20th Expert Committee on Selection and Use of Essential Medicines

Peer Review Report #1

Diffuse Large B-cell Lymphoma (DLBCL)

Proposed medicines(s) for treatment of DLBCL (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>rituximab</td>
<td>☐</td>
<td>☑️</td>
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<tr>
<td>cyclophosphamide</td>
<td>☑️</td>
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<tr>
<td>doxorubicin</td>
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<td>☐</td>
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<tr>
<td>vincristine</td>
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<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 ☐

Diffuse Large B Cell Lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma. The disease is responsive to chemotherapy, and the majority of patients with DLBCL can now be cured with modern therapy. Many affected patients are young adults, so the impact of therapy is substantial in terms of life-years gained. It should be noted that although DLBCL occurs in children and adolescents, pediatric patients with DLBCL are generally treated on regimens suitable for the B-cell lymphomas that occur in childhood (including Burkitt lymphoma). Such treatment regimens have proven to be quite effective. Thus CHOP and R-CHOP are not standard regimens for children with DLBCL.

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

Yes ☑️ No ☐

Early studies have demonstrated the efficacy of the CHOP regimen for management of patients with DLBCL. The addition of rituximab to CHOP (R-CHOP) has been demonstrated in randomized trials to improve the outcome further (up to 20% improvement in overall survival). Subsets of DLBCL can be defined through gene-expression profiling and other molecular studies which have proven to be prognostic, so that the efficacy of R-CHOP varies according to subtype. Such studies are noteworthy, but have not altered the utility of R-CHOP for all subsets of DLBCL.
Although the list of references is not exhaustive, R-CHOP is now the standard of care for adults with DLBCL.

3) Does the application provide adequate evidence of efficacy/effectiveness of the proposed treatment regimen(s)?
   - Yes ☑
   - No ☐

Early studies have demonstrated the efficacy of the CHOP regimen for management of patients with DLBCL, and it emerged as the standard of care for adults with this disease. The addition of rituximab to CHOP (R-CHOP) has been demonstrated in randomized trials to improve the outcome further (up to 20% improvement in overall survival). Thus, evidence to support the inclusion of rituximab to the current EML is incontrovertible.

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 ☑
   - No ☐

CHOP and R-CHOP have been used for years. The acute and late toxicities of therapy are well-described and manageable in settings with experience with administration of anti-neoplastic chemotherapy.

ADDITIONAL CONSIDERATIONS:

5) Are there special requirements or training needed for the safe, effective and/or appropriate use of the proposed treatment(s)?
   - Yes ☑
   - No ☐

The relative rarity of DLBCL mandates that therapy should be undertaken in centers with appropriate diagnostic and therapeutic expertise and the availability of suitable supportive care facilities and specialists experienced with management of chemotherapy complications. Toxicities of therapy and potential complications have been well described and are manageable in centers with appropriate experience.

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 ☐
   - No ☑
The agents in CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) are known effective agents indicated for treatment of lymphoma. Rituximab has been approved for treatment of CD20+ lymphomas (including DLBCL) based on randomized studies documenting its efficacy in this setting. The utility of rituximab in other settings has been demonstrated, although many such uses of the agent constitute off-label use.

(7) **Comment briefly on issues regarding cost and affordability of treatment.**

The agents in the CHOP regimen are all older chemotherapeutic agents that are off patent and relatively inexpensive. However, supportive care, including anti-emetics and management of marrow suppression contribute substantially to the cost of care. Rituximab remains on patent and is relatively expensive and requires technical expertise for its administration.

(8) **Any additional comments on the application?**

Although the addition of rituximab to CHOP increases the complexity and cost of management of patients with DLBCL, its contribution to substantial improvement in survival (and cure) is indisputable. Patients with DLBCL cured of their disease can be expected to live normal, productive lives after therapy.

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

Addition of rituximab to the List of Essential cytotoxic and adjuvant medicines for use in patients with DLBCL in conjunction with CHOP chemotherapy. The agents in the CHOP regimen (cyclophosphamide, doxorubicin, vincristine and prednisone) are already on the EML. The addition of rituximab is well-supported by available evidence that it contributes to significantly improve outcome.