Thames Valley
Strategic Clinical Network

BUSULFAN

INDICATION

Polycythaemia Vera (PV)
Essential Thrombocythaemia (ET)
Myelofibrosis (MF)
Chronic Phase Chronic Myeloid Leukemia (CML)

Available as 2mg tablets

TREATMENT INTENT

PV – haematologic remission
ET – haematologic remission
MF – occasionally required for control of blood counts
CML – palliative

PRE-ASSESSMENT

1. Blood tests - FBC, U&Es, urate, LFTs, glucose
2. Ensure diagnosis is confirmed prior to administration of chemotherapy and document in notes
3. Record stage of disease
4. Urine pregnancy test – for all women of childbearing age unless they are postmenopausal, have been sterilised or undergone a hysterectomy.
5. Record performance status (WHO/ECOG)
6. Record height and weight (also needed to calculate CrCl)
7. 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
8. Fertility - it is very important the patient understands the potential risk of infertility, all patients should be offered fertility advice
9. Consider lung function test for patient with risk factor for toxicity
10. For patients prescribed oral chemotherapy, ensure pre-chemotherapy counselling in line with NPSA recommendation and chemotherapy measures
11. Treatment should be agreed in the relevant MDT

DRUG REGIMEN / CYCLE FREQUENCY

Busulfan can be administered in a variety of dosing regimens:

PV, ET and MF

INTERMITTENT REGIMEN

BUSULFAN 2mg to 4mg PO once daily for 7 to 14 days. Check blood tests every 2 weeks and continue dosing until platelet count is reduced to < 400 x10^9/L. Only prescribe 2 weeks at a time (or 4 weeks in selected patients after discussion with consultant). The dose must then be interrupted until the platelet count rises above this level as continued dosing may lead to prolonged cytopenia. This regimen should be used with caution and requires frequent blood count monitoring due to the risk of bone marrow aplasia.

SINGLE DOSE REGIMEN

BUSULFAN 20mg PO (single dose) every 4 to 6 weeks. This is usually given in outpatient clinic/day treatment unit under supervision.

CML - Adult Induction (Very rarely used in the TKI era)

BUSULFAN 0.06mg/kg/day (maximum 4mg) PO once daily
FBC must be monitored at least weekly during induction.
Increase dose only if the response is inadequate after 3 weeks.
Continue until total WBC count has fallen to 15 - 25 x 10^9/L (typically 12 to 20 weeks).
Treatment may then be interrupted, following which a further fall in WBC count may occur over the next 2 weeks. Continued treatment at induction dose after this or following depression of Plt < 100 x 10^9/L is associated with a significant risk of prolonged and possibly irreversible bone marrow aplasia.

CML - Adult Maintenance

BUSULFAN 2mg PO once daily, individually tailored
Control of CML may be achieved for long periods without further Busulfan; further courses are usually given when WBC > 50 x 10^9/L or symptoms return.
Continuous treatment is more practical when the duration of unmaintained remissions is short. Aim to maintain WBC 10 - 15 x 10^9/L. Perform FBC at least every 4 weeks. Should a patient require an average daily dose of less than the content of one tablet (2mg), adjust the maintenance dose by introducing Busulfan free days between treatment days.

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

RESTAGING

Regular blood count monitoring as above

DOSE MODIFICATIONS

Obese

Consider dosing based on adjusted ideal body weight for obese patients.

Renal / Hepatic Impairment

Renal impairment	Hepatic impairment
Caution. No dose reduction necessary.	Mild/moderate: 100% dose Severe: Not recommended Consider dose reduction in patients with raised liver enzymes

SPECIAL WARNINGS / PRECAUTIONS / MONITORING

Discontinue Busulfan if lung toxicity develops. Other cytotoxic agents may cause additive lung toxicity. If anaesthesia is required in patients with possible pulmonary toxicity, the concentration of inspired oxygen should be kept as low as safely as possible and careful attention given to post-operative respiratory care.

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

Busulfan is ineffective once blast transformation has occurred.

Hyperuricaemia and/or hyperuricosuria are not uncommon in patients with CML and should be corrected before starting treatment with Busulfan. During treatment, hyperuricaemia and the risk of uric acid nephropathy should be prevented by adequate prophylaxis, including adequate hydration and the use of Allopurinol.

Monitor FBC throughout treatment to avoid excessive myelosuppression and the risk of irreversible bone marrow aplasia.

Hepatic veno-occlusive disease is a major complication that can occur during treatment with Busulfan. Patients who have received prior radiation therapy, for 3 or more cycles of chemotherapy, or prior progenitor cell transplant may be at an increased risk of developing hepatic veno-occlusive disease.

Very careful consideration should be given to the use of Busulfan for the treatment of PV and ET in view of the drug's carcinogenic (leukaemogenic) potential. The use of Busulfan for these indications should be avoided in younger or asymptomatic patients. If the drug is considered necessary treatment courses should be kept as short as possible.

INVESTIGATIONS

Regular blood count monitoring as above

CONCURRENT MEDICATION

Allopurinol 300mg PO once daily for 7 days can be considered in selected cases.

EMETIC RISK

Low

DRUG INTERACTIONS

(Consult with pharmacist and refer to SPC for full details)

Avoid the use of azole antifungal during busulfan treatment due to risk of veno-occlusive disease if possible.

Patients co-administered azole antifungals or Metronidazole with conventional dose Busulfan should be monitored for signs of Busulfan toxicity. Weekly FBC is recommended when co-administering if not avoidable.

Effects of other cytotoxics producing pulmonary toxicity may be additive.

Paracetamol may decrease glutathione levels in blood and tissues, and may therefore decrease Busulfan clearance when used in combination

Increases in busulfan exposure have been observed at concomitant administration of busulfan and deferasirox. 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.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

Very commonly reported:
Dose-related bone marrow failure, manifesting as leucopenia and particularly thrombocytopenia, male infertility, azoospermia and testicular atrophy in male patients

TREATMENT RELATED MORTALITY

No clear data relating to mortality with busulfan in MPN although the risk is low (<1%). Prolonged use of busulfan is associated with risk of profound aplasia that can lead to death and patients should be consented accordingly.

REFERENCES

1. Aspen. Busulfan 2mg tablets Summary of Product Characteristics. Updated 12/10/2021. Accessed on 5/11/2021 via http://www.medicines.org.uk/
2. Krens S D et al (2019). Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. *Lancet Oncol*; **20:** e201–08
3. McMullin MF et al (2019), A guideline for the diagnosis and management of polycythaemia vera. A British Society for Haematology Guideline. Br J Haematol, 184: 176-191. https://doi.org/10.1111/bjh.15648
4. Reilly et al (2012) BCSH Guideline for the diagnosis and management of myelofibrosis. BJH 158(4):453-71
5. Harrison et al (2014) Modification of BCSH diagnostic criteria for essential thrombocythaemia. BJH 167(3):421-3
6. Harrison et al (2010) BCSH Guideline for investigation and management of adults and children presenting with a thrombocytosis. BJH 149(3): 352-75

REVIEW

Name	Revision	Date	Version	Review date
Julia Wong	New protocol	Mar 2017	1.0	
Cheuk-kie Jackie Cheung, Haematology Pharmacist. NSSG Myeloid Group	Annual protocol meeting	Oct 2019	1.1	Oct 2021
Yen Lim, Haematology Pharmacist. NSSG Myeloid Group	Annual protocol meeting	Nov 2021	1.2	Nov 2023