Chemotherapy Protocol

MYELOMA

Carfilzomib (14 day)-Dexamethasone (20)

Regimen

- Myeloma – Carfilzomib-Dexamethasone (20)

Indication

- Carfilzomib in combination with dexamethasone is an option for treating multiple myeloma in adults;

  - relapsed or progressing disease
  - if the patient has received 1 and only 1 prior line of treatment and that the numbering of a line of treatment is in accordance with the International Myeloma Workshop Consensus recommendations for the uniform reporting of clinical trials (http://doi.org/10.1182/blood-2010-10-299487). A line of therapy is defined as one or more cycles of a planned treatment program. This may consist of one or more planned cycles of single-agent therapy or combination therapy, as well as a sequence of treatments administered in a planned manner (eg induction chemotherapy/chemotherapies if followed by stem cell transplantation is considered to be 1 line of therapy). A new line of therapy starts when a planned course of therapy is modified to include other treatment agents (alone or in combination) as a result of disease progression, relapse or toxicity. A new line of therapy also starts when a planned period of observation off therapy is interrupted by a need for additional treatment for the disease.Note that the use of carfilzomib in combination with dexamethasone in patients who have had **1 and only 1** prior line of therapy is because of NICE's specific recommendation for routine commissioning. The use of carfilzomib in combination with dexamethasone in the 2- or more prior line patient groups is not permitted.
  - one of the following options applies as to any previous systemic therapy with bortezomib for this patient:
    1. patient has received prior bortezomib as part of 1st line treatment and there has been at least a 6- month proteasome inhibitor treatment-free interval from the last bortezomib dose
    2. patient has not received any previous treatment with bortezomib
  - carfilzomib will only be administered in combination with dexamethasone and with no other systemic anticancer therapies
  - WHO performance status 0, 1, 2

Toxicity

Drug	Adverse Effect
Carfilzomib	Anaemia, fatigue, diarrhoea, thrombocytopenia, cardiac toxicity, nausea, pyrexia, dyspnoea, respiratory tract infection, cough and peripheral oedema, confusional states, herpes zoster infection
Dexamethasone	Weight gain, gastrointestinal disturbances, hyperglycaemia, CNS disturbances, cushingoid changes, glucose intolerance.

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

Monitoring

- FBC, LFT and U&Es prior to day 1 of treatment
- Regular monitoring of blood glucose is considered good practice.

Dose Modifications

The dose modifications listed are for haematological, liver and renal function and drug specific toxicities only. Dose adjustments may be necessary for other toxicities as well.

In principle all dose reductions due to adverse drug reactions should not be re-escalated in subsequent cycles without consultant approval. It is also a general rule for chemotherapy that if a third dose reduction is necessary treatment should be stopped.

Please discuss all dose reductions / delays with the relevant consultant before prescribing, if appropriate. The approach may be different depending on the clinical circumstances.

Haematological

Dose modifications for haematological toxicity in the table below are for general guidance only. Always refer to the responsible consultant as any dose reductions or delays will be dependent on clinical circumstances and treatment intent. Low counts can be a consequence of bone marrow infiltration as well as drug toxicity. Consider blood transfusion if patient symptomatic of anaemia or has a haemoglobin of less than 8g/dL (80g/L).

Prior to starting a new cycle of treatment;

- neutrophils should be greater than or equal to $1x10^9$/L
- platelets should be greater than or equal to $50x10^9$/L
- non-haematological toxicity should resolve to NCI-CTC grade 1 or below or baseline

Haematological dose modifications – Carfilzomib This table refers to toxicity during a cycle of treatment (nadir / mid cycle)	
Neutrophils	**Dose**
Greater than or equal to $0.5x10^9$/L	100%
Less than $0.5x10^9$/L	• Withhold dose until neutrophils recover to $0.5x10^9$/L or above • 1st occurrence: After neutrophil recovery restart at current dose level • 2nd occurrence: After neutrophil recovery restart and consider 1 dose level reduction (see table below)
Platelets	**Dose**
Greater than $10x10^9$/L	100%

