PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

Intravenous Cyclophosphamide Myeloma

PROTOCOL REF: MPHAINCYMY
(Version No. 1.0)

Approved for use in:

- Relapsed / refractory myeloma patients who have previously been treated with immunomodulatory or protease inhibitor therapy

Blueteq registration is not required

Dosage:

Drug	Dose	Route	Frequency
Cyclophosphamide	**1200mg/m^2**	IV infusion	Days 1
Mesna	**800mg**	Oral	Three doses on days 1. To be given at 4 hourly intervals starting 2 hours before cyclophosphamide.
Filgrastim	**30 or 48 million units****	S/C injection	Days 6, 7 if neutrophils <1.0 x 10^9/L
******Dose is weight dependent. Give 30 million units if <70kg or 48 million units if ≥70kg.			

Cycle frequency every 14 days. Continued until unacceptable toxicity or disease progression

Administration:

- Encourage oral fluids – a minimum of 2-3 Litres, 24 hours before and after cyclophosphamide administration
- Cyclophosphamide will be given as an intravenous infusion.

- Filgrastim will be supplied to the patient to self-administer at home. Refer to community nursing teams if patient is unable to self-administer.

Emetogenic risk:

Moderately emetogenic.

Supportive treatments:

- Allopurinol PO 300mg once daily (reduce dose in renal impairment) for cycle one only
- Aciclovir PO 400mg twice daily
- Co-trimoxazole PO 480mg once daily
- Metoclopramide PO 10mg three times a day when required
- Mesna PO 800mg for 3 doses at 4 hourly intervals starting 2 hours prior to cyclophosphamide infusion. The dose may be increased to four dosed at 3 hourly intervals in patients at higher risk of urothelial toxicity.

Extravasation risk:

Cyclophosphamide: Non vesicant

Refer to the CCC policy for the 'Prevention and Management of Extravasation Injuries'

Dosing in renal and hepatic impairment:

Renal	**Cyclophosphamide**	CrCl (mL/min)	Modification
		>20	100%
		10-20	75%
		<10	50%

Hepatic	**Cyclophosphamide**	No dose adjustments necessary

Interactions:

Substances that reduce the efficacy of cyclophosphamide include:

Aprepitant, bupropion, busulfan, ciprofloxacin, chloramphenicol, azole-antimycotics (e.g., fluconazole and itraconazole, CYP2B6 and CYP3A4 inhibitors (e.g. nevirapin and ritonavir): co-administration may reduce the efficacy of cyclophosphamide, prasugrel, sulphonamides, e.g.

sulfadiazine, sulfamethoxazole and sulfapyridine, thiotepa, grapefruit (fruit or juice), rifampicin, St. John's wort.

An increased risk of side-effects may occur with:
Azathioprine: increased risk of hepatotoxicity (liver necrosis), chloral hydrate, cimetidine, disulfiram, glyceraldehyde, protease inhibitors, saquinavir, rifampin, phenobarbital, carbamazepine, phenytoin, St. John's wort, benzodiazepines, corticosteroids and dabrafenib.

There is an increased risk of cardiotoxicity when cyclophosphamide is co-administered with:
anthracyclines, mitomycin, cytarabine, pentostatin and radiation therapy.

Please see SPC for full details of interactions.

Treatment schedule:

Day	Drug	Dose	Route	Diluent and rate
1	**Mesna**	**800mg**	**Oral**	Three doses to be given at 4 hourly intervals starting 2 hours before cyclophosphamide.
1	**Cyclophosphamide**	**1200mg/m^2**	**IV**	250mL sodium chloride 0.9% Over 30 minutes
6 & 7	**Filgrastim***	**30 or 48 million units**	**S/C**	S/C injection once daily
*Filgrastim should be considered if neutrophils <1.0 x 10^9/L				

Main toxicities:

Thrombocytopenia, neutropenia, anaemia, nausea, vomiting, diarrhoea and cardiotoxicity and haemorrhagic cystitis, haematuria.

Investigations and treatment plan:

	Pre	Cycle 1	Cycle 1 Day 5	Cycle 1 Day 8	Cycle 2	Cycle 3+	Ongoing
Informed consent	X						
Clinical Assessment	X	X			X	X	
SACT Assessment (including performance status and toxicity assessment)		X			X	X	
FBC	X	X	X	X	X	X	Check FBC prior to day 6 in subsequent cycles at clinician discretion
U&E & LFTs & Calcium profile	X	X	X	X	X	X	
CrCl (Cockcroft and Gault)	X						
Serum Igs/electrophoresis/serum free light chains (if indicated)	X	X			X	X	
HbA1C and blood glucose	X						Repeat as clinically indicated
Imaging as per NICE/network guidance and clinical indication	X						Repeat as clinically indicated
Height	X						
Weight	X	X			X	X	Every cycle
Pregnancy test	X						If clinically indicated

Dose Modifications and Toxicity Management:

Haematological toxicity:

Proceed on day 1 if-

Neutrophils ≥ 1.0 x 10^9/L	Platelets ≥ 50 x 10^9/L

Neutrophils (x 10^9/L)	Modification
<1 on day of treatment	Delay cycle by 1 week. Discuss use of G-CSF or dose reductions for further cycles with consultant
Any febrile neutropenia following any cycle of cyclophosphamide	Consider dose reduction. All subsequent cycles should be given with GCSF support.
Febrile neutropenic episode despite G-CSF support	Consider reduction of cyclophosphamide by 50% for all subsequent cycles
Platelets (x 10^9/L)	Modification
<100 on day of treatment	Delay cycle by 1 week.
Second delay due to thrombocytopenia	Consider reducing dose of cyclophosphamide for all subsequent cycles

References:

1. Summary of Product Characteristics, Cyclophosphamide 500mg Powder for Solution for Injection or Infusion, Sandoz Limited. June 2017. Monograph available from: http://www.medicines.org.uk [accessed Oct 2022].
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. BNF available via: https://bnf.nice.org.uk/
5. A Nikonova et al. High-Dose Cyclophosphamide in Highly Refractory Multiple Myeloma Patients As a Bridge to Further Novel Therapies. *Blood* (2016) 128 (22): 5676. Available online: https://doi.org/10.1182/blood.V128.22.5676.5676 [accessed Oct 2022]

Circulation/Dissemination

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Date document posted on the Intranet	N/A

Version History

Date	Version	Author name and designation	Summary of main changes
October 2022	1.0	**Daniel Dutton – Pharmacist**	New Protocol Created