SACT PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

MIDOSTAURIN
ACUTE MYELOID LEUKAEMIA (AML)

PROTOCOL REF: MPHAMIDHAE
(Version No. 2.0)

Approved for use in:

Midostaurin is recommended for FLT-3 mutation positive acute myeloid leukaemia (AML) in either of the following:

- Newly diagnosed patients fit for intensive treatment with daunorubicin and cytarabine (DA) induction therapy and high-dose cytarabine (HDAC) as consolidation therapy. Midostaurin should be given alongside each cycle of DA and HDAC as per dosing below.
- Maintenance monotherapy following complete remission to induction/consolidation therapy.

Blueteq request must be completed prior to initiation

Dosage:

Alongside Induction and Consolidation therapy

Drug	Dose	Route	Frequency
Midostaurin	**50mg**	Oral	Twice daily (12 hourly intervals) **On days 8 to 21** (14 days) of DA or HDAC

Maintenance therapy

Drug	Dose	Route	Frequency
Midostaurin	**50mg**	Oral	Twice daily (12 hourly intervals) continuous

Maintenance: maximum of 12 x 28-day cycles

Must be permanently discontinued 48 hours prior to stem-cell transplant conditioning therapy

Administration (+/- Counselling Points):

- Midostaurin should be taken with food. The capsules should be swallowed whole with a glass of water. They should not be opened, crushed or chewed to ensure proper dosing and avoid the unpleasant taste of the capsule content.
- If a dose is missed, the patient should take the next dose at the scheduled time. If vomiting occurs, the patient should not take an additional dose of Rydapt, but should take the next scheduled dose.
- This medicinal product contains 666 mg of alcohol (ethanol) in each 200 mg dose (maximum daily dose), which is equivalent to 14 vol. % ethanol anhydrous. The amount in a 200 mg dose is equivalent to 16.9 ml beer or 7.0 ml wine. The small amount of alcohol in this medicine will not have any noticeable effects but may be harmful in patients with alcohol related problems, epilepsy or liver problems or during pregnancy or breast feeding.
- It is currently unknown whether midostaurin may reduce their effectiveness. Women using hormonal contraceptives should add a barrier method of contraception.
- Midostaurin contains macrogolglycerol hydroxystearate, which may cause stomach discomfort and diarrhoea.
- Caution is warranted in patients at risk of QTc prolongation (e.g. due to concomitant medicinal products and/or electrolyte disturbances). Interval assessments of QT by ECG should be considered if midostaurin is taken concurrently with medicinal products that can prolong QT interval.
- Interstitial lung disease (ILD) and pneumonitis, have occurred in patients treated with midostaurin - monitor closely for pulmonary symptoms

Emetogenic risk:

Mildly emetogenic

Supportive treatments:

- Supportive medications to be prescribed as per DA or HDAC protocol if being used alongside induction or consolidation cycles. **Voriconazole** and **Posaconazole** can be used at the same time as midostaurin with monitoring of midostaurin toxicity, in particular ECG changes.
- Metoclopramide 10mg three times daily prn if prescribed as maintenance

Dosing in renal and hepatic impairment:

Renal Dose Modifications	
Midostaurin	No dose adjustment is required for patients with mild or moderate renal impairment. Clinical experience in patients with severe renal impairment is limited and no data are available in patients with end-stage renal disease

Hepatic Dose Modifications	
Midostaurin	No dose adjustment is required in patients with mild or moderate (Child-Pugh A or B) hepatic impairment. No study has been completed in patients with severe (Child-Pugh C) hepatic impairment

Interactions:

Please refer to the SPC for full list of interactions and further information

- Concomitant use of midostaurin with strong inducers of CYP3A4 (e.g. carbamazepine, rifampicin, enzalutamide, phenytoin, St. John's Wort [*Hypericum perforatum*]) is contraindicated as they decrease exposure of midostaurin and its active metabolites.
- Caution is required when concomitantly prescribing midostaurin with medicinal products that are strong inhibitors of CYP3A4, such as, but not limited to, antifungals (e.g. ketoconazole), certain antivirals (e.g. ritonavir), macrolide antibiotics (e.g. clarithromycin) and nefazodone because they can increase the plasma concentrations of midostaurin especially when (re-)starting with midostaurin treatment. Alternative medicinal products that do not strongly inhibit CYP3A4 activity should be considered. In situations where satisfactory therapeutic alternatives do not exist, patients should be closely monitored for midostaurin-related toxicity.

