Chemotherapy Protocol

Multiple Myeloma
Selinexor with Bortezomib and Dexamethasone

Regimen
- SELINEXOR (PO) – BORTEZOMIB (SC) – DEXAMETHASONE (PO)

Indication
Selinexor plus bortezomib and dexamethasone is recommended as an option for treating multiple myeloma in adults if the following criteria is met:
- 1 previous line of treatment, and their condition is refractory to both daratumumab and lenalidomide, or
- 2 previous lines of treatment and their condition is refractory to lenalidomide.

Toxicity

Drug	Adverse Effect
Selinexor	Infections, thrombocytopenia, neutropenia, anaemia, GI disturbances, hyponatremia, changes in weight, cataract, tumour lysis syndrome, confusion, fatigue, diarrhoea, dizziness
Bortezomib	GI disturbances, peripheral neuropathy, hypotension, dizziness, blurred vision, headache, musculoskeletal pain, pyrexia
Dexamethasone	Weight gain, GI 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 further details.

Monitoring

- FBC, Renal and LFTs, weight, nutritional status and sodium levels assessed at baseline, during treatment, and as clinically indicated. Monitor more frequently during the first two months of treatment.
- Paraprotein and / or light chains prior to each cycle.
- Regular monitoring of blood glucose is considered good practice.
- Ophthalmologic evaluation may be performed as clinically indicated.

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.

No dose modifications of Selinexor are required for patients with mild hepatic impairment or patients with mild, moderate or severe renal impairment. There is insufficient data in patients

with moderate or severe hepatic impairment or end stage renal disease or haemodialysis to support a dose recommendation.

Elderly

No dose adjustment required for patients over 65 years of age.

	Selinexor in combination with Bortezomib and Dexamethasone (SVd)
Recommended starting dose	100 mg once weekly
First reduction	80 mg once weekly
Second reduction	60 mg once weekly
Third reduction	40 mg once weekly

Table 1: Prespecified dose modification steps for adverse reactions

* If symptoms do not resolve, treatment should be discontinued.

Haematological

Neutrophils ($x10^9$/L)	**Dose Modifications (Selinexor and Bortezomib)**
0.5 to 1.0 without fever	• Reduce Selinexor by 1 dose level (see **Table 1).** Continue bortezomib.
less than 0.5 OR Febrile neutropenia	• Interrupt Selinexor. • Monitor until neutrophil counts return to 1.0 or higher. • Restart Selinexor at 1 dose level lower (see **Table 1**). Bortezomib - Consider treatment delay or dose reduction or growth factor support. Seek consultant advice.
Thrombocytopenia ($x10^9$/L)	**Dose Modifications**
Platelet count 25 to less than 75	• Reduce Selinexor by 1 dose level (see Table 1). Continue bortezomib.
Platelet count 25 to less than 75 with concurrent bleeding	• Interrupt Selinexor. • Restart Selinexor at 1 dose level lower (see Table 1), after bleeding has resolved. Continue bortezomib.
Platelet count less than 25	• Interrupt Selinexor. • Monitor until platelet count returns to at least 50. • Restart Selinexor at 1 dose level lower (see Table 1). Bortezomib - Consider treatment delay or dose reduction or platelet transfusion. Seek consultant advice.
Anaemia	**Dose Modifications**
Haemoglobin less than 8 g/dL	• Reduce Selinexor by 1 dose level (see **Table 1**). • Administer blood transfusions as per Trust guidelines.
Life-threatening consequences (urgent intervention indicated)	• Interrupt Selinexor. • Monitor haemoglobin until levels return to 8 g/dL or higher. • Restart Selinexor at 1 dose level lower (see **Table 1**). • Administer blood transfusions as per Trust guidelines.

Hepatic Impairment

Drug	Bilirubin	Dose
Bortezomib	1.5xULN or below	100%
	greater than 1.5xULN	Initiate treatment at 0.7mg/m^2. The dose may be escalated to 1mg/m^2 or reduced to 0.5mg/m^2 in subsequent cycles based on patient tolerability.
Selinexor	No dose modifications of Selinexor are required for patients with mild hepatic impairment. There is insufficient data in patients with moderate or severe hepatic impairment to support a dose recommendation.	

Renal Impairment

Drug	Creatinine Clearance (ml/min)	Action
Bortezomib	greater than 20	100%
	20 and below	Clinical decision
Selinexor	No dose modifications of Selinexor are required for patients with mild, moderate or severe renal impairment. There is insufficient data in patients with end stage renal disease or haemodialysis to support a dose recommendation.	

