Thames Valley
Strategic Clinical Network

MIDOSTAURIN + DA + HD Cytarabine

INDICATION

Newly diagnosed FLT3 mutation positive acute myeloid leukaemia (AML), in combination with DA (daunorubicin + cytarabine) induction, high-dose cytarabine consolidation, followed by single agent maintenance for twelve 28-day cycles or until alloHSCT. **(NICE TA523 - Blueteq required)**

Separate protocol exists for Midostaurin for advanced systemic mastocytosis.

The induction regimen in this protocol is different to that used in RATIFY trial but has been deliberately aligned with the DA protocol and AML19 trial, to enable DA to be started prior to FLT3 mutation status being available. This has been approved by the NSSG Myeloid subgroup.

Midostaurin is available as 25mg capsules only.

TREATMENT INTENT

Curative

PRE-ASSESSMENT

1. Blood tests - FBC, coagulation screen, DAT, U&Es, LDH, ESR, urate, calcium, magnesium, creatinine, serum bicarbonate, LFTs, glucose, Hepatitis B core antibody and Hepatitis B surface Ag, Hepatitis C antibody, EBV, CMV, VZV, HIV 1+2 after consent, group and save.
2. Ensure bone marrow findings and dates of findings are confirming diagnosis and are documented in notes prior to administration of therapy.
3. Urine pregnancy test - before cycle 1 of each new therapy course for women of child-bearing age unless they are post-menopausal, have been sterilised or undergone a hysterectomy
4. ECG
5. ECHO or MUGA if there is history or risk factors of congestive heart failure
6. Record performance status (WHO/ECOG)
7. Record height and weight
8. Consent - ensure patient has received adequate verbal and written information regarding their disease, treatment and potential side effects. Document in medical notes all information that has been given. Obtain written consent on the day of treatment
9. Fertility - it is very important the patient understands the potential risk of infertility; all patients should be offered fertility advice (see fertility guidelines).
10. Treatment should be agreed in the relevant MDT
11. Hydration and tumour lysis prevention; refer to tumour lysis protocol.
12. Consider dental assessment.
13. Central venous access should be used, e.g. Hickman line or PICC. In urgent cases it may be necessary to start chemotherapy via a peripheral cannula
14. Before starting midostaurin, AML patients must have confirmation of FLT3 mutation (internal tandem duplication [ITD] or tyrosine kinase domain [TKD])
15. For patients prescribed oral chemotherapy, ensure pre-chemotherapy counselling in line with NPSA recommendation and chemotherapy measures

DRUG REGIMEN / CYCLE FREQUENCY

INDUCTION (Maximum 2 cycles)

Cycle 1 Induction - DA 3+10

Days 1, 3 and 5	**DAUNORUBICIN** 60 mg/m^2 daily in 250mL sodium chloride 0.9% intravenous infusion over 1 hour (3 doses)
Days 1 to 10	**CYTARABINE** 100 mg/m^2 12 hourly slow intravenous bolus (20 doses)
Day 8* onwards	**MIDOSTAURIN** 50mg PO twice daily, with food **for 14 days**

* Midostaurin should start on day 8 as per SPC until day 21. If there is a delay in obtaining FLT3 mutation status, this could be started at day 11 and continued for 14 days.

A bone marrow examination should be performed on completion of midostaurin. If there was definitive evidence of clinically significant residual leukaemia, a second cycle of induction therapy may be administered. Patients who achieved complete remission after induction therapy will receive four cycles of consolidation treatment:

Cycle 2 Induction - DA 3+8
Only start if neutrophils ≥ 1.0 x 10^9/L and platelets ≥ 100 x 10^9/L

Days 1, 3 and 5	**DAUNORUBICIN** 50 mg/m^2 daily in 250mL sodium chloride 0.9% intravenous infusion over 1 hour (3 doses)
Days 1 to 8	**CYTARABINE** 100 mg/m^2 12 hourly slow intravenous bolus (16 doses)
Day 8 to 21	**MIDOSTAURIN** 50mg PO twice daily, with food **for 14 days**

CONSOLIDATION (Maximum 4 cycles)

Cycle 3 to 6
Only start if neutrophils ≥ 1.0 x 10^9/L and platelets ≥ 100 x 10^9/L

Days 1, 3 and 5	**CYTARABINE** 3 g/m^2 **twice daily** in 250mL sodium chloride 0.9% intravenous infusion over 3 hours (6 doses) *Consider dose reduction to 1.5g/m^2 for patient ≥60 years old and for patient under 60 years old with co-morbidities at the discretion of clinician and as discussed at the MDT.
Day 8 to 21	**MIDOSTAURIN** 50mg PO twice daily, with food **for 14 days**.

