SACT PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

Nilotinib
Chronic Myeloid Leukaemia

PROTOCOL REF: MPHANILHA
(Version No. 2.0)

Approved for use in:

Untreated chronic phase Philadelphia chromosome (BCR-ABL) positive (Ph+) chronic myeloid leukaemia (CML) who cannot have imatinib for a clinical reason **(TA426)**.

Blueteq registration MUST be completed prior to initiation for this indication

Chronic or accelerated Ph+ CML in adults who are intolerant to imatinib or their disease is imatinib-resistant **(TA425)**.

Blueteq registration is NOT required for this indication

Dosage:

Chronic phase CML

Drug	Dose	Route	Frequency
Nilotinib	300mg	PO	Twice daily continuous. Also see de-escalation advice below

Consider increase to 400mg twice daily if suboptimal response (off-label)

Chronic and accelerated phase CML with prior imatinib resistance/ intolerance

Drug	Dose	Route	Frequency
Nilotinib	400mg	PO	Twice daily continuous

De-escalation:

Certain patients with excellent responses to nilotinib after several years of treatment may be eligible for de-escalation of their treatment, with the aim of stopping their treatment completely. This de-escalation procedure is managed by the CML team who follow the *DESTINY* trial (see references). The British Society of Haematology also provides guidance on de-escalation. Please contact the CML team for further information if required.

Administration:

- Doses should be taken approximately 12 hours apart and must not be taken with food
- No food should be consumed for 2 hours before and 1 hour after each dose
- For patients who are unable to swallow hard capsules, the content of each hard capsule may be dispersed in one teaspoon of apple sauce (puréed apple) and should be taken immediately. Not more than one teaspoon of apple sauce and no food other than apple sauce must be used.
- If a patient is also taking a H2 antagonists they should be advised that this must be taken at least 10 hours before or 2 hours after their nilotinib
- Antacids containing aluminium hydroxide / magnesium hydroxide may reduce exposure to nilotinib. Therefore these should be administered 2 hours prior to 2 hours after nilotinib.

Anti-emetic risk:

Low Risk

Supportive treatments:

Consider allopurinol 300mg once daily during first cycle

Dosing in renal and hepatic impairment:

Renal	Hepatic
A decrease in total body clearance is not anticipated in patients with renal impairment.	Dose adjustment is not considered necessary in patients with hepatic impairment. However, patients with hepatic impairment should be treated with caution.

Interactions:

- Concomitant use of CYP3A4 inducers including dexamethasone, phenytoin, carbamazepine, rifampicin, and phenobarbital should be avoided as this may significantly reduce exposure to nilotinib.
- Concomitant use of strong CYP3A4 inhibitors including ketoconazole, itraconazole, voriconazole, erythromycin and clarithromycin should be avoided as this may significantly increase exposure to nilotinib.
- Caution should be taken when co-administrating nilotinib with substrates of CYP3A4 with a narrow therapeutic index (alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, sirolimus and tacrolimus) as this can increase exposure to the CYP3A4 substrate.

Main toxicities:

Common: QT prolongation, arrhythmia, palpitations, fluid retention, folliculitis, URTI, neutropenia, thrombocytopenia, hypophosphataemia, anxiety, depression, dizziness, vertigo, liver enzyme abnormalities, hypercholesterolaemia and muscle cramps, excessive sweating, decreased appetite, headache, nausea, vomiting, constipation, diarrhoea, abdominal pain, dyspepsia, rash, puritus, alopecia, dry skin, muscle cramps/pain, fatigue

Less Common: hepatitis B reactivation, hyperthyroidism, hypothyroidism, gynaecomastia and pleural effusion.

Less commonly cardiovascular events including peripheral arterial occlusive disease, ischaemic heart disease and ischaemic cerebrovascular events have been reported with nilotinib use. Patients should be advised to seek immediate medical attention if they experience acute signs or symptoms of cardiovascular events. The cardiovascular status of patients should be evaluated and cardiovascular risk factors monitored and actively managed during nilotinib therapy according to standard guidelines.

Please refer to the relevant SPC for more information on toxicities.

