5g/day to 6g a day on day 4. Closer monitoring is required for signs of toxicity
- Once therapeutic levels have been reached the dose can be reduced by 1-2g/day
- Mitotane has a large volume of distribution and a long half-life and therefore changes in dosage may take weeks to take effect.

Supportive medication:

Hydrocortisone tablets (dose dependent)

Administration:

- Take mitotane around the same times every day.
- It should be swallowed whole with a glass of water; do not crush, chew or break.

- Mitotane should be taken with meals containing fat-rich foods such as milk, chocolate and oil.

Extravasation risk:

Not applicable

Drug Interactions

Drug	Interaction	Action
Spironolactone	Blocks action of mitotane	Not given together
Warfarin and coumarin-like anticoagulants	Mitotane has been reported to accelerate the metabolism of warfarin through hepatic microsomal enzyme induction, leading to an increase in dose requirements for warfarin.	Closely monitor for a change in anticoagulant dose requirements..
Substances metabolised through cytochrome P450, anticonvulsants, rifabutin, rifampicin, griseofulvin and St. John's wort (*Hypericum perforatum*).	Mitotane has been shown to have an inductive effect on cytochrome P450 enzymes. The plasma concentrations of the substances metabolised via cytochrome P450 may be modified.	Caution when prescribing
Cytochrome 3A4 substances e.g. sunitinib and midazolam.	Mitotane has been shown to have an inductive effect modifying plasma concentrations.	Caution should be taken when co-prescribing active substances.
Medicinal products active on central nervous system	Mitotane can cause central nervous system undesirable effects at high concentrations	Caution when prescribing
Hormone binding protein e.g.sex hormone-binding globulin (SHBG) and corticosteroid-binding globulin (CBG).	Mitotane has been shown to increase plasma levels of hormone binding proteins	This should be taken into account when interpreting the results of hormonal assays and may result in gynaecomastia

Main Toxicities:

- Elevated liver enzymes,
- Increased plasma cholesterol and triglyceride levels
- Immunosuppression and prolonged bleeding time
- GI toxicity – nausea, vomiting, diarrhoea, mucositis
- Sleepiness,
- Vertigo

- Headache
- Dizziness
- Mental confusion
- Rash
- Gynaecomastia
- Adrenal insufficiency
- Neurologic toxicity has been associated with levels **above 20 mg/l** and therefore this threshold should **not** be reached

Patients should be counselled not to drive

Investigations and treatment plan

	Pre	Cycle 1		Cycle 2	Cycle 3	Cycle 4	Cycle 5	Ongoing
		WK1	WK 3	WK6	WK12	WK18	WK24	
Informed Consent	X							
Clinical Assessment	X	X	X	X		X		Every second cycle
SACT Assessment (to include PS and toxicities)	X	X	X	X	X	X	X	Every cycle
FBC	X		X	X	X	X	X	Every cycle
U&E & LFT	X		X	X	X	X	X	Every cycle
Thyroid function	X				X		X	Every second cycle
Mitotane levels			X	X	X	X	X	Every cycle
24 hour urinary free cortisol	X		X	X	X	X	X	Every cycle
ACTH	X			X	X	X	X	Every cycle
CT scan	X			X		X		Every second cycle
Renin	X						X	Every 24 weeks
DHEA, testosterone, androstenedione, estradiol, progesterone	X							Repeat during therapy if elevated at baseline or if symptoms of hypogonadism emerge
Fasting cholesterol and lipid profile (if used in adjuvant setting)					X		X	Every second cycle
Weight recorded	X	X	X	X	X	X	X	Every cycle
Blood pressure	X	X	X	X	X	X	X	Every cycle

Dose Modifications and Toxicity Management:

Plasma Levels

Dosing should be individually adjusted based on mitotane plasma levels monitoring and clinical tolerance until mitotane plasma levels reach the therapeutic window 14 - 20 mg/l. The target plasma concentration is usually reached within a period of 3 to 5 months.

Mitotane plasma levels should be assessed after each dose adjustment and at frequent intervals (e.g. every two weeks), until the optimal maintenance dose is reached. Monitoring should be more frequent (e.g. every week) when a high starting dose has been used. It should be taken into account that dose adjustments do not produce immediate changes in plasma levels of mitotane. In addition, because of tissue accumulation, mitotane plasma levels should be monitored regularly (e.g. monthly) once the maintenance dose has been reached.

