SACT PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

# BUSULFAN
# MYELOPROLIFERATIVE DISORDERS (MPN) & CML

PROTOCOL REF: MPHABMDMC
(Version No. 1.0)

## Approved for use in:

- For the management of: Polycythaemia vera (PV/PRV), essential thrombocythaemia (ET), myelofibrosis (MF) where hydroxycarbamide is ineffective/unsuitable.
  *Very careful consideration should be given to the use of busulfan for the treatment of MPN in younger or asymptomatic patients in view of the drug's carcinogenic potential.*
- For the management of chronic myeloid leukaemia (CML)
  - Rarely used now tyrosine kinase inhibitors are routinely used
- Use is limited, in general, to second line in patients over 75 years of age due to the associated risk of leukaemia.

**No Blueteq registration is required**

## Dosage:

| Drug | | Dose | Route | Frequency |
|---|---|---|---|---|
| **Busulfan** | **Option 1** | **2mg or 4mg** | **Oral** | For 7-14 days only |
| | **Option 2** | **2mg** | **Oral** | Continuously/ continuously on alternate days until platelets <400 |
| | **Option 3a** | Standard Israel Protocol: month one: 4mg OD days 1 to 7 then 2mg OD days 8 to 28. Month 2: 2mg alternate day until platelets <400x$10^9$/L | | |
| | **Option 3b** | Modified Israel Protocol: 2 or 4mg OD days 1 to 7 then 2mg on alternate days until platelets <400x$10^9$/L | | |
| | **Option 4** | **20mg** | **Oral** | As a single dose |

**Cycle length: 28 days. No maximum number of cycles**

**PATIENTS SHOULD NEVER BE PRESCRIBED MORE THAN 4 WEEKS SUPPLY OF BUSULFAN TO AVOID THE RISK OF INDUCING BONE MARROW APLASIA.**

## Administration:

- The tablets must not be crushed, chewed or halved. They should be swallowed whole.
- Available in 2mg tablets only
- Dose can be split into 2mg BD to lesson GI side-effects
- Busulfan is now very rarely used and so it should only be prescribed by a haematologist experienced in its use.

## Emetogenic risk:

Mildly emetogenic

## Supportive treatments:

- Allopurinol PO 100mg or 300mg OD (depending on renal function) for first cycle (or longer if clinically indicated)
- Ondansetron 8mg STAT alongside busulfan when single dose regimen used

## Dosing in renal and hepatic impairment:

| | | |
|---|---|---|
| **Renal** | Renal impairment and haemodialysis | No dose reduction necessary but use with caution |

| | | |
|---|---|---|
| **Hepatic** | Mild/moderate<br><br><u>Mild:</u> bil >1.0-1.5 x ULN and any AST or bil ≤ULN and AST >ULN;<br><u>Moderate:</u> bil 1.5-3 x ULN, with any AST | 100% dose |
| | Severe<br><br>Bilirubin >3.0-10 x ULN, with any AST | Not recommended. Consider dose reduction in patients with raised liver enzymes. |

## Interactions:

The main interactions are outlined below however, for more detailed interaction information please refer to the drug specific SPC

- Co-administration with other cytotoxics that also have the risk of causing pulmonary toxicity may result in an additive effect.
- Paracetamol is described to decrease glutathione levels in blood and tissues, and may therefore decrease busulfan clearance when used in combination. The clinical relevance of this interaction is unclear. The manufacturers of busulfan advise caution on concurrent use and when paracetamol is given during the 72-hour period before busulfan is given.
- Increases in busulfan exposure have been observed at concomitant administration of busulfan and deferasirox. The mechanism behind the interaction is not fully elucidated. It is recommended to regularly monitor busulfan plasma concentrations and, if necessary, adjust the busulfan dose in patients who are or have recently been treated with deferasirox.
- Patients who are concurrently treated with the conventional dose of busulfan and itraconazole or metronidazole should be closely monitored for signs of busulfan toxicity. At concomitant use of these agents with busulfan weekly blood counts are recommended.

