Chemotherapy Protocol

Chronic Lymphocytic Leukaemia (CLL)

Idelalisib-Rituximab

Regimen

- CLL – Idelalisib-Rituximab

Indication

- Chronic lymphocytic leukaemia in adults when the disease has been treated but has relapsed within 24 month
- Disease modification

Toxicity

Drug	Adverse Effect
Idelalisib	Diarrhoea, colitis, pneumonitis, rash
Rituximab	Severe cytokine release syndrome, increased incidence of infective complications, progressive multifocal leukoencephalopathy

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

Monitoring

- FBC, U&Es and LFTs on day one of the cycle and at least every 14 days for the first 6 months of treatment (every 7 days when the neutrophil count is less than $1x10^9$/l).
- CMV PCR in blood (EDTA) should be monitored every 4 weeks throughout treatment. Idelalisib should be discontinued during confirmed CMV viraemia (PCR positivity in more than two consecutive samples taken one week apart).
- Hepatitis B status prior to starting treatment with rituximab

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. 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.

Consider blood transfusion or the use of erythropoietin according to NICE TA323 if the patient is symptomatic of anaemia or where the haemoglobin is less than 8g/dL (80g/L)

If the neutrophil count is $1x10^9$/L or above continue with idelalisib at the recommended dose. If the neutrophils are between $0.5\text{-}1x10^9$/L maintain the idelalisib dosing and monitor the neutrophil count weekly. If the count drops below $0.5x10^9$/L then interrupt the idelalisib dosing and monitor the counts weekly. Once the counts recover re-start treatment at 100mg twice a day

The dose of rituximab is rarely adjusted for haematological parameters.

Hepatic Impairment

Patients with hepatic impairment should be closely monitored for signs and symptoms of toxicity.

If the ALT rises to between 3-5xULN, then monitor the liver function more regularly. Idelalisib should be discontinued if the ALT is greater than 5xULN, until it falls to less than 3xULN. The idelalisib can then restart at 100mg twice a day, considering an increase back up to 150mg twice a day if the liver function remains stable. If the ALT rises again to more than 5xULN, withhold idelalisib until it is less than 3xULN and consider restarting at 100mg twice a day at the discretion of the consultant.

Rituximab does not require dose adjustment in hepatic impairment.

Renal Impairment

Dose adjustment is not considered necessary in renal impaired patients.

Patients with evidence of impaired renal function should be carefully monitored as they are prone to additional myelosuppression.

Rituximab does not require dose adjustment in renal impairment.

Other

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.

In general for all other non-haematological NCI-CTC grade 3 and above toxicities delay treatment until the adverse effect has resolved to NCI-CTC grade 2 or below. The dose should then be reduced to 75% of the original dose. If toxicity recurs delay until recovery and further dose reduce to 50% of the original dose or discontinue as appropriate.

Idelalisib

Diarrhoea

Idelalisib must be withheld in the event of an NCI-CTC grade 3 or above diarrhoea. It may be restarted once the diarrhoea has resolved to grade 1 or less at 100mg twice a day. If the symptom does not re-occur then the dose may be incremented back to 150mg twice a day.

Pneumonitis

Idelalisib must be withheld in the event of suspected pneumonitis and the patient treated accordingly. Once the pneumonitis has resolved and re-treatment is considered appropriate, resume at 100mg twice a day.

Rash

Withhold idelalisib in the event of a NCI-CTC grade 3 or above rash. Once the rash has resolved to grade 1 or less, restart the idelalisib at 100mg twice a day. Consider re-escalation to 150mg twice a day if the rash does not recur.

Rituximab

Infusion Related Reactions

Infusion related adverse reactions have been observed in 10% of patients treated with rituximab.

Rituximab administration is associated with the onset of cytokine release syndrome. This condition is characterised by severe dyspnoea, often accompanied by bronchospasm and hypoxia, in addition to fever, chills, rigors, urticaria, and angioedema. It may be associated with some features of tumour lysis syndrome such as hyperuricaemia, hyperkalaemia, hypocalcaemia, acute renal failure, elevated lactate dehydrogenase (LDH) and can lead to acute respiratory failure and death. This effect on the lungs may be accompanied by events such as pulmonary interstitial infiltration or oedema, visible on a chest x-ray.

Cytokine release syndrome frequently occurs within one or two hours of initiating the first infusion.