Investigations and treatment plan:

	Pre	Cycle 1	Cycle 2 onwards	Ongoing
Informed Consent	X			
Clinical Assessment	X	X	X	Prior to every cycle
ECHO and ECG	X			As clinically indicated
SOKAL	X			
QRISK3	X			To guide suitability for nilotinib therapy
BCR-ABL PCR	X	X	X	PCR test can take a few days to process so results will be reviewed retrospectively. Monthly for the first three months, three monthly thereafter.
FBC, U&Es & LFTs	X	X	X	Prior to every cycle. A cycle may extend to three months in length once patients are stable on treatment. FBC should be taken within 7 days of prescribing but may be taken up to 14 days prior to prescription at clinician's discretion. **Prescribers must check results prior to prescribing and document that this check has taken place in the medical notes.**
Amylase/lipase	X			As clinically indicated
Blood Pressure	X	X	X	Prior to each prescription
BNP	X			Annually
TFTs	X			When clinically necessary
Serum lipid profile	X			Repeat 3 months and 6 months after initiation and then monitor at least yearly
HbA1c	X			Monitor throughout treatment as clinically indicated
Height	X			
Weight	X	X	X	Prior to every cycle
Pregnancy test	X			If clinically indicated
Hepatitis B (including surface antigen and HB core antibody) and Hepatitis C testing	X			

Dose Modifications and Toxicity Management:

Haematological toxicity:

Newly diagnosed chronic phase CML *(300mg BD)* Or Imatinib-resistant or intolerant CML in chronic phase *(400mg BD)*	ANC <1.0 x10^9/L and/or Platelets <50 x10^9/L	1. Stop nilotinib treatment 2. Resume treatment within 2 weeks at the same dose if ANC > 1.0 x10^9/L and/or platelets > 50 x10^9/L 3. If counts remain low dose can be reduced to 400mg once daily
Imatinib-resistant or intolerant CML in accelerated phase (400mg BD)	ANC <0.5 x109/L and/or Platelets <10 x109/L	1. Stop nilotinib treatment 2. Resume treatment within 2 weeks at the same dose if ANC > 1.0 x109/L and/or platelets > 20 x109/L 3. If counts remain low dose can be reduced to 400mg once daily

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:

If clinically significant non-haematological toxicity develops, dosing should be interrupted, and may be resumed at 400 mg once daily once the toxicity has resolved. A more cautious re-introduction may be consider at consultant discretion e.g. 150mg BD.

If clinically appropriate, re-escalation of the dose to the starting dose of 300 mg twice daily in newly diagnosed patients with CML in the chronic phase or to 400 mg twice

daily in patients with imatinib-resistant or intolerant CML in chronic phase and accelerated phase should be considered.

Elevated serum lipase: For Grade 3-4 serum lipase/amylase elevations, doses should be reduced to 400 mg once daily or interrupted. Serum lipase/amylase levels should be tested as clinically indicated.

Elevated bilirubin and hepatic transaminases: For Grade 3 - 4 bilirubin and hepatic transaminase elevations, doses should be reduced to 400 mg once daily or treatment interrupted. Bilirubin and transaminases levels should be tested monthly or as clinically indicated.

Nilotinib has been associated with an increased risk of cardiovascular complications. If a vascular event occurs during nilotinib treatment, consider a change of TKI. Nilotinib should be used with caution in patients with known vascular disease or with vascular risk factors with careful consideration of risk versus benefit.

Increases in both total serum cholesterol and blood glucose levels have been reported with nilotinib therapy. Lipid profiles and HbA1c should be assessed prior to initiation. Lipid profiles should then be assessed at 3 months, 6 months and then at least yearly, HbA1c should be measured at least yearly throughout treatment.

References:

1. Novartis. Tasigna 50mg Hard Capsules. Summary of Product Characteristics. Updated 08/03/22. Accessed 09/06/23
2. NICE. Dasatinib, nilotinib and high-dose imatinib for treating imatinib-resistant or intolerant chronic myeloid leukaemia (TA425). Published 21st December 2016. https://www.nice.org.uk/guidance/ta425/ Accessed 09/06/23
3. NICE. Dasatinib, nilotinib and imatinib for untreated chronic myeloid leukaemia (TA426). Published 21st December 2016. https://www.nice.org.uk/guidance/ta426 Accessed 09/06/23

4. MHRA (2016) Drug Safety Update: BCR-ABL tyrosine kinase inhibitors: risk of hepatitis B reactivation
5. Lancet Haematology (2019). De-escalation of tyrosine kinase inhibitor therapy before complete treatment discontinuation in patients with chronic myeloid leukaemia (DESTINY): a non-randomised, phase 2 trial

Circulation/Dissemination

Date added into Q-Pulse	For completion by DCM
Date document posted on the Intranet	For completion by DCM

Version History

		Author name and designation	Summary of main changes
			To be completed by author
11/05/20	v1.0	**Mark Nelson**	**Protocol created**
Aug 2023	v2.0	**Jade Marsh**	**Protocol reviewed, new protocol template used. Minor changes**