Midostaurin

Indication

Midostaurin is recommended as an option in adults for treating newly diagnosed acute FLT3-mutation-positive acute myeloid leukaemia with standard daunorubicin and cytarabine as induction therapy, with high-dose cytarabine as consolidation therapy, and alone after complete response as maintenance therapy.

(NICE TA523)

(Midostaurin is also licenced for monotherapy in mastocytosis (dose of 100mg BD) but this is not currently funded for use in the NHS).

ICD-10 codes

C92.1

Regimen details

With induction or consolidation chemotherapy:

Day	Drug	Dose	Route
8-21	Midostaurin	50mg BD	PO

In patients aged ≥60 years, midostaurin should be used only in patients eligible to receive intensive induction chemotherapy with adequate performance status and without significant comorbidities.

For patients who have a complete response

Midostaurin single agent maintenance therapy:

Day	Drug	Dose	Route
1-28	Midostaurin	50mg BD	PO

If patients are receiving a haematopoietic stem cell transplant, treatment should be discontinued 48 hours prior to commencing the conditioning regimen.

Cycle frequency

Induction or consolidation - usually 28 day cycle
Maintenance - 28 day cycle

Number of cycles

Up to 12 cycles.

Administration

Midostaurin is available as 25mg capsules. They should be taken orally twice daily approximately 12-hours apart. The capsules should be swallowed whole with a glass of water and taken with food.

If a dose is missed or if the patient vomits, it should be omitted and next planned dose taken.

If patients are receiving a haematopoietic stem cell transplant, treatment should be discontinued 48 hours prior to commencing the conditioning regimen.

Pre-medication
Nil

Emetogenicity
Midostaurin has mild emetic potential.

Additional supportive medication
Antiemetics if required.
See individual chemotherapy protocol.

Note: itraconazole is commonly used as antifungal prophylaxis for intensively treated patients with AML. When used with midostaurin it can increase midostaurin availability by approximately 20% and potentially increase in side effects – concomitant use requires careful monitoring.

Extravasation
N/A

Investigations – pre first cycle

Investigation	Validity period
FBC	96 hours
U+Es	96 hours
LFTs	96 hours
Glucose	96 hours
Echocardiogram	Baseline
Pregnancy test (women of childbearing potential)	7 days

Investigations – pre subsequent cycles

Investigation	Validity period
FBC	96 hours
U+Es	96 hours
LFTs	96 hours
Glucose	As clinically indicated
Echocardiogram	As clinically indicated

Standard limits for administration to go ahead
If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant

Investigation	Limit
Neutrophils	≥ 1.0 x 10^9/L
Platelets	> 50 x 10^9/L
CrCl	> 30 mL/min
Bilirubin	See below
AST/ALT	See below

Dose modifications
- **Haematological toxicity**

With induction or consolidation chemotherapy
Refer to relevant chemotherapy protocol.

Maintenance
Withhold treatment until neutrophils ≥ 1.0 x 10^9/L, then resume at 50mg BD.
If neutrophils < 1.0 x 10^9/L for more than 2 weeks and suspected to be due to midostaurin, discontinue treatment.

- **Renal impairment**

No dose adjustment is required for patients with mild or moderate renal impairment. Clinical experience in patients with severe renal impairment (CrCl < 30mL/min) is limited and no data is available in patients with end-stage renal disease.

- **Hepatic impairment**

No dose adjustment is required in patients with mild or moderate (Child-Pugh A or B) hepatic impairment. No studies have been completed in patients with severe (Child-Pugh C) hepatic impairment.

- **Other toxicities**

Toxicity	Definition	Dose adjustment
Pulmonary toxicity	Grade 3-4	Withhold midostaurin for the remainder of the cycle. Recommence at same dose when resolves to ≤ Grade 1. Midostaurin should be permanently discontinued if symptoms of interstitial lung disease.
Other non haematological toxicity	Grade 3-4	Withhold midostaurin until ≤ Grade 2. Recommence at same dose.
QTc interval	>470 msecs and ≤500 msecs	Reduce midostaurin dose to 50mg OD for remainder of cycle. - If QTc improves to ≤470 msecs prior to the next cycle, resume at the initial dose. - If QTc interval does not improve continue at 50mg OD.
	>500 msecs	Withhold midostaurin for remainder of cycle. - If QTc improves to ≤470 msecs prior to the next cycle, resume at the initial dose. - If QTc interval does not improve by start of next cycle omit midostaurin for that cycle. Withhold midostaurin for as many cycles as necessary until improves.

