SACT PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

Dasatinib
Chronic Myeloid Leukaemia (CML)

PROTOCOL REF: MPHADASHA
(Version No. 2.0)

Approved for use in:

- Untreated chronic phase Philadelphia Chromosome (BCR-ABL) positive (Ph+) chronic myeloid leukaemia (CML) and in whom imatinib is inappropriate (TA426) **(i.e 1st line treatment).**

Blueteq registration is required for this indication

- Chronic or accelerated phase Ph+ CML in adults who cannot have imatinib due to intolerance or their disease is imatinib-resistant (TA425) **(i.e 2nd line treatment).**

Blueteq registration is not required for this indication

Dosage:

Chronic Phase

Drug	Dose	Route	Frequency
Dasatinib	100mg	PO	Daily continuous. Dose may be increased to 140mg if necessary. Also see de-escalation advice below

Accelerated Phase

Drug	Dose	Route	Frequency
Dasatinib	140mg	PO	Daily continuous

De-escalation:

Certain patients with excellent responses to dasatinib after several months of treatment may be eligible for de-escalation from 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. The British Society of Haematology also provides guidance on de-escalation. Please contact the CML team for further information if required.

Administration:

- Dasatinib can be taken with or without food.
- Tablets should not be crushed, cut or chewed. Consider oral suspension in those who cannot tolerate the tablets (discuss with pharmacy)
- Patients should be encouraged to report severe oedema early to their haematology team.
- Avoid grapefruit juice due to potential drug interaction.

Emetogenic risk:

Low risk

Supportive treatments:

Consider allopurinol 300mg once daily during first cycle

Dosing in renal and hepatic impairment:

Renal	Hepatic
As renal clearance of dasatinib and its metabolites is < 4%, clearance is not expected to be affected in patients with renal sufficiency	Patients with mild, moderate or severe hepatic impairment may receive the recommended starting dose, but used 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 dasatinib.
- Concomitant use of CYP3A4 inhibitors including ketoconazole, itraconazole, voriconazole, erythromycin, clarithromycin and grapefruit juice should be avoided as this may significantly increase exposure to dasatinib.
- Caution should be taken when co-administrating dasatinib with substrates of CYP3A4 with a narrow therapeutic index; astemizole, terfenadine, cisapride, pimozide, quinidine, bepridil or ergot alkaloids as this can increase exposure to the CYP3A4 substrate.
- Concomitant use of H_2 antagonists, proton pump inhibitors or aluminium hydroxide / magnesium hydroxide may reduce exposure to dasatinib. Therefore, these should be administered up to 2 hours prior or 2 hours after dasatinib.

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

Main toxicities:

Dasatinib
Infection, myelosuppression, change in appetite, headache, mood changes, congestive heart failure, pericardial effusion, cardiac issues, pulmonary issues, arrhythmia, palpitations, haemorrhage, flushing, diarrhoea, nausea, vomiting, skin rash, joint pain, myalgia gastrointestinal disturbance, hepatitis B reactivation,

Investigations and treatment plan:

	Pre	Cycle 1 D1	Cycle 1 D8	Cycle 1 D15	Cycle 1 D22	Cycle 2 +	Ongoing
Informed Consent	X						
Clinical Assessment	X	X				X	Prior to every cycle
ECG and ECHO	X						If clinically indicated. Note dasatinib can prolong the QTc
Chest X-Ray	X						Prior to treatment. Repeat as clinically indicated
Respiratory assessment	X						If clinically indicated. Spirometry/ PFTs
SOKAL score	X						
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&E's, LFTs	X	X	X	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 FBC prior to prescribing and document that this check has taken place in the medical notes.**
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:

Proceed with cycle if:

ANC ≥ 0.5 x10^9/L	Platelets ≥ 50 x10^9/L

Chronic Phase CML (starting dose 100mg)			
ANC	**And/or**	**Platelets**	**Modification**
<0.5x10^9/L		<50 x10^9/L	1. Stop treatment until ANC ≥ 1 x10^9/L and platelets ≥ 50 x10^9/L. 2. Resume treatment at the original starting dose. 3. If platelets < 25 x10^9/L and/or recurrence of ANC < 0.5 x10^9/L for > 7 days, repeat step 1 and resume treatment at a reduced dose of 80 mg once daily (second episode). In the event of a third episode, either reduce to 50mg once daily (for newly diagnosed patients) or discontinue therapy (for patients resistant or intolerant to prior therapy including imatinib) 4. Consider GCSF if recurrent neutropenia.
Accelerated phase CML (starting dose 140mg)			
ANC	**And/or**	**Platelets**	**Modification**
<0.5x10^9/L		<10 x10^9/L	1. Check if cytopenia is related to leukaemia (marrow aspirate or biopsy). 2. If cytopenia is unrelated to leukaemia, stop treatment until ANC ≥ 1 x10^9/L and platelets ≥ 20 x10^9/L and resume at the original starting dose. 3. If recurrence of cytopenia, repeat step 1 and resume treatment at a reduced dose of 100mg once daily (second episode) or 80mg once daily (third episode). 4. If cytopaenia is related to leukaemia, consider dose escalation to 180 mg once daily.

Dose Reduction Steps for Haematology Toxicity				
Indication	**Dose escalation**	**Starting Dose**	**1st Dose Reduction**	**2nd Dose Reduction**
Chronic Phase		100mg daily	80mg daily	50mg daily
Accelerated Phase	180mg daily	140mg daily	100mg daily	80mg 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:

Grade 2 non-haematological toxicity: interrupt treatment until the event has resolved or returned to baseline. Resume at the same dose if this is the first occurrence and at a reduced dose if this is a recurrent event.

Grade 3 or 4 non-haematological toxicity: treatment must be withheld until the event has resolved. Thereafter, treatment can be resumed as appropriate at a reduced dose level depending on the severity of the initial reaction.

Dose Reduction Steps for Non-Haematology Toxicity			
Indication	**Starting Dose**	**1st Dose Reduction**	**2nd Dose Reduction**
Chronic Phase	100mg daily	80mg daily	50mg daily
Accelerated Phase	140mg daily	100mg daily	50mg daily

References:

1. Summary of Product Characteristics. Dasatinib. Update 13/12/22. Available: Dasatinib 100 mg Film-coated Tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)
2. Dosage Adjustment for Cytotoxics in Hepatic Impairment. January 2009 UCLH - Dosage Adjustment for Cytotoxics in Hepatic Impairment (Version 3 - updated January 2009)
3. Dosage Adjustment for Cytotoxics in Renal Impairment. January 2009 UCLH - Dosage Adjustment for Cytotoxics in Renal Impairment (Version 3 - updated January 2009)

4. NICE TA 425. Dasatinib, nilotinib and high dose imatinib for treating imatinib resistant or intolerant CML. December 2016
5. NICE TA 426. Dasatinib, nilotinib and imatinib for untreated CML. December 2016

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
May 2020	1.0	**Mark Nelson – Senior Pharmacist HO**	**New Protocol**
Aug 2023	2.0	**Jade Marsh – Advanced Pharmacist HO**	**Transferred to new template. Updated dose reduction steps. Addition of 180mg dose escalation information.**