Fludarabine, Cyclophosphamide, Rituximab (FCR) for CLL

**Indication:**
First line treatment for CLL in people for whom fludarabine in combination with cyclophosphamide is deemed appropriate.

Relapsed or refractory CLL (but not if relapsed within 2 – 3 years or less of first line FCR therapy)

Rituximab for first line treatment of CLL and for relapsed / refractory CLL are approved by NICE.

**Regimen details:**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose/Cycle</th>
<th>Route</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab</td>
<td>375mg/m^2</td>
<td>IV</td>
<td>Day 1* cycle 1</td>
</tr>
<tr>
<td>Rituximab</td>
<td>500mg/m^2</td>
<td>IV</td>
<td>Day 1 cycles 2 to 6</td>
</tr>
</tbody>
</table>

*Patients with a high tumour burden / lymphocyte count ≥25 x 10^9/L are at high risk of severe cytokine release syndrome. Consider a reduced infusion rate for the first infusion and a split dosing over two days during the first cycle, i.e.

| Rituximab | 100mg | IV | Day 1 (cycle 1 only) |
| Rituximab | 375mg/m^2 minus 100mg | IV | Day 2 (cycle 1 only) |

Cyclophosphamide and fludarabine can be given orally or IV:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose/Cycle</th>
<th>Route</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide</td>
<td>150mg/m^2</td>
<td>orally</td>
<td>Days 2 to 6 cycle 1</td>
</tr>
<tr>
<td>Fludarabine</td>
<td>24mg/m^2</td>
<td>orally</td>
<td>Days 1 to 5 cycles 2 to 6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Days 2 to 6 cycle 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Days 1 to 5 cycles 2 to 6</td>
</tr>
</tbody>
</table>

In elderly / frail patients, reduce the schedule to:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose/Cycle</th>
<th>Route</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide</td>
<td>150mg/m^2</td>
<td>orally</td>
<td>Days 2 to 4 cycle 1</td>
</tr>
<tr>
<td>Fludarabine</td>
<td>24mg/m^2</td>
<td>orally</td>
<td>Days 1 to 3 cycles 2 to 6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Days 2 to 4 cycle 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Days 1 to 3 cycles 2 to 6</td>
</tr>
</tbody>
</table>

Round the cyclophosphamide dose to the nearest 50mg.
Round the fludarabine dose to the nearest 10mg.
Note that it is recommended to first take the cyclophosphamide tablets at breakfast time and the fludarabine tablets at lunchtime.

OR

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose/Cycle</th>
<th>Route</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide</td>
<td>250mg/m^2</td>
<td>IV</td>
<td>Days 1 to 3</td>
</tr>
<tr>
<td>Fludarabine</td>
<td>25mg/m^2</td>
<td>IV</td>
<td>Days 1 to 3</td>
</tr>
</tbody>
</table>
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Administration:
- Fludarabine: Orally or IV in 100ml sodium chloride 0.9% over 30 minutes
- Cyclophosphamide: Orally or IV as a bolus or in 100 – 250ml sodium chloride 0.9% over 30 minutes
- Rituximab: in 100-500ml Sodium Chloride 0.9% IV

Rituximab administration:
The first cycle should be administered according to the manufacturer’s instruction i.e. initial rate 50 mg/hr; after the first 30 minutes, escalated in 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr.
The manufacturer recommends that if the first dose is tolerated, subsequent doses of rituximab can be infused at an initial rate of 100 mg/hr, and increased by 100 mg/hr increments at 30 minutes intervals, to a maximum of 400 mg/hr.

However, if the first cycle was tolerated without any infusion related toxicities, the ‘rapid rituximab protocol’ can be followed. Give 100ml of the volume in the bag (20% of the dose) over 30 minutes, and the remainder (80% of the dose) over 60 minutes, total infusion time of 90 minutes.

Premedication:
- 30 to 60 minutes prior to Rituximab administration:
  - Chlorphenamine 10mg IV
  - Paracetamol 1000mg orally
  - Hydrocortisone 100mg IV (if clinically appropriate)

If the lymphocyte count is > 25 x 10⁹/L, in addition to a split dosing over two days during the first cycle, administer 100mg prednisolone orally prior to each dose.

Frequency:
- Every 28 days, for up to 6 cycles

Extravasation:
- Cyclophosphamide and fludarabine are not vesicants.

Anti-emetics:
- Minimal emetogenic potential (< 10%)

Supportive medication:
- Allopurinol 100 - 300 mg od (dependent on renal function) for first 2 to 3 cycles.
- PCP prophylaxis as per local policy until 6 months after the last cycle or CD4 > 200 x 10⁹/L.
- Antifungal prophylaxis as per local policy.
- Antiviral prophylaxis as per local policy.
- Consider GCSF support as per local policy starting on day 6.