Less than $10x10^9$/L	• Withhold dose until the platelets are $10x10^9$/L or above • 1st occurrence: After platelet recovery and / or bleeding controlled, continue at current dose level • 2nd occurrence: After platelet recovery and / or bleeding controlled, restart carfilzomib and consider 1 dose level reduction (see table below)

Hepatic impairment

Drug	Dose
Carfilzomib	No information available

Renal Impairment

Renal dose modifications - Carfilzomib	
Renal function	**Dose (% of original dose)**
Creatinine greater than or equal to 2x baseline, and / or	• Withhold dose • Restart carfilzomib when renal function has recovered to within 25% of baseline (consider 1 dose level reduction) – see table below.
CrCl less than 15ml/min, and / or	
CrCl decreased to less than or equal to 50% of baseline	

Other

Other non-haematological toxicity	Recommended action
Grade 3 or 4 toxicity	• Stop until toxicity resolved / returned to baseline • Consider restarting at 1 dose level reduction

Carfilzomib dose level reductions:*	Normal dose	1st reduction	2nd reduction	3rd reduction
	$56mg/m^2$	$45mg/m^2$	$36mg/m^2$	$27mg/m^2$

*Note: carfilzomib dose and dose reductions differ depending on regimen used.

Dose reductions or interruptions in therapy are not necessary for those toxicities that are considered unlikely to be serious or life threatening. For example, alopecia, altered taste or nail changes.

For all other non-haematological NCI-CTC toxicities refer to manufacturer information.

Carfilzomib

Infusion reactions

Infusion reactions, including life-threatening reactions, have been reported in patients who received carfilzomib. Symptoms may include fever, chills, arthralgia, myalgia, facial flushing, facial oedema, vomiting, weakness, shortness of breath, hypotension, syncope, chest tightness, or angina. These reactions can occur immediately following or up to 24 hours after administration of carfilzomib. Dexamethasone should be administered prior to carfilzomib to reduce the incidence and severity of reactions.

Monitor for signs and symptoms of an infusion-related reaction. Interrupt or slow the rate of infusion in patients with mild or moderate infusion reactions and consider pre-medications prior to subsequent doses.

Dexamethasone

Dose Level	Dose
2 (starting)	20mg
1	10mg

If recovery from toxicities is prolonged beyond 14 days, then the dose of dexamethasone will be decreased by one dose level.

Toxicity	Grade (NCI-CTC)	Dose modification
Dyspepsia	1 - 2	Maintain dose and treat with histamine (H_2) antagonist or proton pump inhibitor. Decrease by one dose level if symptoms persist.
	3 or above	Interrupt dose until symptoms are controlled. Add H_2 blocker or proton pump inhibitor and decrease one dose level when dose restarted.
Oedema	3 or above	Use diuretics as needed and decrease dose by one dose level.
Confusion or mood alteration	2 or above	Interrupt dose until symptoms resolve. When dose restarted decrease dose by one dose level.
Muscle weakness	2 or above	Interrupt dose until the muscle weakness is grade 1 or below. Restart with dose decreased by one level.
Hyperglycaemia	3 or above	Decrease dose by one dose level. Treat with insulin or oral hypoglycaemic agents as needed
Acute pancreatitis		Discontinue patient from dexamethasone treatment regimen.
Other	3 or above	Stop dexamethasone dosing until adverse event resolves to grade 2 or below. Resume with dose reduced by one level.

Regimen

Warning, the day one dexamethasone is incorporated into the regimen as a dose to be administered prior to the carfilzomib by the nursing staff. If the day one carfilzomib is suspended for any reason the schedule of the dexamethasone may need to be adjusted and the administration instructions amended.