Hypersensitivity reactions, including anaphylaxis, have been reported following the intravenous administration of proteins. In contrast to cytokine release syndrome, true hypersensitivity reactions typically occur within minutes of starting the infusion. Medicinal products for the treatment of allergic reactions should be available for immediate use in the event of hypersensitivity developing during the administration of rituximab.

Progressive Multifocal Leukoencephalopathy

Use of rituximab may be associated with an increased risk of progressive multifocal leukoencephalopathy (PML). Patients must be monitored at regular intervals for any new or worsening neurological, cognitive or psychiatric symptoms that may be suggestive of PML. If PML is suspected, further dosing must be suspended until PML has been excluded. If PML is confirmed the rituximab must be permanently discontinued.

Regimen

28 day cycle for 6 cycles

Cycle 1

Drug	Dose	Days	Administration
Idelalisib	150mg twice a day	1-28 inclusive	Oral
Rituximab	100mg	1	Intravenous infusion in 50ml sodium chloride 0.9% over 120 minutes
Rituximab	325mg/m^2	2	Intravenous infusion in 500ml sodium chloride 0.9% starting at a rate of 50mg/hour and, if tolerated, increasing by 50mg/hour every 30 minutes to a maximum rate of 400mg/hour
Rituximab	500mg/m^2	14	Intravenous infusion in 500ml sodium chloride 0.9% as per your local rituximab administration guidelines*

Cycle 2

Drug	Dose	Days	Administration
Idelalisib	150mg twice a day	1-28 inclusive	Oral
Rituximab	500mg/m^2	1, 14	Intravenous infusion in 500ml sodium chloride 0.9% as per your local rituximab administration guidelines*

Cycle 3, 4, 5, 6

Drug	Dose	Days	Administration
Idelalisib	150mg twice a day	1-28 incl.	Oral
Rituximab	500mg/m^2	1	Intravenous infusion in 500ml sodium chloride 0.9% as per your local rituximab administration guidelines*

*If the lymphocyte is greater than $25x10^9$/L on day one then consider fractionating the dose of rituximab as follows;

Day 1 - rituximab 125mg/m^2 in 100ml sodium chloride 0.9%
Day 2 - rituximab 375mg/m^2 in 500ml sodium chloride 0.9%

If there were no problems with the previous infusion then start both fractions at 100mg/hour and escalate the rate in 100mg/hour increments every 30 minutes to a maximum rate of 400mg/hour. If reactions occurred with the previous cycle, give both fractions starting at a rate of 50mg/hour and, if tolerated, increasing by 50mg/hour every 30 minutes to a maximum rate of 400mg/hour

Dose Information

- Idelalisib is available as 100mg and 150mg film-coated tablets.
- The dose of rituximab for the 50mg/m^2 - 125mg/m^2 dose will be rounded as per the national dose bands (10mg/ml)
- The dose of rituximab from 325mg/m^2 and above will be dose rounded to the nearest 100mg (up if halfway)

Administration Information

- Idelalisib should be swallowed whole, either with or without food.
- If the patient misses a dose of idelalisib within 6 hours of the time it is usually taken, the patient should take the missed dose as soon as possible and resume the normal dosing schedule. If a patient misses a dose by more than 6 hours, the patient should not take the missed dose and simply resume the usual dosing schedule.
- The rate of administration of rituximab varies. Please refer to the rituximab administration guidelines.

Additional Therapy

- No routine anti-emetics are required. They may be added from "favourites" on ARIA for individual patients who may require treatment for nausea and vomiting.
- Rituximab pre-medication

  30 minutes prior to rituximab

  - chlorphenamine 10mg intravenous
  - hydrocortisone 100mg intravenous
  - paracetamol 1000mg oral
- Rituximab infusion reactions

  - hydrocortisone 100mg intravenous when required for rituximab infusion related reactions
  - salbutamol 2.5mg nebule when required for rituximab related bronchospasm
  - consider pethidine 25mg intravenous bolus for rituximab related rigors that fail to respond to corticosteroids. This should follow a verbal confirmation from a doctor that the dose is to be administered.
- Anti-infective prophylaxis as follows

  - aciclovir 400mg twice a day oral
  - co-trimoxazole 960mg once a day on Monday, Wednesday and Friday only oral

  (this should be continued for up to six months after treatment has finished)
- Patients with CLL are at risk of tumour lysis syndrome (TLS). The British Society of Haematology guidelines are a useful reference source. Oral allopurinol is one option for prophylaxis (300mg once a day oral for 7 days in he first cycle will be set in

ARIA). Intravenous rasburicase can be considered in high risk individuals.

