**Chemotherapy Protocol**

## LYMPHOMA

## CYCLOPHOSPHAMIDE–FLUDARABINE–RITUXIMAB

## (RFC Oral Lite)

### Regimen

- Lymphoma – RFC PO (Lite) - Cyclophosphamide-Fludarabine-Rituximab PO (Lite)

### Indication

- CD20 Positive Non-Hodgkin Lymphoma (Follicular)

### Toxicity

| Drug | Adverse Effect |
|---|---|
| Cyclophosphamide | Dysuria, haemorrhagic cystitis (rare), taste disturbances |
| Fludarabine | Transfusion related GVHD, neurotoxicity, opportunistic infections, GI disturbances |
| Rituxumab | Severe cytokine release syndrome, increased incidence of infective complications, progressive multifocal leukoencephalopathy |

Patients treated with fludarabine carry a lifelong risk of transfusion associated graft versus host disease (TA-GVHD). Where blood products are required these patients must receive only irradiated blood products for life. Local blood transfusion departments must be notified as soon as the decision to treat is made and the patient must be issued with an alert card to carry with them at all times.

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

### Monitoring

#### *Drugs*

- FBC, LFTs and U&Es prior to day one of treatment
- Direct Coombs test prior to starting treatment
- Check hepatitis B status before 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.

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. Irradiated blood products must be used (fludarabine)**.**

Dose modifications based on haematological parameters apply to cyclophosphamide and fludarabine

Please note these dose adjustments are taken from the PACIFICO study and vary from CSCCN standard dose adjustments for oral fludarabine and cyclophosphamide.

| **Neutrophils ($x10^9$/L)** | **Dose Modifications (cyclophosphamide and fludarabine)** |
|---|---|
| greater than or equal to 1 | 100% |
| less than 1 | Delay until recovery to $1x10^9$/L or above.<br>If recovery occurs within 7 days continue with 100% dose and give prophylactic growth factors with all subsequent courses<br>If recovery takes more than 7 days give 75% of the original dose by omitting day 4 of treatment and give prophylactic growth factors with all subsequent courses<br>If recovery takes longer than 3 weeks discontinue treatment |
| **Platelets ($x10^9$/L)** | **Dose Modifications (cyclophosphamide and fludarabine)** |
| greater than or equal to 75 | 100% |
| Less than 75 | Delay until recovery to $75x10^9$/L or above.<br>If recovery occurs within 7 days continue with 100% dose<br>If recovery takes more than 7 days give 75% of the original dose by omitting day 4 of treatment<br>If recovery takes longer than 3 weeks discontinue treatment |

### *Haemoglobin*

Patients who develop red-cell transfusion dependent or develop increasing transfusion requirements reduce the dose of subsequent cycles to 75% dose by omitting day 4 of treatment.

If red-cell transfusion requirements continue to increase despite dose reduction then discontinue treatment.

### *Hepatic Impairment*

Please note that the approach may be different where abnormal liver function tests are due to disease involvement.

| Drug | Recommendation |
|---|---|
| Cyclophosphamide | Evidence suggests dose reduction not necessary |
| | |
| Fludarabine | No dose adjustment required |
| | |
| Rituximab | No dose adjustment needed |

### *Renal Impairment*

Please note these dose adjustments are taken from the PACIFICO study and vary from CSCCN standard dose adjustments for oral fludarabine and cyclophosphamide.

The table below shows the recommended dose of each drug based on surface area and renal function.

| BSA ($m^2$) | Fludarabine | Cyclophosphamide |
|---|---|---|
| | eGFR 30-49 | eGFR 30-49 |
| less than 1.4 | 20mg | 100mg |
| 1.4 - 2 | 30mg | 150mg |
| more than 2 | 40mg | 200mg |

No dose adjustment is necessary for rituximab in patients with impaired renal function.

### *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.

### *Severe Nausea and Vomiting*

Consider changing to an intravenous version of this regimen if severe nausea and vomiting becomes a problem.

*Rituximab*

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.

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.

The presence of a viral upper respiratory tract infection prior to treatment may increase the risk of rituximab associated hepatotoxicity. Patients should be assessed for any cold or flu-like symptoms prior to treatment

Regimen

**Cycles 1 – 4, 28 day cycle**

| Drug | Dose | Days | Administration |
|---|---|---|---|
| Cyclophosphamide | 120mg/m$^2$ | 1,2,3,4 | Oral |
| Fludarabine | 25mg/m$^2$ | 1,2,3,4 | Oral |
| Rituximab | 375mg/m$^2$ | 1 | Intravenous infusion in 500ml sodium chloride 0.9% |

**Cycles 5 – 8, 28 day cycle**

| Drug | Dose | Days | Administration |
|---|---|---|---|
| Rituximab | 375mg/m$^2$ | 1 | Intravenous infusion in 500ml sodium chloride 0.9% |

## Dose Information

- Cyclophosphamide is available as 50mg tablets and will be rounded to the nearest 50mg (up if halfway).
- Fludarabine is available as 10mg tablets and will be rounded to the nearest 10mg (up if halfway).
- Rituximab will be dose rounded to the nearest 100mg (up if halfway)

## Administration Information

### *Extravasation*

- Rituximab – neutral

### *Other*

- Cyclophosphamide should be taken with food, swallowed whole with a full glass of water
- Fludarabine should be taken with food, swallowed whole with a full glass of water
- The rate of administration of rituximab varies. Please refer to the rituximab administration guidelines.