Patients who remain in remission after completion of consolidation therapy continue to maintenance.

MAINTENANCE

Continuous **MIDOSTAURIN** 50mg PO twice daily, with food, for twelve 28-day cycles.

Note: Midostaurin for AML is excluded from the NHSE Treatment Break policy.
In patients receiving a haematopoietic stem cell transplant (SCT), midostaurin should be discontinued 48 hours prior to the conditioning regimen for SCT.

ADMINISTRATION

Midostaurin capsules should be swallowed whole with a glass of water **with/after food**. The capsules 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 or vomiting occurs, no additional dose is required and the next dose should be taken at the scheduled time.

DOSE MODIFICATIONS

Haematological Toxicity

Induction & Consolidation	No dose modification required. Start the next cycle when ANC ≥ 1 x10^9/L & Platelet ≥ 100 x10^9/L
Maintenance	If ANC < 0.5 x10^9/L, withhold midostaurin until ANC ≥ 1 x10^9/L and resume at 50mg twice a day. If ANC < 1 x 10^9/L for > 2 weeks and is suspected to be midostaurin-related, discontinue midostaurin.

Cytarabine

Renal impairment	Hepatic impairment
Induction phase: No dose reduction necessary normally as doses not considered high dose **Consolidation phase:** GFR < 31-59 mL/min: give 50% dose GFR < 30 mL/min: omit Haemodialysis: give 50% dose, start HD 4-5 hours after administration	Mild/moderate impairment: no dose adjustment necessary Severe impairment: 25-50% dose and increase as tolerated

Daunorubicin

Renal impairment	Hepatic impairment
GFR 30-50 mL/min or Cr 105-265 micromol/L: give 75% dose GFR <30 mL/min or Cr > 266 micromol/L: give 50% dose Haemodialysis: give 50% dose	Bilirubin 20-50 micromol/L: give 75% dose Bilirubin > 50 micromol/L: give 50% dose

Maximum cumulative dose = 600 mg/m^2 (in normal cardiac function)
= 400 mg/m^2 (in patients with cardiac dysfunction or exposed to mediastinal irradiation).

Midostaurin

Renal Impairment	**Hepatic Impairment**
No dose adjustment is required for patients with any level of renal impairment. Limited data is available for severe or end-stage renal impairment.	No dose adjustment is required in patients with mild or moderate (Child-Pugh A or B) hepatic impairment. Not recommended in severe hepatic impairment (Child-Pugh C).
Cardiac Toxicity	
For QTc > 470 and ≤ 500 msec, Decrease midostaurin to 50mg once daily for the remainder of the cycle. Check magnesium and potassium levels and correct any abnormalities. Stop any medications that may prolong the QTc interval if possible. Resume at the previous dose if QTc improves to ≤470msec.	
For QTc interval > 500 msec, Withhold midostaurin. Resume at the previous dose if QTc improves to ≤470msec. If QTc interval is not improved in time to start the next cycle do not administer midostaurin that cycle	
Nausea	
Grade 3/4 nausea and/or vomiting despite optimal anti-emetic therapy	Withhold midostaurin for 3 days (6 doses), then resume at 50 mg twice daily.

INVESTIGATIONS

- FBC, U&E, LFT, serum amylase and lipase monthly
- ECG 24 hours and 72 hours after initiation, then weekly in the first month. Monthly thereafter.

CONCURRENT MEDICATION

Drug	**Dose and duration**
Allopurinol	300 mg daily for first 14 days of initial induction chemotherapy. (If a remission is attained the subsequent use of allopurinol is not required)
Aciclovir	200 mg three times a day for duration of treatment and for 3 months after completion
Fungal prophylaxis	As per local protocol
Proton pump inhibitor	As per local formulary
Prednisolone 0.5 – 1% eye drops or Dexamethasone 0.1% eye drops (depending on local formulary)	**Consolidation phase only:** One drop into each eye QDS. Continue for 5 days after cytarabine (due to risk of cytarabine-induced conjunctivitis). In the event of conjunctivitis consider increasing the frequency to 2-hourly until resolution of symptoms. Liaison with local ophthalmologists may be necessary in this situation

EMETIC RISK

Induction phase: Days 1-5 Moderate, Days 6 onwards: Low
Consolidation phase: Days 1-5: Moderate
Maintenance phase: Low

DRUG INTERACTION

Concomitant strong CYP3A4 inducers (e.g. carbamazepine, rifampicin, enzalutamide, phenytoin, St. John's Wort etc) are contraindicated with midostaurin.

