20th Expert Committee on Selection and Use of Essential Medicines

Peer Review Report #1

Chronic Lymphocytic Leukemia (CLL)

Proposed medicines(s) for treatment of CLL (refer to application for specific protocols):

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Currently on EML</th>
<th>Addition</th>
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<tbody>
<tr>
<td>fludarabine (oral &amp; IV)</td>
<td>☐</td>
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<tr>
<td>cyclophosphamide</td>
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<tr>
<td>rituximab</td>
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<tr>
<td>bendamustine</td>
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<td>☐</td>
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<tr>
<td>vincristine</td>
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<tr>
<td>prednisone</td>
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(1) Does the application adequately address the issue of the public health need for the treatment of the disease?

Yes ☑ No ☐

Comments: very extensive review, very complete. Some remarks:
- There should be a mention about MBL (Monoclonal B-cell lymphocytosis), which is much more frequent than CLL but often misdiagnosed as CLL. MBL (<5'000 L monoclonal lymphocytes) transforms to CLL in only a minority of cases with a rate of about 1%/year, so much less than M-GUS in myeloma.
- Considering also developing countries, bone marrow examination should be stated to be desirable and not important. Even in the European guidelines it is not stated that this is important!

(2) Have all important studies that you are aware of been included in the application?

Yes ☑ No ☐

Comments:

(3) Does the application provide adequate evidence of efficacy/effectiveness of the proposed treatment regimen(s)?

Yes (X) No ☐
Comments: R-CVP should be omitted. Under supportive care “regular immunoglobulin replacement therapy” it should be added “might reduce infection rates” and perhaps there should be a limit < 3g/l?

(4) Does the application provide adequate evidence of safety for the proposed treatment regimen(s)? Are there any adverse effects of concern, or that may require special monitoring?

Yes (X) No

Comments:
- There should be a word of caution to limit the use of steroids to immune-related cytopenias since abuse of steroids might increase the rate of infections.
- Dosage of Bendamustine (90 mg/m²): it should be specified that this for not pre-treated patients and for patients who are very fit. Otherwise, in order to avoid important myelotoxicity, dosage should be reduced to 70-80 mg/m².
- The serious myelo-suppression with FCR is described, but it could perhaps be stated that if growth factors are not available, caution should be used in frail patients as they might have a very profound toxicity.

ADDITIONAL CONSIDERATIONS:

(5) Are there special requirements or training needed for the safe, effective and/or appropriate use of the proposed treatment(s)?

Yes (X) No

Comments: All these treatments require specialised training and should be limited to tertiary centers.

(6) Are there any issues regarding the registration of the proposed medicines by regulatory authorities? (e.g., recent registration, new indications, off-label use)

Yes (X) No

Comments:

(7) Comment briefly on issues regarding cost and affordability of treatment.
The cost of Rituximab should be discussed, although the drug (as for lymphomas) is necessary. It has to be hoped that biosimilars will soon become available and be less costly.

(8) Any additional comments on the application?

No

(9) Please summarise the action(s) you propose the Expert Committee take.

Add Fluradabine, Rituximab and Bendamustine to EML.