- Loperamide 4mg after the first loose stool and 2mg after each loose motion thereafter to a maximum of 16mg / 24 hours when required for the relief of diarrhoea

- 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.

Additional Information

- The National Patient Safety Alert on oral chemotherapy (NPSA/2008/RRR001) must be followed in relation to idelalisib.

- It must be made clear to all staff, including those in the community, that idelalisib should only be prescribed under the supervision of a consultant haematologist.

- Idelalisib is associated with many drug interactions.

Coding

- Procurement – X

- Delivery – X

References

1. Furman R et al. Idelalisib in relapsed chronic lymphocytic leukemia. N Engl J Med (2014): 370: 997-1007

REGIMEN SUMMARY

Idelalisib-Rituximab

Cycle 1

Day 1

1. Chlorphenamine 10mg intravenous
2. Hydrocortisone 100mg intravenous
3. Paracetamol 1000mg oral
4. Rituximab 100mg intravenous infusion in 50ml sodium chloride 0.9% over 120 minutes
5. Hydrocortisone 100mg intravenous once only when required for the relief of rituximab infusion related reactions
6. Pethidine 25mg intravenous bolus in 10ml sodium chloride 0.9% over 5 minutes for the relief of rigors
   Administration Instructions
   For the relief of rigors following a verbal confirmation from a doctor that the dose is to be given.
7. Salbutamol 2.5mg nebule once only when required for the relief of rituximab related bronchospasm

Day 2

8. Chlorphenamine 10mg intravenous
9. Hydrocortisone 100mg intravenous
10. Paracetamol 1000mg oral
11. Rituximab 325mg/m^2 intravenous infusion in 500ml sodium chloride 0.9%
    Administration Instructions
    Administer at a rate of 50mg/hour increasing by 50mg/hour every 30 minutes if tolerated to a maximum rate of 400mg/hour.
12. Hydrocortisone 100mg intravenous once only when required for the relief of rituximab infusion related reactions
13. Pethidine 25mg intravenous bolus in 10ml sodium chloride 0.9% over 5 minutes for the relief of rigors
    Administration Instructions
    For the relief of rigors following a verbal confirmation from a doctor that the dose is to be given.
14. Salbutamol 2.5mg nebule once only when required for the relief of rituximab related bronchospasm

Day 14

15. Chlorphenamine 10mg intravenous
16. Hydrocortisone 100mg intravenous

17. Paracetamol 1000mg oral

18. Rituximab 500mg/m^2 intravenous infusion in 500ml sodium chloride 0.9%
    Administration Instructions
    Administer as per your local administration guidelines

    If the lymphocyte is greater than $25x10^9$/L on day one then consider fractionating the dose of rituximab as follows;

    Day 1 - rituximab 125mg/m^2 in 100ml sodium chloride 0.9%
    Day 2 - rituximab 375mg/m^2 in 500ml sodium chloride 0.9%

    If there were no problems with the previous infusion then start both fractions at 100mg/hour and escalate the rate in 100mg/hour increments every 30 minutes to a maximum rate of 400mg/hour. If reactions occurred with the previous cycle, give both fractions starting at a rate of 50mg/hour and, if tolerated, increasing by 50mg/hour every 30 minutes to a maximum rate of 400mg/hour

19. Hydrocortisone 100mg intravenous once only when required for the relief of rituximab infusion related reactions

20. Pethidine 25mg intravenous bolus in 10ml sodium chloride 0.9% over 5 minutes for the relief of rigors
    Administration Instructions
    For the relief of rigors following a verbal confirmation from a doctor that the dose is to be given.

21. Salbutamol 2.5mg nebule once only when required for the relief of rituximab related bronchospasm

Take Home Medicines (day one only)

22. Idelalisib 150mg twice a day for 28 days oral
    Administration Information
    Oral chemotherapy. Idelalisib should be swallowed whole, either with or without food.