Maintenance only

For any persistent Grade 1-2 toxicity withhold treatment for up to 28 days. If this does not resolve discontinue treatment.

For any Grade 3-4 toxicity discuss with consultant.

Any active serious infection should be under control prior to starting monotherapy. Patients should be monitored for signs and symptoms of infection and if a diagnosis of infection is made appropriate treatment must be commenced promptly and midostaurin discontinued.

Adverse effects

- **Serious side effects**

Myelosuppression, neutropenia
Pulmonary toxicity
Cardiotoxicity
Hyperglycaemia
Exfoliative dermatitis

- **Frequently occurring side effects**

Myelosuppression
Nausea and vomiting
Diarrhoea
Dermatitis, rash
Fever
Headache
Hypokalaemia
Hypernatremia
Insomnia
Back pain
Arthralgia

- **Other side effects**

Fluid retention
Abnormal LFTs

Significant drug interactions

Midostaurin undergoes extensive hepatic metabolism mainly through CYP3A4 enzymes which are either induced or inhibited by a number of concomitant medicinal products.

CYP3A4 inhibitors: e.g. antifungals (e.g. ketoconazole, itraconazole), certain antivirals (e.g. ritonavir), macrolide antibiotics (e.g. clarithromycin) and nefazodone: avoid concomitant use as may increase plasma concentration of midostaurin.

CYP3A4 inducers: e.g. carbamazepine, rifampicin, enzalutamide, phenytoin, St. John's Wort: Concomitant use contraindicated as may decrease exposure to midostaurin.

Midostaurin and/or its metabolites may have the potential to inhibit CYP1A2, CYP2D6, CYP2C8, CYP2C9, CYP2E1 and CYP3A4/5 enzymes.

Midostaurin and/or its metabolites may have the potential to induce CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP3A4/5 enzymes. Midostaurin inhibited OATP1B1, BCRP and P-glycoprotein (P-gp) in vitro.

Medicinal products with a narrow therapeutic range that are substrates of CYP1A2 (e.g. tizanidine), CYP2D6 (e.g. codeine), CYP2C8 (e.g. paclitaxel), CYP2C9 (e.g. warfarin), CYP2C19 (e.g. omeprazole), CYP2E1 (e.g. chlorzoxazone), CYP3A4/5 (e.g. tacrolimus), CYP2B6 (e.g. efavirenz), P-gp (e.g. paclitaxel), BCRP (e.g. atorvastatin) or OATP1B1 (e.g. digoxin) should be used with caution when administered concomitantly with midostaurin.

Oral contraceptives: It is unknown whether midostaurin may reduce the effectiveness of hormonal contraceptives, and therefore women using hormonal contraceptives should add a barrier method of contraception.

Additional comments

Pregnant women should be informed of the potential risk to a foetus; females of reproductive potential should be advised to have a pregnancy test within 7 days prior to starting treatment and to use effective contraception during treatment and for at least 4 months after stopping treatment. Women using hormonal contraceptives should add a barrier method of contraception.

Because of the potential for serious adverse reactions in breast-feeding infants, women should discontinue breast-feeding during treatment and for at least 4 months after stopping treatment.

References

- National Institute for Health and Clinical Excellence. NICE TA523. Accessed 10 October 2018 via www.nice.org.uk
- Summary of Product Characteristics Midostaurin (Novartis) accessed 10 October 2018 via www.medicines.org.uk
- Stone, R.M, et al Midostaurin plus Chemotherapy for Acute Myeloid Leukemia with a *FLT3* Mutation. N Engl J Med 2017; 377:454-464.

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Date: November 2018