Cyclophosphamide for PBSC mobilisation

Indication

Mobilisation of peripheral blood stem cells (PBSC) for future stem cell rescue following high dose chemotherapy for non-Hodgkin's Lymphoma, Hodgkin's disease, multiple myeloma and acute leukaemias.

ICD-10 codes

Codes pre-fixed with C81, C82, C83, C84, C85, C86 and C90.

Standard outpatient regimen details

Day	Time	Drug	Dose	Route
1	T_0	Mesna	300mg/m^2	IV bolus
1	T_0	Cyclophosphamide	1500mg/m^2	IV infusion
1	T_0 + 2 hours	Mesna	600mg/m^2	PO
1	T_0 + 6 hours	Mesna	600mg/m^2	PO
5 onwards	-	GCSF	As per local policy (usually 10 micrograms/kg/day)	SC

Patients should be advised to drink 2-3 litres of fluid per day.
Mesna is available as 400mg and 600mg tablets. Dose should be rounded up if necessary.
An additional dose of oral mesna should be supplied (in case of vomiting).

Inpatient regimen details

To be considered if concerns surrounding renal function and/or patients ability to maintain adequate oral intake.

Day	Time	Drug	Dose	Route
1	T_0	Mesna	500mg/m^2	IV infusion
1	T_0	Cyclophosphamide	1500mg/m^2	IV infusion
1	T_0 + 1 hour	Mesna	1800mg/m^2	IV infusion
5 onwards	-	GCSF	As per local policy (usually 10 micrograms/kg/day)	SC

Note pre and post hydration required (see below)
Additional doses of mesna may be required in the case of haematuria.

Mobilisation may be delayed so aim to give the cyclophosphamide on a Friday so that day +11 falls on a monday.

Harvesting

Stem cell collection Day +11 – Ensure apheresis slots are booked prior to start of cyclophosphamide.

Assessment

An adequate yield >2 x 10^6 $CD34^+$ cells/kg. An optimal target yield would contain 4-5 x10^6 $CD34^+$ cells/kg.

Cycle frequency

N/A

Number of cycles

N/A

Outpatient regimen administration

Mesna 300mg/m^2 is administered immediately prior to cyclophosphamide as an IV bolus.

Cyclophosphamide 1500mg/m^2 is administered as an IV infusion in 500mL sodium chloride 0.9% over 2 hours.

Mesna 600mg/m^2 is given orally at 2 and 6 hours after the start of the cyclophosphamide infusion.

Inpatient regimen administration

Prior to mesna, pre hydration with 20mmol potassium chloride in 1000mL sodium chloride 0.9% is administered over 6 hours.

Cyclophosphamide 1500mg/m^2 and mesna 500mg/m^2 are administered together as an IV infusion in 500mL sodium chloride 0.9% over 1 hour.

Immediately after the cyclophosphamide has finished, mesna 1800mg/m^2 is infused over 18 hours in 500mL sodium chloride 0.9% concurrently with post hydration.

Post hydration is administered immediately after cyclophosphamide infusion has finished, concurrently with the 18 hour mesna infusion. Three bags of 20mmol potassium chloride in 1000mL sodium chloride 0.9% are administered over 6 hours each (total 3 x 1000mL over 18 hours).

Patients should be advised to drink at least 2-3 L of fluid per day for the following 48 hours.

GCSF is prescribed in line with local policy to start on day 5 and continue until stem cells have been harvested.

Pre-medication

Antiemetics as per local policy
Pre hydration as above

Emetogenicity

This regimen has high emetic potential

Extravasation

Cyclophosphamide is neutral (Group 1)

Pre-treatment evaluation

Investigation	Validity period
FBC	14 days
U+E (including creatinine)	14 days
LFTs	14 days

Other pre-treatment investigations:
Hepatitis B and C and HIV serology
Cardiopulmonary assessment, ECG and echocardiogram if suspected cardiac impairment.

Regular investigations

Investigation	Validity period
Urinalysis (for haematuria)	Each urine passed
FBC	Daily from day +11
CD34+	*Daily from day +11

* Aim for peripheral blood CD34+ count of >10/microlitre (i.e. >1% CD34+ cells with WBC>5 x 10^9/L) before commencing harvest

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant

Investigation	Limit
Neutrophils	≥ 1.0 x 10^9/L
Platelets	≥ 75 x 10^9/L
Creatinine Clearance (CrCl)	> 20mL/min
Bilirubin	≤ 1.5 ULN
AST/ALT	≤ 3 x ULN

Ensure platelet count > 40 x 10^9/L on the days of harvest.

Dose modifications

- **Haematological toxicity**

N/A

- **Renal impairment**

This protocol should only be used if CrCl > 20mL/min. Consider if renal function adequate for patient to undergo high dose therapy.

- **Hepatic impairment**

Reduced activation of cyclophosphamide pro-drug in severe hepatic impairment, however high dose therapy unlikely to be appropriate in this scenario.

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Myelosuppression
Acute pulmonary toxicity
Cardiotoxicity
Haemorrhagic cystitis

- **Frequently occurring side effects**

Myelosuppression
Nausea and vomiting
Alopecia
Fever, chills, myalgia, bone pain (due to GCSF)

- **Other side effects**

Fluid retention

Significant drug interactions – for full details consult product literature/ reference texts

Warfarin/coumarin anticoagulants: increased or fluctuating anticoagulant effects. Avoid if possible, consider switching patient to a low molecular weight heparin during treatment or if the patient continues taking an oral anticoagulant monitor the INR at least once a week and adjust dose accordingly.

Cyclophosphamide:
Amiodarone: increased risk of pulmonary fibrosis – avoid if possible
Clozapine: increased risk of agranulocytosis – avoid concomitant use
Digoxin tablets: reduced absorption – give as liquid form
Indapamide: prolonged leucopenia is possible - avoid
Azole antifungals (eg Fluconazole, Itraconazole, Voriconazole, Posaconazole): may increase adverse effects of cyclophosphamide.
Phenytoin: reduced absorption - may need to increase dose of phenytoin
Grapefruit juice: decreased or delayed activation of cyclophosphamide. Patients should be advised to avoid grapefruit juice for 48 hours before and on day of cyclophosphamide dose.

Additional comments

Patients should be advised to avoid grapefruit juice for 48 hours before and on day of cyclophosphamide dose.

Ensure that blood products transfused within 14 days of harvest are irradiated.

References

- Summary of Product Characteristics Cyclophosphamide accessed via http://www.mhra.gov.uk/Safetyinformation/Medicinesinformation/SPCandPILs
- To LB, et al. The optimisation of collection of peripheral blood stem cells for autotransplantation in acute myeloid leukaemia. BMT, 1989, 4: 41-7.
- To LB, et al. A comparative study of the phenotype and proliferative capacity of peripheral blood (PB)CD34+ cells mobilised by four different protocols and those of steady-phase PB and bone marrow CD34+ cells. Blood, 1994, 84: 2930-9.
- Dreger P, Schmitz N. Sources of stem cells: autografts. In: The EBMT handbook-blood and marrow transplantation, European School of Haematology, 1998:72-86.
- Duong HK, et al. Peripheral blood progenitor cell mobilization for autologous and allogeneic hematopoietic cell transplantation: guidelines from the American Society for Blood and Marrow Transplantation. Biology of Blood and Marrow Transplantation. 2014 Sep 30;20(9):1262-73.

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