23. Allopurinol 300mg once a day for 7 days oral

24. Aciclovir 400mg twice a day for 28 days oral

25. Co-trimoxazole 960mg once a day on Monday, Wednesday and Friday for 28 days oral
    Administration Instructions
    This may be taken as 480mg twice a day on Monday, Wednesday and Friday only

26. Loperamide 4mg after the first loose stool then 2mg after each loose motion thereafter to a maximum of 16mg/24 hours
    Administration Instructions
    Please supply an original pack (28 capsules or nearest equivalent)

Cycle 2

Day 1, 14

27. Chlorphenamine 10mg intravenous

28. Hydrocortisone 100mg intravenous

29. Paracetamol 1000mg oral

30. Rituximab 500mg/m^2 intravenous infusion in 500ml sodium chloride 0.9%
    Administration Instructions
    Administer as per your local administration guidelines

    If the lymphocyte is greater than 25x10^9/L on day one then consider fractionating the dose of rituximab as follows;

    Day 1 - rituximab 125mg/m^2 in 100ml sodium chloride 0.9%
    Day 2 - rituximab 375mg/m^2 in 500ml sodium chloride 0.9%

    If there were no problems with the previous infusion then start both fractions at 100mg/hour and escalate the rate in 100mg/hour increments every 30 minutes to a maximum rate of 400mg/hour. If reactions occurred with the previous cycle, give both fractions starting at a rate of 50mg/hour and, if tolerated, increasing by 50mg/hour every 30 minutes to a maximum rate of 400mg/hour

31. Hydrocortisone 100mg intravenous once only when required for the relief of rituximab infusion related reactions

32. Pethidine 25mg intravenous bolus in 10ml sodium chloride 0.9% over 5 minutes for the relief of rigors
    Administration Instructions
    For the relief of rigors following a verbal confirmation from a doctor that the dose is to be given.

33. Salbutamol 2.5mg nebule once only when required for the relief of rituximab related bronchospasm

Take Home Medicines (day one only)

34. Idelalisib 150mg twice a day for 28 days oral
    Administration Information
    Oral chemotherapy. Idelalisib should be swallowed whole, either with or without food.

35. Aciclovir 400mg twice a day for 28 days oral

36. Co-trimoxazole 960mg once a day on Monday, Wednesday and Friday for 28 days oral
    Administration Instructions
    This may be taken as 480mg twice a day on Monday, Wednesday and Friday only

Cycles 3, 4, 5, 6

Day 1

37. Chlorphenamine 10mg intravenous

37. Hydrocortisone 100mg intravenous

38. Paracetamol 1000mg oral

39. Rituximab 500mg/m^2 intravenous infusion in 500ml sodium chloride 0.9%
    Administration Instructions
    Administer as per your local administration guidelines

    If the lymphocyte is greater than 25x10^9/L on day one then consider fractionating the dose of rituximab as follows;

    Day 1 - rituximab 125mg/m^2 in 100ml sodium chloride 0.9%
    Day 2 - rituximab 375mg/m^2 in 500ml sodium chloride 0.9%

    If there were no problems with the previous infusion then start both fractions at 100mg/hour and escalate the rate in 100mg/hour increments every 30 minutes to a maximum rate of 400mg/hour. If reactions occurred with the previous cycle, give both fractions starting at a rate of 50mg/hour and, if tolerated, increasing by 50mg/hour every 30 minutes to a maximum rate of 400mg/hour

40. Hydrocortisone 100mg intravenous once only when required for the relief of rituximab infusion related reactions

41. Pethidine 25mg intravenous bolus in 10ml sodium chloride 0.9% over 5 minutes for the relief of rigors
    Administration Instructions
    For the relief of rigors following a verbal confirmation from a doctor that the dose is to be given.

42. Salbutamol 2.5mg nebule once only when required for the relief of rituximab related bronchospasm

Take Home Medicines (day one only)

43. Idelalisib 150mg twice a day for 28 days oral
    Administration Information
    Oral chemotherapy. Idelalisib should be swallowed whole, either with or without food.

44. Aciclovir 400mg twice a day for 28 days oral

45. Co-trimoxazole 960mg once a day on Monday, Wednesday and Friday for 28 days oral
    Administration Instructions
    This may be taken as 480mg twice a day on Monday, Wednesday and Friday only

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	February 2017	None	Dr Deborah Wright Pharmacist	Dr Helen Dignam Consultant Hamematologist

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 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.