42 day cycle until disease progression or intolerance occurs (12 cycles will be set in ARIA)

Drug	Dose	Days	Administration
Carfilzomib	56mg/m^2 (max 120mg)	1, 15, 29	Intravenous infusion in 100ml glucose 5% over 30 minutes
Dexamethasone	20mg	1, 2, 15, 16, 29, 30	Oral

Dose Information

- Carfilzomib will be dose banded in accordance with the nationally agreed dose bands (2mg/ml)
- Carfilzomib will be dose capped at 2.2m$^{2.}$ This equates to 120mg when using the national dose bands.
- Dexamethasone is available as 500microgram, 2mg and 4mg tablets and as a 2mg/5ml oral liquid.

Administration Information

- Dexamethasone should be taken in the morning, with or after food

Extravasation

- Carfilzomib - neutral

Additional Therapy

- No antiemetics are required.
- Carfilzomib pre-hydration with sodium chloride 0.9% 500ml over 30minutes
- Carfilzomib post hydration with sodium chloride 0.9% 500ml over 30 minutes
- For the treatment of carfilzomib related Infusion reactions
    - chlorphenamine 10mg intravenous injection once only when required for infusion related reactions
    - hydrocortisone 100mg intravenous when required for infusion related reactions

- salbutamol 2.5mg nebule when required for related bronchospasm
- paracetamol 1000mg oral once only when required for infusion related reactions

- Consider allopurinol 300mg oral once a day for seven days for the first cycle only

- Consider anti-infective prophylaxis including;
  - aciclovir 400mg twice a day oral
  - co-trimoxazole 960mg once a day oral on Monday, Wednesday and Friday only
  - fluconazole 50mg once a day oral

- Bisphosphonates in accordance with local policies.

- Mouthwashes according to local or national policy on the treatment of mucositis.

- Gastric protection with a proton pump inhibitor or a H_2 antagonist may be considered in patients considered at high risk of GI ulceration or bleed.

References

1. National Institute of Health and Clinical Excellence. NICE Technology Appraisal guidance [TA457]. Carfilzomib for previously treated multiple myeloma. 19th July 2017. Available from: https://www.nice.org.uk/guidance/ta457
2. Electronic medicines compendium - Krypolis summary of product characteristics. Last updated April 2018. Available from: https://www.medicines.org.uk/emc/product/5061#POSOLOGY

REGIMEN SUMMARY

Carfilzomib (14 day)-Dexamethasone (20)

Cycle 1 Day 1, 15, 29

1. Dexamethasone 20mg oral 30 minutes prior to the carfilzomib
   Administration Instructions
   Administer at least 30 minutes and up to four hours prior to the start of the carfilzomib infusion

2. Sodium chloride 0.9% 500ml intravenous infusion over 30 minutes

3. Carfilzomib 56mg/m^2 (maximum 120mg) intravenous infusion in 100ml glucose 5% over 30 minutes

4. Sodium chloride 0.9% 500ml intravenous infusion over 30 minutes

5. Chlorphenamine 10mg intravenous injection once only when required for infusion related reactions.

6. Hydrocortisone 100mg intravenous injection once only when required for infusion related reactions

7. Salbutamol 2.5mg nebule once only when required for infusion related bronchospasm

8. Paracetamol 1000mg oral once only when required for infusion related reactions
   Administration Instructions
   Please check if the patient has taken paracetamol. Maximum dose is 4g per 24 hours. There should be 4 hours between doses

Take home medicines

9. Dexamethasone 20mg once a day on day 2, 16, 30 oral
   Administration Information
   Please supply three doses of dexamethasone on day 1 of the cycle, ONE dose to be taken on days 2, 16 and 30 of the cycle once a day in the morning.
   Take with or after food.

10. Co-trimoxazole 960mg once a day on Monday, Wednesday and Friday for 42 days oral
    Administration Instructions
    Co-trimoxazole 960mg once a day on Mondays, Wednesdays and Fridays. Please supply 42 days. This may be dispensed as 480mg twice a day on Mondays, Wednesdays and Fridays according to local practice.

