Midostaurin (DAUNOrubicin and Cytarabine) Induction Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Midostaurin is indicated in combination with standard DAUNOrubicin and cytarabine induction chemotherapy for adult patients with newly diagnosed acute myeloid leukaemia (AML) who are FLT3 mutation positive	C92	00682a	Midostaurin: CDS 01/10/2021 DAUNOrubicin: Hospital Cytarabine: Hospital

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

- Induction treatment is administered as detailed in the treatment table below.
- If Complete Remission (CR) is not achieved, a second cycle of induction therapy may be administered at the discretion of the prescribing Consultant. If blasts >25% consideration should be given to changing therapy.
- Patients who achieve CR after Cycle 1 induction therapy may receive a second cycle of induction therapy as described below or proceed to Consolidation Therapy (Ref NCCP Regimen 00683a Midostaurin Consolidation Therapy) at the discretion of the prescribing Consultant.

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate
1	1 to 3 inclusive	DAUNOrubicin	60mg/m^2 daily	IV bolus	Slow IV push via side arm NaCl 0.9% infusion. (A central line is preferred)
2	1 to 7 inclusive	Cytarabine	100mg/m^2 **AM**	IV infusion	100ml NaCl 0.9% over 30 mins
3	1 to 7 inclusive	Cytarabine	100mg/m^2 **PM** **(12 hours after start of AM infusion)**	IV infusion	100ml NaCl 0.9% over 30 mins
4	8 to 21 inclusive	Midostaurin	50mg twice daily	PO	
Lifetime cumulative dose of DAUNOrubicin is 550mg/m^2. **In establishing the maximal cumulative dose of an anthracycline, consideration should be given to the risk factors[i] and to the age of the patient.**					
Midostaurin capsules should be taken with food at approximately 12 hour intervals.					
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 midostaurin, but should take the next scheduled dose.					

ELIGIBILITY:

- Indication as above
- AML diagnosis with FLT3 mutation confirmed using a validated test excluding FLT 3 positive acute promyelocytic leukaemia

EXCLUSIONS:

- Hypersensitivity to DAUNOrubicin, cytarabine, midostaurin or to any of the excipients
- Concomitant administration of potent CYP3A4 Inducers
- Symptomatic congestive heart failure
- Bilirubin > 2.5 x upper limit of normal

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Haematologist working in the area of haematological malignancies.

TESTS:

Baseline tests:

- FBC, renal and liver profiles, magnesium level
- Chest x-ray
- TFT, ECG (QTc interval)
- MUGA or ECHO
- Virus serology: cytomegalovirus(CMV) infection, HIV (human immunodeficiency virus), hepatitis B (HBsAg, HBcoreAb), C.
  *Hepatitis B reactivation: See Adverse effects/ Regimen specific complications
- ßhCG pregnancy test

Regular tests:

- FBC, renal and liver profiles
- Coagulation profile: APTT, PT, fibrinogen level
- ECG (QTc interval) Day 8 (prior to commencing midostaurin) and as clinically indicated thereafter
- LVEF when clinically indicated

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant.
- **Dose reductions not generally undertaken in induction regimens.**
- **Elderly (≥65 years)**: No dose adjustment is required in patients aged over 65 years. There is limited experience with midostaurin in AML patients aged 60-70 years and no experience in AML patients above 70 years. 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.

Renal and Hepatic Impairment:

Table 1: Dose modification in renal and hepatic impairment

Drug	Renal Impairment		Hepatic Impairment	
DAUNOrubicin	**Creatinine (micromol/L)**	**Dose**	**Bilirubin (micromol/L)**	**Dose**
	<105	100%	<20	100%
	105-265	75%	20-50	75%
	>265	50%	>50	50%
Cytarabine	No dose reduction necessary		If bilirubin >34micromol/L, give 50% dose. Escalate doses in subsequent cycles in the absence of toxicity.	
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.		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.	

Management of adverse events:

Table 2: Dose Modification of midostaurin for Adverse Events

Criteria	Midostaurin dosing
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.

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

DAUNOrubicin: Moderate **(Refer to local policy)**
Cytarabine: Low **(Refer to local policy)**
Midostaurin: Moderate to High **(Refer to local policy)**

PREMEDICATIONS: None usually required

OTHER SUPPORTIVE CARE:

- Tumour lysis syndrome prophylaxis **(Refer to local policy)**
- Proton pump Inhibitor **(Refer to local policy)**
- Anti-viral prophylaxis **(Refer to local policy)**
- Anti-fungal prophylaxis **(Refer to local policy).** Strong CYP3A4 inhibitors (e.g. posaconazole) can increase midostaurin exposure. If concomitant use is required, an ECG should be performed prior to commencement of the CYP3A4 inhibitor to assess the QTc and QTc should continue to be monitored by regular ECGs. In addition, monitoring of posoconazole levels is recommended.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS:

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

Midostaurin:

Midostaurin is subject to additional monitoring. Healthcare professionals are asked to report any suspected adverse reactions.