Main toxicities:

Please refer to the SPC for full list of toxicities and further information

Midostaurin
Febrile neutropenia, nausea, exfoliative dermatitis, vomiting, headache, petechiae, pyrexia, lymphopenia, hyperglycaemia, interstitial lung disease. Raised ALT/AST and hypokalaemia. QTc prologation.

Investigations and treatment plan:

	Pre	Induction	Consolidation	Maintenance	Ongoing
Informed Consent	X				
Clinical Assessment & SACT assessment	X	X	X	X	Every cycle
FBC, U&E & LFT & Mg	X	X	X	X	Every cycle
Creatinine clearance	X	X	X	X	Every cycle
FLT3 mutation test	X				
CT scan	X				End of treatment or as clinically indicated
Echo or MUGA	X				Repeat if clinically indicated
TFTs	X				Repeat if clinically indicated
ECG	X				Repeat if clinically indicated
Chest X-ray	X				Repeat if clinically indicated
Bone marrow	X	X	X	X	Repeat if clinically indicated
PS recorded	X	X	X	X	Every cycle
Weight recorded	X	X	X	X	Every cycle
Pregnancy	X				If clinically appropriate

Dose Modifications and Toxicity Management:

Haematological toxicity:

Alongside Induction / Consolidation

Cycles can proceed as per DA or HDAC protocols

Maintenance therapy

Cycles can proceed if-

ANC ≥ 0.5 x 10^9/L

If ANC < 0.5 x10^9 /L, withhold midostaurin until ANC ≥1.0 x10^9/L and resume at 50mg twice a day. If ANC <1.0 x 10^9/L for > 2 weeks and is suspected to be midostaurin-related, discontinue midostaurin.

Note therapy can proceed if values are below these levels if cytopenias known to be secondary to disease.

These haematological guidelines assume that patients are well with good performance status, that other acute toxicities have resolved and the patient has not had a previous episode of neutropenic sepsis.

Non- Haematological toxicity:

See section entitled 'Dosing in Renal and Hepatic Impairment'

Phase	Criteria	Midostaurin dosing
Induction, consolidation and maintenance	Grade 3/4 pulmonary infiltrates	Interrupt midostaurin for the remainder of the cycle. Resume midostaurin at the same dose when infiltrate resolves to Grade ≤1.
	Other Grade 3/4 non-haematological toxicities	Interrupt midostaurin until toxicities considered at least possibly related to midostaurin have resolved to Grade ≤2, then resume midostaurin.
	QTc interval >470 msecs and ≤500 msecs	Decrease midostaurin to 50 mg once daily for the remainder of the cycle. Resume midostaurin at the initial dose in the next cycle provided that QTc interval improves to ≤470 msecs at the start of that

		cycle. Otherwise continue midostaurin 50 mg once daily.
	QTc interval >500 msecs	Withhold or interrupt midostaurin for the remainder of the cycle. If QTc improves to ≤470 msecs just prior to the next cycle, resume midostaurin at the initial dose. If QTc interval is not improved in time to start the next cycle do not administer midostaurin during that cycle. midostaurin may be held for as many cycles as necessary until QTc improves.
Maintenance only	Grade 4 neutropenia (ANC <0.5 x 10^9/l)	Interrupt midostaurin until ANC ≥1.0 x 10^9/l, then resume at 50 mg twice daily. If neutropenia (ANC <1.0 x 10^9/l) persists >2 weeks and is suspected to be related to midostaurin, discontinue midostaurin.
	Persistent Grade 1/2 toxicity	Persistent Grade 1 or 2 toxicity that patients deem unacceptable may prompt an interruption for as many as 28 days.

References:

- https://www.medicines.org.uk/emc - midostaurin (accessed 23/3/2023)
- NICE TA 523 Midostaurin for untreated acute myeloid leukaemia

Circulation/Dissemination

Date added into Q-Pulse	7th September 2023
Date document posted on the Intranet	N/A

Version History

Date	Version	Author name and designation	Summary of main changes
	1.0	**Dan Collins**	New protocol
June 2023	2.0	**Jennifer Gibson**	**Transferred to new template.**