Caution is required with strong CYP3A4 inhibitors because they can increase the plasma concentrations of midostaurin. Consider alternative medicinal products that do not strongly inhibit CYP3A4 activity. In situations where suitable therapeutic alternatives do not exist, patients should be closely monitored for midostaurin-related toxicity.

Voriconazole and **Posaconazole** can be used at the same time as midostaurin with monitoring of midostaurin toxicity, in particular ECG changes.

Hormonal contraceptives- It is currently unknown whether midostaurin may reduce their effectiveness. Women using hormonal contraceptives should add a barrier method of contraception.

Caution with drugs that prolong QT interval – regular assessments of QT by ECG should be considered if midostaurin is taken concurrently with QT prolonging drugs

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

Commonly reported (>10%): Febrile neutropenia, thrombocytopenia, anaemia, leucopenia, infections, diarrhoea, nausea, vomiting, headache, exfoliative dermatitis, petechiae, electrolyte imbalance.

Other drug specific adverse effects:

Daunorubicin: Posterior Reversible Encephalopathy Syndrome (PRES), alopecia, mucositis, chronic and acute cardiac failure and dysrrhythmias,. There is a recommended maximum cumulative lifetime dose of daunorubicin of 600 mg/m^2.

Low Dose Cytarabine (<1g/m^2): diarrhoea, abdominal pain, oral ulceration, hepatic dysfunction.

High Dose Cytarabine (≥1g/m^2): CNS, GI and pulmonary toxicity, reversible corneal toxicity, somnolence, convulsion, pulmonary oedema.

A cytarabine syndrome is also recognised in which patients suffer from fever, myalgia, bone pain, occasional chest pains, maculopapular rash, conjunctivitis and malaise. It usually occurs 6 to 12 hours following administration.

Midostaurin: deranged LFTs, elevated serum lipase, hyperglycaemia, hypotension. QT prolongation, pulmonary toxicity (pneumonitis/ILD)

EXTRAVASATION RISK

Cytarabine: neutral
Daunorubicin: vesicant

TREATMENT-RELATED MORTALITY

5%

REFERENCES

1. Stone RM et al. Midostaurin plus Chemotherapy for Acute Myeloid Leukaemia with a FLT3 Mutation. N Eng J Med 2017. 377(5) 45-464.
2. NICE. TA523 Midostaurin for untreated acute myeloid leukaemia. Published 13/06/2018. Accessed 25/10/2021 via http://www.nice.org.uk/ta523.
3. Novartis. Rydapt 25mg soft capsules summary of product characteristics. Updated 04/02/2021. Accessed via http://www.medicines.org.uk/emc on 25/10/2022
4. Zentiva. Daunorubicin 20mg Powder for IV injection. Updated 19/03/2020. Accessed via http://www.medicines.org.uk/emc on 25/10/2022
5. Pfizer Ltd. Cytarabine 100mg/ml. Updated 29/11/2017. Accessed via http://www.medicines.org.uk/emc
6. Cardiff University. Adults with Acute Myeloid Leukaemia or High-Risk Myelodysplastic Syndrome (AML19) Trial Protocol v10.0. Updated 27/04/2021
7. Krens S D et al (2019). Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. *Lancet Oncol*; **20:** e201–08

REVIEW

Name	Revision	Date	Version	Review date
Cheuk-kie Jackie Cheung, Haematology Pharmacist. NSSG Myeloid Group	New document. Annual protocol meeting.	Oct 2019	1.0	Oct 2021
Yen Lim, Haematology Pharmacist. NSSG Myeloid Group Prof Paresh Vyas, Consultant Haematologist	DA dosing schedule updated to match DA protocol and midostaurin regimen amended. Annual protocol meeting.	Nov 2021	2.0	Nov 2023
Yen Lim, Haematology Pharmacist. Prof Paresh Vyas & Dr Andy Peniket, Consultant Haematologists	Midostaurin start day amended to day 8	Apr 2022	2.1	Nov 2023
Yen Lim, Haematology Pharmacist. Prof Paresh Vyas & Dr Andy Peniket, Consultant Haematologists	Urgent protocol amendment for midostaurin duration in consolidation cycles – should be 14 days total	Jan 2023	2.2	Nov 2023