- **Neutropenia and infections:** Neutropenia has occurred in patients receiving midostaurin as monotherapy and in combination with chemotherapy. White blood cell counts (WBCs) should be monitored regularly, especially at treatment initiation. In patients who develop unexplained severe neutropenia beyond what is usually expected in AML induction, treatment with midostaurin should be interrupted until ANC is $\geq 1.0 \times 10^9$/L. Midostaurin should be discontinued in patients who develop recurrent or prolonged severe neutropenia that is suspected to be related to midostaurin. Any active serious infection should be under control prior to starting treatment with midostaurin monotherapy.
- **Cardiac dysfunction:** Patients with symptomatic congestive heart failure were excluded from clinical studies. In patients at risk, midostaurin should be used with caution and the patient closely monitored by assessing LVEF when clinically indicated (at baseline and during treatment). An increased frequency of QTc prolongation was noted in midostaurin–treated patients, however, a mechanistic explanation for this observation was not found. 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.
- **Pulmonary toxicity:** Interstitial lung disease (ILD) and pneumonitis, in some cases fatal, have occurred in patients treated with midostaurin monotherapy or in combination with chemotherapy. Patients should be monitored for pulmonary symptoms indicative of ILD or pneumonitis and midostaurin discontinued in patients who experience pulmonary symptoms indicative of ILD or

pneumonitis that are ≥ Grade 3 (NCI CTCAE).

- **Embryofoetal toxicity:** 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 with midostaurin and to use effective contraception during treatment with midostaurin and for at least 4 months after stopping treatment. Women using hormonal contraceptives should add a barrier method of contraception.
- **Hepatitis B Reactivation:** Patients should be tested for both HBsAg and HBcoreAb as per local policy. If either test is positive, such patients should be treated with anti-viral therapy **(Refer to local infectious disease policy).** These patients should be considered for assessment by hepatology.

DAUNOrubicin:

- **Cardiotoxicity:** Extreme caution should be exercised when using DAUNOrubicin in patients with cardiac disorders or in the elderly. Cardiotoxicity if it occurs is likely to be heralded by either a persistent tachycardia, shortness of breath, swelling of feet and lower limbs or by minor changes in the electrocardiogram and for this reason an electrocardiographic examination should be made at regular intervals during the treatment. Cardiotoxicity usually appears within 1 to 6 months after initiation of the therapy. It may develop suddenly and not be detected by routine ECG. It may be irreversible and fatal but responds to treatment if detected early.
- **Extravasation:** DAUNOrubicin is a potent vesicant. Give through the side arm of a fast flowing infusion ideally through a central access line to avoid/minimise the risk of extravasation.

Cytarabine:

- **Cytarabine syndrome**: Treatment with cytarabine may cause a 'Cytarabine Syndrome' characterised by flu-like symptoms, skin rash and occasionally chest pain.
- **Myelosuppression**: Cytarabine is a potent bone marrow suppressant. Patients receiving this drug must be under close medical supervision and should have leucocyte and platelet counts performed daily.
- **Neurotoxicity**: This may occur in patients treated with high dose cytarabine. Assess cerebellar function prior to each cytarabine dose. The risk of neurotoxicity is enhanced in the presence of renal impairment. Ensure that dose of cytarabine is adjusted in renal impairment.

DRUG INTERACTIONS:

- Medicinal products or substances known to affect the activity of CYP3A4 may affect the plasma concentrations of midostaurin and therefore the safety and/or efficacy of midostaurin.
  - Concomitant use of midostaurin with strong inducers of CYP3A4 (e.g. carbamazepine, rifampicin, enzalutamide, phenytoin, St. John's Wort [Hypericum perforatum]) is contraindicated - strong CYP3A4 inducers decrease exposure of midostaurin and its active metabolites.
  - Strong CYP3A4 inhibitors such as azole antifungals may increase midostaurin blood concentrations.
- It is currently unknown whether midostaurin may reduce the effectiveness of hormonal contraceptives, and therefore women using hormonal contraceptives should add a barrier method of contraception.
- Current drug interaction databases should be consulted for more information.

REFERENCES:

1. Stone RM et al. Midostaurin plus Chemotherapy for Acute Myeloid Leukemia with a FLT3 Mutation. N Engl J Med. 2017 Aug 3;377(5):454-464. doi: 10.1056/NEJMoa1614359. Epub 2017 Jun 23. PMID: 28644114; PMCID: PMC5754190.
2. Dosage Adjustment for Cytotoxics in Renal Impairment January 2009; North London Cancer Network.
3. Dosage Adjustment for Cytotoxics in Hepatic Impairment January 2009; North London Cancer Network.
4. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V3 2021. Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp-classification-document-for-systemic-anti-cancer-therapy-sact-induced-nausea-and-vomiting.pdf
5. DAUNOrubicin (Cerubidin®) Summary of Product Characteristics. Accessed July 2021. Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA0540-096-001_28062019145807.pdf
6. Cytarabine Solution for Injection Summary of Product Characteristics. Accessed July 2021. Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA0822-200-002_18082021114137.pdf
7. Midostaurin (Rydapt®) Summary of Product Characteristics. Accessed July 2021. Available at: https://www.ema.europa.eu/en/documents/product-information/rydapt-epar-product-information_en.pdf

Version	Date	Amendment	Approved By
1	01/10/2021		NCCP Myeloid Clinical Advisory Group
2	28/01/2022	Updated recommendations in relation to second cycle of induction treatment. Updated Supportive Care: Anti-fungal prophylaxis	NCCP Myeloid Clinical Advisory Group

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

---

[i] Cardiotoxicity is a risk associated with anthracycline therapy that may be manifested by early (acute) or late (delayed) effects.

Risk factors for developing anthracycline-induced cardiotoxicity include:

- high cumulative dose, previous therapy with other anthracyclines or anthracenediones
- prior or concomitant radiotherapy to the mediastinal/pericardial area
- pre-existing heart disease
- concomitant use of other potentially cardiotoxic drugs

In establishing the maximal cumulative dose of an anthracycline, consideration should be given to the risk factors above and to the age of the patient.