Fludarabine, Cyclophosphamide and Rituximab (FCR)

Indication

First line or relapsed chronic lymphocytic leukaemia (CLL).

(NICE TA174 and TA193)

CD20-positive indolent non-Hodgkin lymphoma.

ICD-10 codes

Codes with a prefix C91.1, C88.4 or C82.97

Regimen details

NHL (all cycles) and CLL (cycle 1)

Day	Drug	Dose	Route
1	Rituximab (see below)	375mg/m²	IV
1 - 5	Fludarabine	24mg/m²	PO
1 - 5	Cyclophosphamide	150mg/m²	PO

For CLL: Give 500mg/m² on day 1 of subsequent cycles as below.

CLL (cycles 2 to 6)

Day	Drug	Dose	Route
1	Rituximab	500mg/m²	IV
1 - 5	Fludarabine	24mg/m²	PO
1 - 5	Cyclophosphamide	150mg/m²	PO

Rituximab

If high tumour burden (lymphocyte count > 25 x 10^9/L) consider splitting the first dose of rituximab to give 50mg/m^2 (maximum dose 100mg) on day 0 and the remainder of the total dose on day 1.

Cycle frequency

Every 28 days

Number of cycles

Maximum of 6 cycles

Administration

Rituximab is administered in 500mL sodium chloride 0.9%. The first infusion should be initiated at 50mg/hour and if tolerated the rate can be increased at 50mg/hour every 30 minutes to a maximum of 400mg/hour. Subsequent infusions should be initiated at 100 mg/hour and if tolerated increased at 100mg/hour increments every 30 minutes to a maximum of 400 mg/hour.

Fludarabine is available as 10mg tablets. Tablets may be taken at lunchtime, with or without food and should be swallowed whole with water. They should not be crushed or chewed.

Cyclophosphamide is available as 50mg tablets. Tablets should be swallowed whole with a full glass of water. Cyclophosphamide should be taken early in the day and patients encouraged to maintain a good fluid intake (a minimum of 3 litres of fluid per 24 hours). The aim is to reduce the amount of drug remaining in the bladder overnight.

Pre-medication

Rituximab premedication:

- Paracetamol 500mg-1g PO 60 minutes prior to rituximab infusion
- Chlorphenamine 10mg IV bolus 15 minutes prior to rituximab infusion
- Dexamethasone 8mg IV bolus or hydrocortisone 100mg IV bolus 15 minutes prior to rituximab infusion

Emetogenicity

This regimen has moderate emetogenic potential.

Additional supportive medication

Allopurinol 300mg (100mg if creatinine clearance <20mL/min) OD for 7 days starting 24 hours prior to chemotherapy (first cycle only).
H_2 antagonist or PPI if required.
Antiviral, antifungal and PCP prophylaxis as per local policy.

Extravasation

Rituximab is neutral (Group 1)

Pre-treatment evaluation

Investigation	Validity period
FBC	7days
U+Es (including creatinine)	7 days
LFTs	7 days
Direct Antiglobulin Test (DAT)	Baseline
Group and Save	7 days

Other pre-treatment investigations:
Hepatitis B and C and HIV 1 and 2 serology

Inform patient and transfusion laboratory that they will require irradiated blood products for all future transfusions.

Regular investigations

Investigation	Validity period
FBC	48 hours
U+Es (including creatinine)	48 hours
LFTs	48 hours

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant

Investigation	Limit
Neutrophils	≥ 1.0 x 10^9/L
Platelets	≥ 75 x 10^9/L
Creatinine clearance	> 70mL/min
Bilirubin	< ULN
AST/ALT	< 3 x ULN

Dose modifications

- **Haematological toxicity**

If neutrophils < 1.0 x 10^9/L and/or platelets < 75 x 10^9/L delay for 1 week until recovery. If not recovered within 2 weeks or neutrophils < 0.5 x 10^9/L consider 50% doses of cyclophosphamide and fludarabine.

If patient elderly or persistent neutropenia is encountered, consider 50% doses of cyclophosphamide and fludarabine.

Rituximab dose should remain at 100%.

- **Renal impairment**

CrCl (mL/min)	**Cyclophosphamide dose**
>20	100%
10-20	75%
<10	50%

CrCl (mL/min)	**Fludarabine dose**
> 70	100%
30-70	50%
< 30	Contra-indicated

Discuss with consultant as some circumstances may warrant 100% dose despite renal impairment.

- **Hepatic impairment**

No dose modification required for fludarabine.

Cyclophosphamide is not recommended if bilirubin > 1.0 x ULN or AST/ALT > 3 x ULN (consultant decision).

- **Other toxicities**

Toxicity	**Definition**	**Dose adjustment**
Haemorrhagic cystitis	Bladder irritation with haematuria	Omit cyclophosphamide

For any grade ≥ 3 non haematological toxicity delay until recovery and clinical decision as to whether to continue at 50% doses or to discontinue treatment.

For any grade autoimmune toxicity, neurotoxicity or pneumonitis discontinue treatment.

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Myelosuppression
Rituximab-related infusion reactions.
Tumour lysis syndrome
Autoimmune haemolytic anaemia
Infertility
Pulmonary fibrosis, pneumonitis

- **Frequently occurring side effects**

Myelosuppression
Rash
Haemorrhagic cystitis
Fatigue
Alopecia
Nausea and vomiting
Diarrhoea
Peripheral neuropathy

- **Other side effects**

Significant drug interactions – for full details consult product literature/ reference texts

Warfarin/coumarin anticoagulants: Avoid use due to elevations in INR. Switch to low molecular weight heparin during treatment.

Fludarabine:
Pentostatin: use in combination not recommended due to risk of pulmonary toxicity.
Dipyridamole and other inhibitors of adenosine: may reduce the therapeutic efficacy of fludarabine.

Cyclophosphamide:
Warfarin/coumarin anticoagulants: increased or fluctuating anticoagulant effects. Avoid if possible, consider switching patient to a low molecular weight heparin during treatment or if the patient continues taking an oral anticoagulant monitor the INR at least once a week and adjust dose accordingly.
Amiodarone: increased risk of pulmonary fibrosis – avoid if possible
Clozapine: increased risk of agranulocytosis – avoid concomitant use
Digoxin tablets: reduced absorption – give as liquid form
Indapamide: prolonged leucopenia is possible – avoid
Itraconazole: may increase adverse effects of cyclophosphamide
Phenytoin: reduced absorption - may need to increase dose of phenytoin
Grapefruit juice: decreased or delayed activation of cyclophosphamide. Patients should be advised to avoid grapefruit juice for 48 hours before and on day of cyclophosphamide dose.

Additional comments

Inform patient and transfusion laboratory that they will require irradiated blood products for all future transfusions. The need for irradiated blood products is indefinite following the administration of fludarabine.

References

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