Other toxicities

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.

Bortezomib

For patients experiencing NCI-CTC grade 1 neuropathy without loss of function or pain continue with full dose bortezomib.
For NCI-CTC grade 1 with pain or grade 2 neuropathy reduce the dose of bortezomib to 1mg/m^2.

For NCI-CTC grade 2 with pain or grade 3 neuropathy discontinue treatment until symptoms have resolved to NCI-CTC grade 1 or less then reinitiate bortezomib at a dose of 0.7mg/m^2.
For NCI-CTC grade 4 neuropathy and/or severe autonomic neuropathy discontinue bortezomib.

For any other NCI-CTC grade 3 non haematological toxicity bortezomib should be discontinued until symptoms have resolve to NCI-CTC grade 1 or below. On the first occurrence treatment may be reinitiated at a dose of 1mg/m^2. Following second occurrence to dose should be further reduced to 0.7mg/m^2 once symptoms have resolved.

If the toxicity is not resolved or if it recurs at the lowest dose, discontinuation of bortezomib must be considered unless the benefit of treatment clearly outweighs the risk.

Regimen

35-day cycle until disease progression or intolerance (6 cycles will be set in ARIA)

Drug	Dose	Days	Administration
Selinexor	100mg	1,8,15,22,29	Oral
Bortezomib	1.3mg/m^2	1,8,15,22	Subcutaneous Injection
Dexamethasone	20mg	1,2,8,9,15,16,22,23,29,30	Oral

Dose Information

- Bortezomib dose will be dose banded according to agreed dose banding
- Dexamethasone is available as 2mg and 500microgram tablets
- Selinexor is available as 20mg tablets

Administration Information

- Concomitant use of strong CYP3A4 inducer might lead to lower exposure of Selinexor.

Additional Therapy

- Anti-emetics: As take home medication
  - Cyclizine 50mg three times a day when required
  - Olanzapine 5mg on for 3 days
  - Ondansetron 8mg twice a day for 2 days
- Anti-infective prophylaxis;
  - Aciclovir 400mg twice a day oral
  - consider co-trimoxazole 960mg once a day oral on Monday, Wednesday and Friday only
- Consider allopurinol 300mg once a day for seven days for the first cycle only
- 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 H2 antagonist may be considered in patients considered at high risk of GI ulceration or bleed.

Additional Information

- Dexamethasone should be taken in the morning, with or after food.
- Selinexor should be swallowed whole with water. It should not be crushed, chewed, broken, or divided in order to prevent risk of skin irritation from the active substance. It can be taken with or without food.

References

1. www.nice.org.uk. (2024). Overview | Selinexor with bortezomib and dexamethasone for previously treated multiple myeloma | Guidance | NICE. [online] Available at: https://www.nice.org.uk/guidance/TA974 [Accessed 3 Jul. 2024].
2. www.medicines.org.uk. (n.d.). NEXPOVIO 20 mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc). [online] Available at: https://www.medicines.org.uk/emc/product/15279/ [Accessed 3 Jul. 2024].
3. www.medicines.org.uk. (n.d.). Bortezomib 1mg powder for solution for injection - Summary of Product Characteristics (SmPC) - (emc). [online] Available at: https://www.medicines.org.uk/emc/product/10551/smpc [Accessed 3 Jul. 2024].

REGIMEN SUMMARY

SELINEXOR (PO) – BORTEZOMIB (SC) – DEXAMETHASONE (PO) (35 day)