## Additional Therapy

- Antiemetics

  As take home medication

  - ondansetron 8mg oral twice a day for 6 days
  - metoclopramide 10mg oral three times a day when required

- 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 25-50mg intravenous for rituximab related rigors that fail to respond to steroids.

- Allopurinol 300mg once a day oral for the first cycle only

- Anti-infective prophylaxis as follows:

    - aciclovir 400mg twice a day oral
    - co-trimoxazole 960mg once a day oral on Monday, Wednesday and Friday only continued for 6 months after the completion of treatment or in accordance with CD4 count.

  Please note that patients treated with fludarabine are at higher risk of fungal and atypical infections. A high level of suspicion must be maintained coupled with a low threshold for prompt and appropriate treatment.

- 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.

## Additional Information

- The National Patient Safety Agency alert NPSA/2008/RRR001 must be followed when prescribing, dispensing or administering oral chemotherapy.

- It must be made clear to all staff, including those in the community, that this is a short course of oral chemotherapy that must not be continued.

- Patients should be assessed for suitability for oral chemotherapy prior to starting treatment.

## Coding (OPCS 4.6)

- Procurement – X71.5

- Delivery – X72.2

References

1. Forconi F, Fabbri A, Lenoci M et al. Low-dose oral fludarabine plus cyclophosphamide in elderly patients with untreated and relapsed or refractory chronic lymphocytic leukaemia. Haem Oncol 2008;26:247-51
2. Pacifico Study Version 6

## REGIMEN SUMMARY

RFC PO (Lite) - Cyclophosphamide-Fludarabine- Rituximab PO (Lite)

### Cycle 1 Day One

1. Warning – Check blood transfusion status
   Administration Instructions
   Patients treated with fludarabine carry a lifelong risk of transfusion associated graft versus host disease.
   Where blood products are required these patients must receive ONLY IRRADIATED BLOOD PRODUCTS for life.
   Ensure transfusion departments are notified and the patient has been issued with an alert card to carry with them at all times.

2. Chlorphenamine 10mg intravenous

3. Hydrocortisone 100mg intravenous

4. Paracetamol 1000mg oral

5. Rituximab 375mg/$m^2$ intravenous infusion in 500ml sodium chloride 0.9% as per the rituximab administration guidelines

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

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

### Take home medicines

8. Cyclophosphamide 120mg/$m^2$ once a day oral for 4 days

9. Fludarabine 25mg/$m^2$ once a day oral for 4 days

10. Allopurinol 300mg once a day for oral 28 days

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

12. Co-trimoxazole 960mg once a day oral on Mondays, Wednesdays and Fridays for 28 days

13. Metoclopramide 10mg three times a day oral when required

14. Ondansetron 8mg twice a day oral for 6 days starting prior to the first dose of oral chemotherapy

### Cycles 2, 3 and 4 Day One

1. Chlorphenamine 10mg intravenous

2. Hydrocortisone 100mg intravenous

3. Paracetamol 1000mg oral

4. Rituximab 375mg/$m^2$ intravenous infusion in 500ml sodium chloride 0.9% as per the rituximab administration guidelines

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

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

**Take home medicines**

7. Cyclophosphamide 120mg/$m^2$ once a day oral for 4 days

8. Fludarabine 25mg/$m^2$ once a day oral for 4 days

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

10. Co-trimoxazole 960mg once a day oral on Mondays, Wednesdays and Fridays for 28 days

11. Metoclopramide 10mg three times a day oral when required

15. Ondansetron 8mg twice a day oral for 6 days starting prior to the first dose of oral chemotherapy

**Cycles 5, 6, 7 and 8 Day One**

1. Chlorphenamine 10mg intravenous

2. Hydrocortisone 100mg intravenous

3. Paracetamol 1000mg oral

4. Rituximab 375mg/$m^2$ intravenous infusion in 500ml sodium chloride 0.9% as per the rituximab administration guidelines

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

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

**Take home medicines**

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

8. Co-trimoxazole 960mg once a day oral on Mondays, Wednesdays and Fridays for 28 days

## DOCUMENT CONTROL

| Version | Date | Amendment | Written By | Approved By |
|---|---|---|---|---|
| 1.2 | Jan 2015 | Header changed<br>“a diagnosis” replaced with “the decision to treat” in TA-GVHD warning<br>Hepatic impairment table updated<br>Metoclopramide dose changed to 10mg<br>Bolus removed from intravenous bolus throughout text<br>Mucositis recommendation changed<br>“Warning-Check blood transfusion status” added to cycle 1<br>Ondansetron TTO clarified<br>OPCS codes updated<br>Disclaimer added | Donna Kimber Pharmacy Technician | Rebecca Wills Pharmacist |
| 1.1 | Sept 2013 | In the regimen summary the ondansetron instructions changed to remove the words start on the evening of day 1.<br>Toxicity removed. | Dr Debbie Wright Pharmacist | Donna Kimber Pharmacy Technician |
| 1 | July 2012 | None | Rebecca Wills Pharmacist<br><br>Dr Debbie Wright Pharmacist | Dr Andrew Davies Consultant Medical Oncologist<br><br>Dr Alison Milne 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 Hospitals 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 which occur as a result of following these guidelines.