Thames Valley
Strategic Clinical Network

Fludarabine Cyclophosphamide Rituximab (FCR) intravenous

INDICATION

Chronic lymphocytic leukaemia (Do not use for p53 mutated CLL) or indolent CD20-positive non-Hodgkin lymphoma (unable to tolerate oral FC)

TREATMENT INTENT

Disease Modification

PRE-ASSESSMENT

1. Ensure histology is confirmed prior to administration of chemotherapy and document in notes.
2. Record stage of disease - CT scan (neck, chest, abdomen and pelvis), presence or absence of B symptoms, clinical extent of disease, bone marrow aspirate and trephine, Cytogenetics/FISH for p53 deletion in patients with CLL
3. Blood tests - FBC, ESR, DAT, U&Es, LDH, urate, calcium, magnesium, creatinine, LFTs, glucose, Igs, β_2 microglobulin, hepatitis B core antibody and hepatitis B surface Ag, hepatitis C antibody, EBV, CMV, VZV, HIV 1+2 after consent.
4. **Send a "group and save" sample to transfusion and inform patient and transfusion laboratory that they will require irradiated blood products for all future transfusions**. Ensure irradiation card is attached to the patient's notes and copy given to the patient. See 'Guidelines for the use of blood components in adult haematology'.
5. Urine pregnancy test - before cycle 1 of each chemotherapy course for women of child-bearing age unless they are postmenopausal, have been sterilised or undergone a hysterectomy.
6. ECG +/- Echo - *if clinically indicated*.
7. Record performance status (WHO/ECOG).
8. Record height and weight.
9. Consent - ensure patient has received adequate verbal and written information regarding their disease, treatment and potential side effects. Document in medical notes all information that has been given. Obtain written consent prior to treatment.
10. Fertility - it is very important the patient understands the potential risk of reduced fertility. All patients should be offered fertility advice by referring to the Oxford Fertility Unit.
11. Hydration - *in patients with bulky disease* pre-hydrate with sodium chloride 0.9% 1 litre over 4-6 hours. For patients at high risk of tumour lysis, refer to tumour lysis protocol.
12. Consider dental assessment / Advise dental check is carried out by patient's own dental practitioner before treatment starts.
13. Treatment should be agreed in the relevant MDT.

DRUG REGIMEN

Day 1 **Premedication**
Paracetamol 1g PO, Chlorphenamine 10 mg IV, Hydrocortisone 100 mg IV. Give 30 minutes before rituximab.

RITUXIMAB 375 mg/m^2 IV infusion in 500 mL sodium chloride 0.9% OR 1400 mg subcutaneous injection over 5 minutes from cycle 2 onwards (as long they have received full dose cycle 1 intravenous rituximab over 1 day and as long as local trust governance and funding agreed) – **NB intravenous only for CLL***.

*If being used for CLL, rituximab dose should be increased to 500 mg/m^2 from cycle 2.

Days 1 to 3 **FLUDARABINE** 25 mg/m^2 IV infusion daily in 100 mL sodium chloride 0.9% over 30 minutes.

Days 1 to 3 **CYCLOPHOSPHAMIDE** 250 mg/m^2 IV infusion daily in 250 mL sodium chloride 0.9% over 30 minutes.

CYCLE FREQUENCY

Cycle repeats every 28 days.

If neutrophil count < 1 x10^9/L or platelets < 75 x10^9/L, consider delaying treatment by one week.

RESTAGING

Maximum 6 cycles. Discuss at lymphoma MDT. Clinical staging before each cycle.
Consider CT and bone marrow biopsy 3 months after completion of treatment.
For non-Hodgkin lymphoma patient, consider re-scanning after 2 and 4 cycles. In these patients, treatment is often no more than 4 courses

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DOSE MODIFICATIONS

Rituximab:
Cycle 1- If lymphocyte count >25 x10^9/L: Give 50 mg/m^2 of Rituximab on day 1
Give the rest (i.e. 325 mg/m^2) on day 2
Give 375 mg/m^2 on day 1 of subsequent cycles for NHL or 500mg/m^2 for CLL

For elderly patients, consider 50% dose reduction of cyclophosphamide and fludarabine.

Cyclophosphamide:

Renal impairment	Hepatic impairment
Clinical decision - consider whether patient is being treated with high dose. CrCl 10-20 ml/min: 75% dose CrCl < 10 ml/min: 50% dose.	Clinical decision. Exposure to active metabolites may not be increased, suggesting dose reduction may not be necessary.

Fludarabine:

Renal impairment	Hepatic impairment
CrCl > 70 ml/min: 100% dose CrCl 30-70 ml/min: 50% dose CrCl < 30 ml/min: Contra-indicated	

INVESTIGATIONS

FBC, renal and liver profiles.

CONCURRENT MEDICATION

Allopurinol	300 mg daily for 7 days, starting 24 to 48 hours prior to chemotherapy (first course / cycle only)
Aciclovir	200 mg three times a day for duration of treatment and for 3 months after completion
Co-trimoxazole	480 mg daily on Monday / Wednesday / Friday for duration of treatment and for 3 months afterwards (consider reducing the dose to 480 mgs twice weekly during neutropenic periods)
Fluconazole	50 mg daily for the duration of treatment

EMETIC RISK

High (avoid the use of Dexamethasone).