Cycle 1

Day 1, 8, 15, 22

1. Bortezomib 1.3mg/m^2 intravenous injection

Take home medicines

2. Selinexor 100mg once a day on day 1,8,15,22,29 of the cycle. Oral.
   Administration instructions
   Please supply five doses of Selinexor. ONE dose to be taken on days 1,8,15,22 and 29 of the cycle. This may be dispensed as a single supply in one container or as separate supplies according to local practice. Oral chemotherapy. Only available as 20mg tablets, pleasure ensure dose modifications occur in multiples of 20mg. Swallow whole with water. It should not be crushed, chewed, broken, or divided in order to prevent risk of skin irritation from the active substance. It can be taken with or without food.
3. Dexamethasone 20mg once a day on days 1,2,8,9,15,16,22,23,29 and 30 of the cycle. Oral.
   Administration Instructions
   Please supply ten doses of dexamethasone, ONE dose to be taken on days 1,2,8,9,15,16,22,23,29 and 30 of the cycle. This may be dispensed as a single supply in one container or as separate supplies according to local practice. Take in the morning with or after food.
4. Cyclizine 50mg three times a day when required for the relief of nausea. Oral.
   Administration Instructions
   When required for the relief of nausea. Please supply 30 tablets or nearest original pack size
5. Olanzapine 5mg once a day at night on days 1,2, 3, 8, 9, 10, 15,16, 17, 22, 23, 24 and 29, 30, 31 of the cycle. Oral.
   Administration Instructions
   Please supply fifteen doses of olanzapine; ONE dose to be taken at 1,2, 3, 8, 9, 10, 15,16, 17, 22, 23, 24 and 29, 30, 31of the cycle (the day of Selinexor and two days after). This may be dispensed as a single supply in one container or as separate supplies according to local practice.
6. Ondansetron 8mg Twice a day starting on day 1,2, 8, 9, 15,16, 22, 23 and 29, 30 of the cycle. Oral.
   Administration Instructions
   Please supply ten doses of ondansetron; ONE dose to be taken twice a day 1, 8, 15, 22 and 29 of the cycle. This may be dispensed as a single supply in one container or as separate supplies according to local practice.
7. Aciclovir 400mg twice a day for 35 days. Oral.
   Administration Instructions
   Please supply 35 days or an original pack if appropriate.
8. Co-trimoxazole 960mg once a day on Monday, Wednesday and Friday for 35 days. Oral.
   Administration Instructions.
   Co-trimoxazole 960mg once a day on Mondays, Wednesdays and Fridays. Please supply 35 days. This may be dispensed as 480mg twice a day on Mondays, Wednesdays and Fridays according to local practice.

9. Allopurinol 300mg once a day for 7 days. Oral.
   Administration Instructions
   Take with or after food with plenty of water. Please supply 7 days.
10. 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 35 days.

Cycle 2 onwards
Day 1, 8, 15, 22, 29

11. Bortezomib 1.3mg/m^2 intravenous injection

Take home medicines

12. Selinexor 100mg once a day on day 1,8,15,22,29 of the cycle. Oral.
    Administration instructions
    Please supply five doses of Selinexor. ONE dose to be taken on days 1,8,15,22 and 29 of the cycle. This may be dispensed as a single supply in one container or as separate supplies according to local practice. Oral chemotherapy. Only available as 20mg tablets, pleasure ensure dose modifications occur in multiples of 20mg. Swallow whole with water. It should not be crushed, chewed, broken, or divided in order to prevent risk of skin irritation from the active substance. It can be taken with or without food.
13. Dexamethasone 20mg once a day on days 1,2,8,9,15,16,22,23,29 and 30 of the cycle. Oral.
    Administration Instructions
    Please supply ten doses of dexamethasone, ONE dose to be taken on days 1,2,8,9,15,16,22,23,29 and 30 of the cycle. This may be dispensed as a single supply in one container or as separate supplies according to local practice. Take in the morning with or after food.
14. Cyclizine 50mg three times a day when required for the relief of nausea. Oral.
    Administration Instructions
    When required for the relief of nausea. Please supply 30 tablets or nearest original pack size
15. Olanzapine 5mg once a day at night on days 1,2, 3, 8, 9, 10, 15,16, 17, 22, 23, 24 and 29, 30, 31 of the cycle. Oral.
    Administration Instructions

    Please supply fifteen doses of olanzapine; ONE dose to be taken at 1,2, 3, 8, 9, 10, 15,16, 17, 22, 23, 24 and 29, 30, 31of the cycle (the day of Selinexor and two days after). This may be dispensed as a single supply in one container or as separate supplies according to local practice.
16. Ondansetron 8mg Twice a day starting on day 1,2, 8, 9, 15,16, 22, 23 and 29, 30 of the cycle. Oral.
    Administration Instructions
    Please supply twenty doses of ondansetron; ONE dose to be taken twice a day 1,2, 8, 9, 15, 16, 22, 23 and 29, 30 of the cycle. This may be dispensed as a single supply in one container or as separate supplies according to local practice.
17. Aciclovir 400mg twice a day for 35 days. Oral.
    Administration Instructions
    Please supply 35 days or an original pack if appropriate.
18. Co-trimoxazole 960mg once a day on Monday, Wednesday and Friday for 35 days. Oral.
    Administration Instructions.

Co-trimoxazole 960mg once a day on Mondays, Wednesdays and Fridays. Please supply 35 days. This may be dispensed as 480mg twice a day on Mondays, Wednesdays and Fridays according to local practice.

19. 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

Please dispense 35 days.

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	July 2024		Aadhya Govil Nanda Basker	Dr Noel Ryman Consultant haematologist

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.