Lymphoid Neoplasia

**Maintenance in CLL**

Tadeusz Robak

In this issue of Blood, Abrisqueta and colleagues report on the outcomes of a phase 2 clinical trial evaluating rituximab maintenance therapy in chronic lymphocytic leukemia (CLL) patients after treatment with rituximab, fludarabine, cyclophosphamide, and mitoxantrone (R-FCM).\(^1\)

**D**espite significant progress, CLL remains an incurable disease and the introduction of new drugs and new therapeutic strategies is still awaited. Consolidation and maintenance therapy is a promising concept that can further improve response quality and duration in CLL patients. In indolent non-Hodgkin lymphoma patients, particularly in follicular lymphoma, large randomized trials have indicated that rituximab maintenance treatment after induction therapy improves results in previously treated and untreated patients.\(^2,3\)

In follicular lymphoma, 2 years of rituximab maintenance therapy significantly improves prolonged progression-free survival (PFS) when given after immunochemotherapy as a first-line treatment of induction and is the current standard of care.

The approval of rituximab-based immunochemotherapy can be viewed as a substantial therapeutic advance in CLL. A large phase 3 randomized trial demonstrated that rituximab combined with fludarabine and cyclophosphamide (RFC) increased the overall response and complete response (CR) rates, prolonged PFS and overall survival (OS) as compared with fludarabine and cyclophosphamide in previously untreated patients.\(^4\) On the basis of these results, RFC has become the first-line treatment of choice for younger CLL patients.

There has also been some exploration of rituximab as maintenance therapy in CLL.\(^5,6\)

In these small studies, maintenance therapy with rituximab was successfully conducted for 6 months or longer. Long-term toxicity, based on hematologic and immunologic parameters, was mild. Encouraging results were also seen in a recently published study by Wiernik and Adiga in which patients receiving rituximab maintenance therapy demonstrated a median duration of response substantially longer than those who did not receive maintenance (35 months vs 14 months, respectively).\(^6\)

In this issue, Abrisqueta et al report a phase 2 clinical trial consisting of an initial treatment with R-FCM followed by rituximab maintenance.\(^1\) Sixty-seven patients achieving response after R-FCM received maintenance therapy with 375 mg/m\(^2\) rituximab every 3 months for 2 years. At the end of the maintenance therapy, 40.6% of patients were in minimal residual disease (MRD)–negative CR, 40.6% were in MRD-positive CR, while 4.8% remained stable in partial response. Importantly, 21% of the patients in CR MRD-positive or in partial response in the end of R-FCM induction therapy improved their response after rituximab maintenance. A 4-year PFS and OS were 69.1% and 90.5% for all patients and 74.8% and 93.7% for patients receiving rituximab maintenance, respectively. These results seem to be better than those reported for RFC therapy from the German CLL Study Group (GCLLSG) CLL8 trial, which concluded with a 65% 3-year PFS and 87% OS. As expected, MRD status after R-FCM therapy was the strongest predictor of PFS. Grade 3/4 neutropenia was observed in 8.5%, and 16 patients experienced grade 3/4 infectious episodes. Maintenance with rituximab after R-FCM improved the quality of the response, particularly in patients who were MRD-positive after initial treatment and who obtained a prolonged PFS. These results are encouraging, but a randomized trial is necessary to establish the possible advantage of such maintenance treatment over standard RFC therapy in previously untreated CLL patients.

We should remember that other agents can also be useful in the maintenance therapy.
Consolidation treatment with alemtuzumab has been evaluated in a randomized, multicenter, phase 3 trial by the GCLLSG.² Patients with CLL responding to standard initial therapy with fludarabine-based regimens were randomized for treatment with alemtuzumab 30 mg 3 times per week for a maximum 12 weeks of observation. Unfortunately, the study was prematurely closed because of severe infections in 7 of 11 patients treated with alemtuzumab. It should be noted, however, that after alemtuzumab treatment, 5 patients achieved molecular remission, while all patients in the control group demonstrated MRD. In addition, an updated analysis after a median follow-up of 48 months confirmed significantly prolonged PFS for patients receiving alemtuzumab consolidation, compared with those who received no further treatment.⁷ This study has shown that, despite toxicity, consolidation treatment with alemtuzumab induces molecular remission, reduces MRD, and translates into a significantly improved long-term clinical outcome. Lenalidomide is another drug with possible applications in maintenance therapy in CLL. It has been recently observed that consolidation improved the quality of response and repaired T-cell immune synapses in CLL patients who received lenalidomide chemotherapy.⁸ A phase 3 study of the efficacy and safety of lenalidomide maintenance vs placebo for high-risk patients with CLL following first-line therapy is ongoing (NCT01556776). Finally, the B-cell receptor-signaling inhibitors, ibrutinib and idelalisib, have demonstrated significant clinical activity against CLL in early clinical trials.⁹ These drugs are available in oral preparations and are given as continuous treatment. They seem to be active in traditionally poor-risk disease groups, including fludarabine-refractory patients. Moreover, they are well tolerated and have an excellent safety profile in patients with CLL. Taken together, although several phase 2 studies of maintenance rituximab have been published after completion of chemoimmunotherapy, the benefit of this strategy is uncertain. At the moment, we do not know what this strategy will imply in terms of events or survival. In particular, there is still no evidence from randomized trials that maintenance with rituximab added to modern immunotherapy induction prolongs survival. In addition, recent data suggest that rituximab maintenance therapy increases the risk of both infection and neutropenia, and possibly other complications, in patients with lymphoma or other hematologic malignancies.¹⁰ Moreover, it is not clear whether prolonged administration of any drug in CLL patients can increase the development of clonal evolution and drug resistance.

In conclusion, better strategies are awaited for maintaining remissions in patients with CLL. In particular, further studies are needed to characterize the benefits of rituximab and other agents in maintenance therapy. Moreover, more effective drugs with low toxicities in optimal doses should be selected for future studies. According to recent guidelines, maintenance or consolidation therapy with rituximab, alemtuzumab, or lenalidomide should not be used outside of clinical trials. Well-designed, carefully controlled, randomized clinical trials should confirm the advantage of maintenance strategies over current standard therapies.

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**REFERENCES**


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**Table 1. Candidate drugs for maintenance therapy in CLL**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Characteristics</th>
<th>Current status in CLL</th>
<th>Clinical trials in CLL: maintenance or consolidation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab</td>
<td>Anti-CD20 mAb</td>
<td>Approved for previously untreated and refractory/relapsed patients</td>
<td>Several phase 2 clinical trials completed; no results of phase 3 randomized trial available</td>
</tr>
<tr>
<td>Alemtuzumab</td>
<td>Anti-CD52 mAb</td>
<td>Approved for previously untreated and refractory/relapsed patients</td>
<td>Several phase 2 clinical trials completed; phase 3 clinical trial stopped prematurely due to severe infections</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>Immunomodulator</td>
<td>Not approved to treat CLL</td>
<td>Phase 2 clinical trials completed; phase 3 clinical trial ongoing</td>
</tr>
<tr>
<td>Ibrutinib</td>
<td>Btk inhibitor</td>
<td>Not approved yet</td>
<td>Phase 2 and 3 clinical trials ongoing</td>
</tr>
<tr>
<td>Idelalisib</td>
<td>PI3Kβ inhibitor</td>
<td>Not approved yet</td>
<td>Phase 2 and 3 clinical trials ongoing</td>
</tr>
</tbody>
</table>

Btk, Bruton tyrosine kinase; mAb, monoclonal antibody; PI3Kβ, phosphatidylinositol 3-kinase β.
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