11. Aciclovir 400mg twice a day for 42 days oral
    Administration Instructions
    Please supply 42 days or an original pack if appropriate

12. Allopurinol 300mg once a day for 7 days oral
    Administration Instructions
    Take with or after food with plenty of water. Please supply 7 days.

13. Gastric Protection
    Administration Instructions
    The choice of gastric protection is dependent on local formulary choice and may include:

    - esomeprazole 20mg once a day oral
    - omeprazole 20mg once a day oral
    - lansoprazole 15mg once a day oral
    - pantoprazole 20mg once a day oral
    - rabeprazole 20mg once a day oral

- cimetidine 400mg twice a day oral
- famotidine 20mg once a day oral
- nizatidine 150mg twice a day oral
- ranitidine 150mg twice a day oral

Please dispense 42 days or nearest original pack size.

Cycle 2 Day 1, 15, 29

14. Dexamethasone 20mg oral 30 minutes prior to the carfilzomib
    Administration Instructions
    Administer at least 30 minutes and up to four hours prior to the start of the carfilzomib infusion

15. Sodium chloride 0.9% 500ml intravenous infusion over 30 minutes

16. Carfilzomib 56mg/m^2 (maximum 120mg) intravenous infusion in 100ml glucose 5% over 30 minutes

17. Sodium chloride 0.9% 500ml intravenous infusion over 30 minutes

18. Chlorphenamine 10mg intravenous injection once only when required for infusion related reactions.

19. Hydrocortisone 100mg intravenous injection once only when required for infusion related reactions

20. Salbutamol 2.5mg nebule once only when required for infusion related bronchospasm

21. Paracetamol 1000mg oral once only when required for infusion related reactions
    Administration Instructions
    Please check if the patient has taken paracetamol. Maximum dose is 4g per 24 hours. There should be 4 hours between doses

Take home medicines

22. Dexamethasone 20mg once a day on day 2, 16, 30 oral
    Administration Information
    Please supply three doses of dexamethasone on day 1 of the cycle, ONE dose to be taken on days 2, 16 and 30 of the cycle once a day in the morning. Take with or after food.

23. Co-trimoxazole 960mg once a day on Monday, Wednesday and Friday for 42 days oral
    Administration Instructions
    Co-trimoxazole 960mg once a day on Mondays, Wednesdays and Fridays. Please supply 42 days. This may be dispensed as 480mg twice a day on Mondays, Wednesdays and Fridays according to local practice.

24. Aciclovir 400mg twice a day for 42 days oral
    Administration Instructions
    Please supply 42 days or an original pack if appropriate

25. Gastric Protection
    Administration Instructions
    The choice of gastric protection is dependent on local formulary choice and may include:
    - esomeprazole 20mg once a day oral
    - omeprazole 20mg once a day oral
    - lansoprazole 15mg once a day oral
    - pantoprazole 20mg once a day oral
    - rabeprazole 20mg once a day oral
    - cimetidine 400mg twice a day oral
    - famotidine 20mg once a day oral
    - nizatidine 150mg twice a day oral
    - ranitidine 150mg twice a day oral

    Please dispense 42 days or nearest original pack size.

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	March 2022	None	Nanda Basker Pharmacist	Dr Mathew Jenner Dr Ed Belsham

This chemotherapy protocol has been developed as part of the chemotherapy electronic prescribing project. This was and remains a collaborative project that originated from the former CSCCN. These documents have been approved on behalf of the following Trusts;

Hampshire Hospitals NHS Foundation Trust
NHS Isle of Wight
Portsmouth Hospitals NHS Trust
Salisbury Hospital NHS Foundation Trust
University Hospital Southampton NHS Foundation Trust
Western Sussex Hospitals NHS Foundation Trust

All actions have been taken to ensure these protocols are correct. However, no responsibility can be taken for errors that occur as a result of following these guidelines. These protocols should be used in conjunction with other references such as the Summary of Product Characteristics and relevant published papers.