Frontline treatment of chronic lymphocytic leukemia with obinutuzumab and chlorambucil: how does it work in “real-life”?

Valentin Goede

Oncogeriatric Unit, Department of Geriatric Medicine, St. Marien Hospital, Cologne, Germany

The majority of patients with chronic lymphocytic leukemia (CLL) are older, and many of them are burdened with comorbidities such as cardiovascular, pulmonary, renal, metabolic, or musculoskeletal diseases. In patients with CLL in need of treatment, advanced age and presence of comorbidities increase the risk of complications and thus have adverse impact on overall prognosis. This clinical problem has been acknowledged by national and international guidelines on CLL, most of which tailor treatment recommendations to patient fitness. The European Society of Medical Oncology guidelines recommend chemoinmunotherapy with combination of obinutuzumab and chlorambucil or single-agent therapy with ibrutinib as initial treatment for unfit and comorbid patients with previously untreated standard-risk CLL (ie, no TP53 alteration).

The recommendation of obinutuzumab–chlorambucil regimen as frontline therapy in this patient population was based on a large randomized phase 3 study (CLL11, 781 enrolled patients in total, 333 treated with obinutuzumab and chlorambucil), which demonstrated superiority of this regimen over both rituximab–chlorambucil and chlorambucil alone with regard to clinical and molecular response rates as well as progression-free and overall survival. The study also showed that impressively long treatment-free intervals (>4.5 years on average) are achievable with obinutuzumab–chlorambucil while treatment toxicity was well manageable. A nonrandomized, large phase 3b study (GREEN, 972 enrolled patients in total, 114 treated with obinutuzumab–chlorambucil) recently confirmed the favorable safety profile.

Despite such compelling trial evidence, performance of the obinutuzumab–chlorambucil regimen in “real-life” remains to be further studied. In this issue of Polish Archives of Internal Medicine (Pol Arch Intern Med), Długosz-Danecka et al report on 86 elderly and comorbid patients with CLL having received obinutuzumab–chlorambucil as frontline treatment outside a clinical trial and being analyzed for outcome as part of the Polish Adult Leukemia Group research project. Overall, the results of this retrospective analysis support the use of obinutuzumab–chlorambucil in this treatment situation. Characteristics of the patient population were very similar to the registry trial, and reported efficacy was well comparable to what had been previously observed in the CLL11 study. Importantly, adverse events occurred at a lower frequency than in the registry trial. This was particularly the case for grade 3 to 5 infusion-related reactions: an obinutuzumab–specific toxicity, which by some experts was initially considered a limitation for its use in elderly and comorbid “real-life” patients. However, the safety findings reported by Długosz-Danecka et al invalidate these initial concerns and suggest that obinutuzumab–chlorambucil can be safely administered not just under clinical trial but also “real-life” conditions.

With the advent of novel drugs for CLL, frontline treatment of elderly and comorbid patients is likely to change in the near future. Chemotherapy-free combinations hold great promise and randomized clinical trials are ongoing, with positive results being expected soon. However, in many countries, these drugs and new combination regimens will not be readily available. Therefore, for some time, obinutuzumab–chlorambucil will remain a valid treatment option in this patient population, based on the pieces of evidence emerging from clinical trials as well as from “real-life” observations such as presented here by Długosz-Danecka et al.

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