## Main toxicities:

Dose-related bone marrow failure, pulmonary toxicity, hyperbilirubinaemia, jaundice, hepato-venoocclusive disease, nausea, vomiting, diarrhoea and mouth ulceration

### Lung toxicity

- Discontinue busulfan if the patient develops lung toxicity
- Co-administration of busulfan alongside other cytotoxic agents known to have the potential to cause lung toxicity may result in additive toxicity

### Radiotherapy

- Busulfan should not generally be given in conjunction or soon after radiotherapy

**Hyperuricaemia**

- Hyperuricaemia and/or hyperuricosuria are not uncommon in CML patients and should be corrected before initiating busulfan
- During treatment hyperuricaemia and the risk of uric acid neuropathy should be prevented with adequate hydration and the use of allopurinol

**Hepatic veno-occlusive disease** is a major complication that can occur with busulfan treatment

- Patients who have received prior radiation therapy for 3 or more cycles, or prior progenitor cell transplant may be at increased risk of developing hepatic veno-occlusive disease

**Leukaemic potential**

- There is growing evidence that alkylating agents such as busulfan increase the risk of developing leukaemia (i.e. leukaemogenic)

## Investigations and treatment plan:

| | Pre | C1 | C2+ | Ongoing |
|---|---|---|---|---|
| Informed Consent | X | | | Pre-initiation |
| Clinical Assessment | X | X | X | Every cycle |
| SACT Assessment (to include PS and toxicities) | X | X | X | Every cycle |
| FBC | X | X | X | Every cycle |
| U&E & LFTs & Urate | X | X | X | Every Cycle |
| CrCl (Cockcroft and Gault) | X | X | X | Every cycle |
| Pregnancy test - in women of childbearing potential | X | | | Repeat as needed |
| Lung function tests | X | | | Consider in patients with a risk factor(s) for lung toxicity |
| Weight recorded | X | X | X | Repeat if clinically indicated |
| Height recorded | X | | | |
| Blood glucose | X | | | Repeat if clinically indicated |

## Dose Modifications and Toxicity Management:

## Haematological toxicity:

Proceed on day of treatment if:

| ANC >2.0 x$10^9$/L |
|---|

The dose of busulfan needs to be carefully titrated to the patient's FBC. For most patient short courses of busulfan will induce long periods of remission. Some clinicians prefer to give continuous maintenance therapy because it is more practical when the duration of unmaintained remissions is short.

For MPN patients the target for platelets should be <400 x $10^9$/L and haematocrit < 45%. Busulfan is usually stopped when platelets are <400 x $10^9$/L.

For induction of remission in CML patients the target WCC is between 15 and 25 x $10^9$/L; this typically takes 12 to 20 weeks. Continued treatment at the induction dose after this point or following depression of the platelet count to below 100 x $10^9$/L is associated with a significant risk of prolonged and possibly irreversible bone marrow aplasia. Further courses are usually given when the WCC rises to 50 x $10^9$/L, or symptoms return. The target WCC for maintenance therapy is between 10 and 15 x $10^9$/L.

Should a patient require an average daily dose of less than the content of one tablet, the maintenance dose may be adjusted by introducing one or more busulfan free days between treatment days.

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'

## References:

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2. Thames Valley Strategic Clinical Network. Myeloid Group. Busulfan v1.2. November 2021. Protocol available from: NSSG Chemotherapy Protocol (oxford-haematology.org.uk)
3. Krens S D, Lassche, Jansman G F G A, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. Lancet Oncol 2019; 20: e201–08
4. Stockley's Drug Interactions. Medicines complete. https://www.medicinescomplete.com/#/interactions/stockley?terms=paracetamol, busulfan. Paracetamol and busulfan. Accessed 25/07/22.
5. Shvidel, L., Sigler, E., Haran, M. et al. Busulphan is safe and efficient treatment in elderly patients with essential thrombocythemia. Leukemia 21, 2071–2072 (2007). https://doi.org/10.1038/sj.leu.2404743

## Circulation/Dissemination

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|---|---|
| Date added into Q-Pulse | 26th January 2023 |
| Date document posted on the Intranet | N/A |

## Version History

| Date | Version | Author name and designation | Summary of main changes |
|---|---|---|---|
| April 2022 | 1.0 | **Jade Marsh**<br>**Advanced HO Pharmacist** | V1<br>New Protocol Regimen |
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