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Perspective
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Chemo-immunotherapy for Older Patients with Chronic Lymphocytic Leukemia – Time to Retire?

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In this issue of *HemaSphere*, Danilov et al suggest, based on the Alliance for Clinical Trials in Oncology study comparing ibrutinib with or without rituximab vs bendamustine and rituximab, that a potential role for chemo-immunotherapy (CIT) still exists in the management of older patients with chronic lymphocytic leukemia (CLL).[1] On the contrary, in our opinion, this paper further supports the central role of the BTK inhibitor (BTKi) in the elderly and finally launches a chemo-free era in CLL.

Clinical trials have been designed in recent years to optimize the management of patients aged ≥65 years or unfit (the vast majority of CLL patients).[2,3] Age alone is a poor prognostic factor for life expectancy and treatment tolerance.[3] Furthermore, elderly CLL patients often present with poor performance status, comorbidities and impaired renal function, which hamper treatment with intensive regimens. Patients enrolled in Woyach et al study, though ≥65 years, should be considered a highly selected population as they were deemed suitable for bendamustine at the full dose of 90 mg/m^2 if randomized to the control arm.[1] The patients functional status performed at baseline is representative of a healthy fit population that does not reflect those normally seen in everyday practice. Even in this selected population, like in previous clinical trials, a high percentage (25–33%) of patients ≥65 years have to discontinue bendamustine before treatment completion or to reduce the dose.[1,4,5] Attenuated doses of the drug are frequently applied outside clinical trials although no prospective studies have been performed supporting such reduction.[6] As a result, the PFS curves observed in trials may not reflect the outcome in common clinical practice. In the Resonate-2 study ibrutinib was the first chemotherapy-free treatment demonstrating a survival advantage in older patients even if a treatment crossover was allowed.[7] The better outcome of this population initiating treatment with ibrutinib reflects the relevance of administering first the most effective and tolerated regimen leading to a rapid disease control. With longer follow-up, ibrutinib continues to demonstrate an OS benefit, of greater magnitude in high-risk disease, with PFS and OS rates being independent of age (≥ or <75 years).[8] Woyach et al demonstrated a PFS advantage with ibrutinib alone or combined with rituximab over bendamustine-based CIT in all the high-risk stratification groups.[1] Similarly, ibrutinib plus obinutuzumab showed superior PFS and reduced risk of needing second line therapy when compared to chlorambucil plus obinutuzumab, considered the CIT of choice in the elderly unfit population.[10]

The matter of ibrutinib tolerability has been analyzed in a post-hoc pooled analysis of 3 phase III randomized trials.[9] Patients ≥75 years treated with the BTKi showed not only a benefit for PFS but also a trend of a better OS. Notably, the favorable outcome was maintained in patients with a past medical history of cardiac disorder, tachyarrhythmia, hypertension, infection, or bleeding. No less important, treatment with the BTKi provides a rapid improvement of anemia and disease symptoms which are fundamental in the elderly population.[7]

With long-term follow-up data becoming available, it is now evident that the adverse event (AE) rate with ibrutinib is reducing over time.[8,11] Most grade 3 or higher AEs occur within the first 12 months, while discontinuation due to side effects and dose reductions are uncommon and lessen over treatment. In the paper with the longest follow-up published to date, the 77% of elderly patients with CLL continued ibrutinib for >4 years, thus proving the general tolerability of the drug.[11] Atrial fibrillation (AF) is common with ibrutinib treatment (10.4%) with a higher incidence compared to the control arms in randomized studies.[12] AF leading to treatment discontinuation is rare overall suggesting that appropriate management and a favorable benefit-risk profile allow patients to continue treatment. The higher number of unexplained deaths in the study of Woyach et al in patients receiving the BTKi raised the concern of a possible excess of ventricular arrhytmias. In the randomized trials any increased risk of ventricular arrhythmias and sudden death was outweighed by the benefits of CLL control and the benefit on OS.[7]

LS: AbbVie, Janssen SpA, Astra-Zeneca Consultancy. AT: AbbVie, Janssen SpA, Sunesis, Astra-Zeneca Consultancy.
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Grade 3–4 cytopenias in treatment-naïve occur at significantly lower rate compared to CIT.[1,7,10] Although the infection rate seems similar it should be emphasized that the safety reporting periods are different and much longer for ibrutinib. In randomized first-line trials the most common infectious complications in the elderly were upper respiratory tract infections and pneumonia.[1,7,10] Pneumocystis jirovecii pneumonia and invasive fungal infections have been reported only sporadically in untreated patients so that according to the recent position paper by the European Conference on Infections in Leukemia prophylaxis it is not routinely recommended in this setting.[13]

It is also worth noting that the vast majority of ibrutinib-related AEs was reversible, at variance with some long-term toxicities reported with CIT (eg, solid tumors and therapy-related acute myeloid leukemia or myelodysplasia).

The future looks even brighter, considering that alternate, more selective, BTK inhibitors are in development to improve efficacy and reduce toxicity compared with ibrutinib. Furthermore, the Bcl-2 inhibitor, venetoclax, is going to revolutionize CLL treatment approach introducing the new concept of fixed duration in targeted therapies, potentially limiting toxicities and resistances. These new treatment approaches on the horizon will allow clinicians to limit the use of chemotherapy at least in the elderly population.

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