Regular monitoring (e.g. every two months) of mitotane plasma levels is also necessary after interruption of treatment. Treatment can be resumed when mitotane plasma levels will be ranged between 14 - 20 mg/l. Due to the prolonged half-life, significant serum concentrations may persist for weeks after cessation of therapy.

Guide for dose modification

Plasma mitotane level	Neurological grade 2 or gastrointestinal grade 3/4		Neuroloigcal grade 3/4
	Absent	Present	Present
< 14 mg/l	Increase daily dose by 1.5 g for 1 week, then another 1.5g in the second week	Reduce daily dose by 1.5 g	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

Adrenal insufficiency

Mitotane will cause hypoadrenalism and this is usually permanent. It is unpredictable how quickly this will occur and therefore unless a patient presents with signs and symptoms of excess steroid production all patients are to be initiated on hydrocortisone with mitotane at a dose of 10mg-10mg-5mg. Since mitotane increases plasma levels of steroid binding proteins and induces cytochrome p450, the dose of hydrocortisone will need increasing during therapy usually up to 20mg-20mg-10mg but some patients may require more. Patients complaining of fatigue attributable to mitotane should be tried with a dose increase of hydrocortisone before interrupting mitotane therapy. Aim for an ACTH in the normal range or slightly above and a 24hour urinary free cortisol in them mid normal range.

PATIENTS MUST HAVE AN ALERT CARD AND ALSO BE ADVISED NOT TO STOP STEROID REPLACEMENT THERAPY. THEY SHOULD ALSO BE ADVISED TO DOUBLE DOSE IF UNWELL.

If mitotane is stopped patients may not regain steroid production and so replacement should be continued. It may be possible to discontinue and patients should be referred to endocrinology for advice on monitoring.

Mineralocorticoid replacement

The zona glomerulosa of the adrenal gland is more resistant to the effects of mitotane and therefore mineralocorticoid deficiency occurs late. It should be considered in patients with hypotension and hypokalaemia. Rising renin levels will indicate mineralocorticoid deficiency. Fludrocortisone 100-200mcg bd should be commenced.

Patients presenting with symptoms of excess steroid production

Patients with excess steroid production (Cushing's syndrome) should be managed with advice from endocrinology. They should be commenced on meytrapone 250mg a day and not be started on fludrocortisone replacement until steroid levels are falling.

Patients with excess mineralocorticoid production (Conn's syndrome) typically have hypertension and hypokalaemia. They should be managed with advice from endocrinology and can be started on amiloride 5mg daily. They require frequent checks of electrolytes as once the endocrine disorder has been corrected, serum potassium can overcorrect rapidly.

Mitotane tissue accumulation

Fat tissue can act as a reservoir for mitotane, resulting in a prolonged half-life and potential accumulation of mitotane Therefore, monitoring of mitotane plasma levels (e.g. every two months) is also necessary after interruption of treatment, as prolonged release of mitotane can occur. Caution and close monitoring of mitotane plasma levels are highly recommended when treating overweight patients.

Hyperlipidaemia

Consider the clinical context before treating hyperlipidaemia. If appropriate to commence lipid lowering therapy, use a drug that is not metabolised by cytochrome p450 such as pravastatin or rosuvastatin.

Hepatic impairment

Mitotane is mainly metabolised through the liver, the plasma levels are expected to increase if liver function is impaired. The use of mitotane in patients with severe hepatic impairment is not recommended. In patients with mild to moderate hepatic impairment, caution should be exercised and monitoring of liver function should be performed. Monitoring of mitotane plasma levels is specially recommended in these patients.

Renal impairment

The use of mitotane in patients with severe renal impairment is not recommended and, in cases of mild to moderate renal impairment, caution should be exercised. Monitoring of mitotane plasma levels is specially recommended in these patients.

References:

Electronic medicines compendium. *Lysodren 500mg tablets.* Available from: https://www.medicines.org.uk/emc/product/80 [Accessed 19/02/2019]

Up to date. *Treatment of adrenocortical carcinoma.* Available from https://www.uptodate.com/contents/treatment-of-adrenocortical-carcinoma? [Accessed on 19/02/19]