Mitotane

Indication
Adrenocortical carcinoma (adjuvant and metastatic)

Regimen details

Mitotane dosing:
Start with 1.5 g/day and increase dose within 4–6 days to 6 g/day
After 3 weeks, adjust dosage according tolerability and blood level (see below)
Maximum dose 12 g/days, but most patients do not tolerate >8 g/days
Target mitotane blood level 14–20 mg/l. Using this regimen, ~50% of patients achieve the target level within 3 months

Number of cycles
Until disease progression

Administration
Take with meals (3-4 divided doses)

Pre-medication
N/A

Emetogenicity
N/A

Additional supportive medication
Thyroid hormone replacement is recommended in patients with clinical symptoms of hypothyroidism
If renin increases in the presence of symptoms suggestive of mineralocorticoid deficiency, fludrocortisones should be added

Investigations – pre first cycle
U&Es, LFTs, FBC, imaging as appropriate

Investigations –pre subsequent cycles
Mitotane serum levels every 2–3 weeks in the first 3 months. After reaching a plateau, the interval can be extended (i.e. every 6 weeks)
Glutamate-Oxaloacetate Transaminase (GOT), Glutamate-Pyruvate Transaminase (GPT), bilirubin, Gamma-Glutamyl-Transferase (GGT). Initially every 4 weeks, after 6 months every 8 weeks. GGT is invariably elevated without clinical consequences. If other liver enzymes are rapidly increasing (>3-fold of baseline), there is a risk of liver failure: stop mitotane
TSH, fT3, fT4 every 3–4 months. Thyroid hormone replacement is recommended in patients with clinical symptoms of hypothyroidism
Testosterone, free testosterone, and sexual hormone binding globulin (SHBG) should be tested in male patients with symptoms of hypogonadism
Renin every 3 months. If renin increases in the presence of symptoms suggestive of mineralocorticoid deficiency, fludrocortisones should be added
Cholesterol (High-Density Lipoprotein (HDL), Low-Density Lipoprotein (LDL)), triglycerides every 3–4 months (in an adjuvant setting). If LDL/HDL cholesterol consistently increases, consider treatment with statins not metabolized by CYP3A4 (e.g. pravastatin, rosuvastatin)

Blood count every 3–4 months

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant.

See above

Dose modifications

See above

Adverse effects –

for full details consult product literature/ reference texts

Adrenal insufficiency: discontinue in the event of shock/trauma. Inform oncologist of any planned surgery
CNS toxicity
Ovarian macrocysts
Anorexia, nausea, vomiting, diarrhoea
Rash
Neutropenia
Growth retardation
Hypothyroidism
Maculopathy
Hepatitis
Gynaecomastia
Hypercholesterolaemia
Hypertriglyceridaemia
Decreased blood androstenedione and decreased blood testosterone in females, increased sex hormone binding globulin in females and males, decreased blood free testosterone in males

Significant drug interactions

– for full details consult product literature/ reference texts

Mitotane is a strong inducer of CYP3A4. Drugs metabolised by this pathway may require dose adjustments

Additional comments

The mechanism of action of mitotane is not fully understood. However, the drug is cytotoxic so appropriate handling measures should be practiced

References

Mitotane SPC https://www.medicines.org.uk/emc/product/80 - accessed July 2020

THIS PROTOCOL HAS BEEN DIRECTED BY DR PARIKH, CONSULTANT CLINICAL ONCOLOGIST

RESPONSIBILITY FOR THIS PROTOCOL LIES WITH THE HEAD OF SERVICE

Date: July 2020
Review: July 2022
VERSION: 2