EXTRAVASATION RISK

Cyclophosphamide: neutral
Fludarabine: neutral
Rituximab: neutral

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

Cyclophosphamide may irritate the bladder mucosa. Patients should be encouraged to drink a minimum of three litres of fluid per 24 hours.

Rituximab - Severe cytokine release syndrome is characterised by severe dyspnoea, often accompanied by bronchospasm and hypoxia, in addition to fever, chills, rigors, urticaria, and angioedema. Hepatitis B reactivation – see pathway for treatment and management of HBV positive patient.

TREATMENT RELATED MORTALITY

2-5%

REFERENCES

1. Keating MJ, O'Brien S, Albitar M, Lerner S, Plunkett W, Giles F, Andreeff M, Cortes J, Faderl S, Thomas D, Koller C, Wierda W, Detry MA, Lynn A, Kantarjian H. Early results of a chemoimmunotherapy regimen of fludarabine, cyclophosphamide, and rituximab as initial therapy for chronic lymphocytic leukemia. J Clin Oncol. 2005 Jun 20;23(18):4079-88.
2. Tam CS, O'Brien S, Wierda W, Kantarjian H, Wen S, Do KA, Thomas DA, Cortes J, Lerner S, Keating MJ. Long-term results of the fludarabine, cyclophosphamide, and rituximab regimen as initial therapy of chronic lymphocytic leukemia. Blood. 2008 Aug 15;112(4):975-80.
3. UCLH - Dosage Adjustment for Cytotoxics in Hepatic Impairment (Version 3 - updated January 2009).
4. UCLH - Dosage Adjustment for Cytotoxics in Renal Impairment (Version 3 - updated January 2009).

Review

Name	Revision	Date	Version	Review date
NSSG Lymphoma Group	Annual protocol review	May 2017	3.9	
NSSG Lymphoma Group	Annual protocol review	May 2019	3.10	May 2021
Quality Manager	Nursing Care Plan added	Sept 2020	3.11	May 2021

Nursing Care Plan: FLUDARABINE, CYCLOPHOSPHAMIDE, RITUXIMAB (FCR) IV

Indication: Chronic lymphocytic leukaemia or indolent CD20-positive non-Hodgkin lymphoma
Frequency: Given every 28 days, maximum 6 cycles (usually only 4 courses required for NHL patients).
Alopecia: yes
Emetic risk: high
Send a group and save sample to blood transfusion and inform patient and laboratory that they will require irradiated blood products for all future transfusions. Give patient an irradiated blood product booklet and card

FLUDARABINE: Antimetabolite
Administered IV over 30 minutes on **days 1-3**.
Classification of extravasation: neutral
Emetic risk: low
Side effects: bone marrow suppression, occasional nausea and vomiting.

CYCLOPHOSPHAMIDE: Alkylating agent.
Administered IV over 30 minutes on **days 1-3**.
Classification of extravasation: neutral.
Emetic risk: high
Side effects: nasal stuffiness (can be reduced by slowing rate of administration), dizziness, nausea and vomiting, diarrhoea, anorexia, taste changes neutropenia, bone marrow suppression, alopecia, risk of haemorrhagic cystitis in patients with pre-existing bladder conditions.

RITUXIMAB: Monoclonal antibody for CD 20.
Administered as IV infusion on **day 1**.
Classification of extravasation: neutral.
Emetic risk: low.
Side effects: risk of anaphylaxis, severe dyspnoea, bronchospasm and hypoxia

- Infusion reactions (Most common during first infusion - PREMED 30 MINS PRIOR TO INFUSION): fever, chills, rigors, urticaria, nausea, hypotension, dizziness, cough, chest tightness, back pain.
- Rituximab can cause hypotension. Consider withholding anti-hypertensives 12 hours prior to Rituximab (especially first dose).
- Risk of tumour-lysis syndrome, especially with bulky disease.
- Post infusion side effects: flu-like symptoms, fever, diarrhoea
- **For first Rituximab:**
    - Ensure patient is treated on a bed.
    - In DTU setting *(where the patient is visually in front of the nursing station with very close observation):* Record baseline vital observations and then if patient reacts. On the ward setting: record vital observations every 30 minutes for the first two hours and then hourly. To have close observation.
    - Have anaphylaxis box nearby.
    - Increment drug infusion rate as per protocol. *Note there are different rates for first and subsequent treatments and for different doses.*
    - Educate patients re possible reactions and the importance of reporting

any symptoms immediately.

- **<u>If patient reacts to Rituximab:</u>**
  - Stop infusion.
  - Record observations.
  - Seek an immediate medical review.
  - Consider administration of Hydrocortisone, Chlorphenamine, Oxygen, Salbutamol nebuliser depending on type and severity of reaction.
  - Restart infusion at same or previous rate after 30 minutes if symptoms resolved.

Regime Specific Considerations

- Advise patients that it is important to maintain fluid intake of at least 3 litres a day for next few days. Cyclophosphamide may irritate bladder mucosa.

- Note that CLL patients cannot be offered subcutaneous rituximab, it must be given IV.

- CLL patients will require staging pre each cycle of treatment