Regular investigations:
- FBC D1
- U&E D1
- LFTs D1
- Baseline DAT
- Bone marrow and CT scan as baseline and at end of therapy
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**Dose Modifications**

**Haematological Toxicity due to treatment:**

Discuss with Consultant if thrombocytopenia due to marrow infiltration present.

<table>
<thead>
<tr>
<th>Neutrophils (x 10⁹/L)</th>
<th>Platelets (x 10⁹/L)</th>
<th>Fludarabine and cyclophosphamide dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1.0 x 10⁹/L &amp; ≥ 75 x 10⁹/L</td>
<td>100% dose</td>
<td></td>
</tr>
<tr>
<td>&lt; 1.0 x 10⁹/L &amp; / or &lt; 75 x 10⁹/L</td>
<td>Delay treatment for 1 week. If after 2 weeks delay the values have not changed, proceed at 50% dose. If patient neutopenic recommend GCSF for subsequent cycles according to local protocol.</td>
<td></td>
</tr>
<tr>
<td>&lt; 0.5 x 10⁹/L &amp; / or &lt; 50 x 10⁹/L</td>
<td>Delay treatment until neutrophils ≥ 1.0 x 10⁹/L and platelets ≥ 75 x 10⁹/L. Dose reduce as above if necessary. If patient neutopenic recommend GCSF for subsequent cycles according to local protocol.</td>
<td></td>
</tr>
</tbody>
</table>

NB The dose of rituximab should remain 100% throughout treatment, regardless of dose reductions on the fludarabine and cyclophosphamide.

**Renal Impairment**

- **Fludarabine:** Creatinine clearance 30 – 60 ml/min give 50% fludarabine dose, < 30ml/min discuss with Consultant and either omit fludarabine or consider a dose reduction.
- **Cyclophosphamide:** Creatinine clearance 10 – 50 ml/min give 75% cyclophosphamide dose

**Hepatic Impairment**

No dose modification is necessary.

**Toxicities:**

- Neutropenia, thrombocytopenia, nausea, infections, cardiovascular events.
- Rituximab – infusion related reactions, including cytokine release syndrome.
- Very rarely, hepatitis B reactivation, progressive multifocal leucoencephalopathy.

**Drug interactions:**

Not applicable

**Comments:**

Blood and platelet transfusion according to unit guidelines. Products must be irradiated as patients are at risk of transfusion-associated graft versus host disease - ensure blood transfusion is notified and patient has received a PIL. *Information for patients needing irradiated blood* and Alert Card.

Patients should be closely monitored for the onset of cytokine release syndrome during / following rituximab infusions. Patients who develop evidence of severe reactions, especially severe dyspnoea, bronchospasm or hypoxia should have the infusion interrupted immediately. The infusion should not be restarted until complete resolution of all symptoms. At this time, the infusion can be initially resumed at not more than one-half...
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the previous rate. If the same severe adverse reactions occur for a second time, the
decision to stop the treatment should be seriously considered on a case by case basis.
Mild or moderate infusion-related reactions usually respond to a reduction in the rate of
infusion. The infusion rate may be increased upon improvement of symptoms.

References:

NICE TAG 174 July 2009 Rituximab for the first-line treatment of chronic lymphocytic
leukaemia
NICE TAG 193 July 2010 Rituximab for the treatment of relapsed or refractory chronic
lymphocytic leukaemia
Early Results of a Chemoimmunotherapy Regimen of Fludarabine, Cyclophosphamide,
and Rituximab as initial therapy for chronic lymphocytic leukaemia. Keating MJ et al. J Clin
Oncol 2005. 23; 18: 4079-4088
Long-term results of the fludarabine, cyclophosphamide, and rituximab regimen as initial
therapy of chronic lymphocytic leukaemia. Tam CS et al. Blood 2008; 112:975-980
Chemoimmunotherapy with Fludarabine, Cyclophosphamide, and Rituximab for Relapsed
23:4070-4078
Fludarabine, cyclophosphamide, and rituximab for the treatment of patients with chronic
lymphocytic leukaemia or indolent non-Hodgkin lymphoma. Tam CS et al. Cancer 2006;
106:2412-2420
Rapid infusion rituximab in combination with corticosteroid-containing chemotherapy or as
maintenance therapy is well tolerated and can be safely delivered in the community
(MRC Working party on Leukaemia in Adults) Chronic Lymphocytic Leukaemia trial 4: A
Randomised Comparison of Chlorambucil, Fludarabine and Fludarabine plus
Cyclophosphamide (This trial has closed and is in follow up. For full protocol details refer
to UKCRN website page http://public.ukcrn.org.uk/search/)

Reason for Update: TAG 193 issued for relapsed/refractory CLL
July 2010

Approved by Consultant: S Devereux

Version: 4
Supersedes: Version 3
Date: 17/12/2012
Prepared by: Laura Cameron
Checked by (Network Pharmacist): J Turner 28/11/2012

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