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Ibrutinib in CLL: benefit for all?

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In this issue of *Blood*, Woyach et al[1] report an update of a pivotal phase 3 trial showing the superiority of ibrutinib (Ibr)-based treatments over chemoimmunotherapy (CIT) in frontline treatment of older adults with chronic lymphocytic leukemia (CLL).

The data represent the third planned interim analysis of the study performed by the National Clinical Trials Network (NCT01886872) that analyzed progression-free survival (PFS) for bendamustine and rituximab (BR) vs Ibr alone or in combination with rituximab.

While confirming that adding rituximab to Ibr does not provide any benefit over Ibr alone, this long-term follow-up of 547 patients with treatment-naive (TN) CLL continued to show a highly significant benefit, with 48-month PFS estimates of 76% in Ibr arms as compared with 47% in the BR arm (hazard ratio 0.36, $P < .0001$ in Ibr arms vs BR). Because BR is a widely adopted CIT regimen,[2] the PFS advantage of Ibr provides solid evidence supporting continuous treatment with Ibr as one of the recommended treatment options in CLL. However, no significant PFS difference in immunoglobulin heavy chain variable gene (IGHV)-mutated cases has been detected in the study arms at 55-month median follow-up. Longer times in the study might be required to document a PFS advantage in this subset of CLL known to respond well to CIT, though it is interesting to note that a second-generation Bruton tyrosine kinase inhibitor (BTKi) (zanubrutinib) was able to show a superiority already at a shorter follow-up when compared with BR.[3] That being said, it remains to be determined whether CIT may still have role in first-line treatment of some older patients with a favorable genetic profile, in particular when access to novel target agents is still limited. This is relevant if we also consider the superimposable overall survival (OS) rate with BTKi and CIT in this and other trials that allowed crossover to BTKi at progression.[4]

Patients with complex karyotype showed shorter PFS, but no difference in PFS has been observed with Ibr regimens in patients with or without *TP53* aberrations suggesting that Ibr, as with second-generation BTKis,[4] is an effective option in this subset of CLL. It will be important in the future to gather data from similar studies to elucidate the prognostic significance of the size of the *TP53* aberrant clone and of double-hit *TP53* aberrations vs single-hit mutations, as this remains an open question due to mixed results reported in previous analyses.[5]

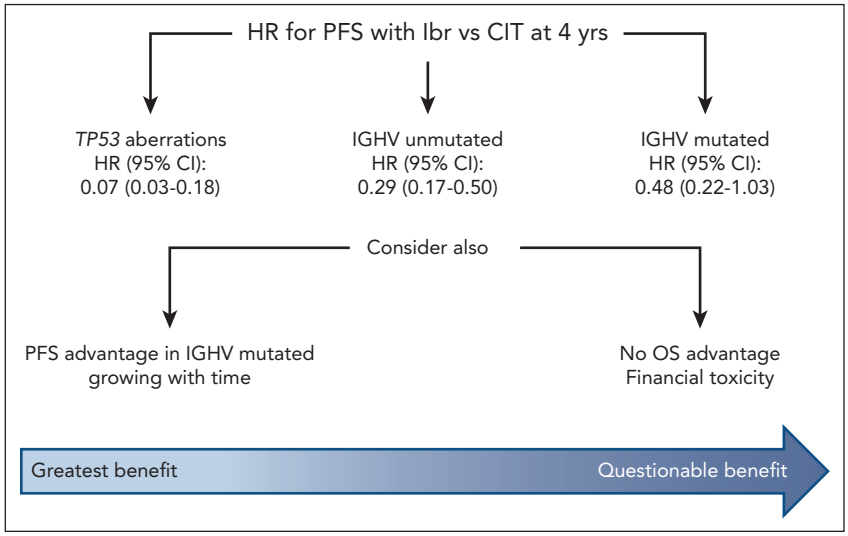
Switching from efficacy to safety, the prolonged monitoring of AE in the study revealed clinically significant toxicity in a fraction of cases. Atrial fibrillation was reported in 18% and hypertension in 55% of patients treated with Ibr. Unexplained unwitnessed deaths on treatment or within 30 days of cassation have been reported in 3 of 176 (1.7%) patients receiving BR and in 13 of 361 (3.6%) patients receiving Ibr. Four cases of fatal cerebral hemorrhage were reported in the Ibr arms and none with BR. Though potentially alarming, one should remember that these data compare continuous treatment to a fixed-duration regimen. A better understanding of toxicity would come from looking at an exposure-adjusted incidence rate, thus reassuring clinicians and patients of the overall safety of continuous BTKi as compared with CIT.

It is also worthwhile considering that in the relapsed or refractory setting, second-generation BTKi showed an improved safety profile to that of Ibr. Thus, it is tempting to speculate that a similar advantage may apply also to TN patients. Along this line, with all the limitations of cross-trial comparison, at data cutoff, 188 of 361 (52%) patients who initiated Ibr with or without rituximab were still on treatment, and 66 patients (18.3%) discontinued treatment due to adverse events (AEs). In the ELEVATE-TN study comparing acalabrutinib regimens vs obinutuzumab plus chlorambucil in older (though less fit) patients with TN CLL, treatment with acalabrutinib single agent was ongoing in 69.3% of the patients at a median follow-up of 46.9 months, and 12.3% of the patients discontinued treatment due to AE.[6] Thirteen percent of patients discontinued treatment with zanubrutinib at a median follow-up of 47.9 months in the SEQUOIA study, where the treatment was compared with BR in elderly patients with CLL.[3]

Interestingly, a study using electronic medical records showed that the patients with reduced doses of Ibr after an AE had a longer time to next antileukemic treatment (TTNT) than patients who did not have reduced-dose prescription.[7] These data raise an interesting hypothesis that tolerability and, consequentially, efficacy of reduced doses of Ibr may be improved, and these results should prompt testing in prospective studies.

The observation of a 24-month median PFS after discontinuing Ibr for AE and probably an even longer TTNT is similar to what was previously shown in the ECOG1912 trial.[8] These findings suggest that there may be the possibility of time-limited treatment with BTKi, giving the prospect of subsequent retreatment, a long-sought approach in the management of patients with CLL.

In conclusion, the study by Woyach et al provides further high-quality evidence in favor of BTKi as one of the preferred options for CLL in the frontline setting and adds to other similar studies with second-generation BTKi. However, the lack of OS advantage in this and other studies comparing new agents with CIT may support the usage of first-line CIT in patients with low-risk disease followed by first salvage with targeted agents, particularly important when considering issues of accessibility and sustainability in different geographical regions. Indeed, the rising cost of CLL treatment may undermine the effectiveness of therapy due to out-of-pocket expenses in some countries. Not



Magnitude of clinical benefit with Ibr vs CIT in older patients with TN CLL. HR, hazard ratio.

surprisingly, a significant proportion of patients chose the lower-cost medicine with shorter median PFS when presented with a choice between 2 medicines and their out-of-pocket cost.[9] With universal national health systems at a breaking point,[10] we are facing times when one has to consider the magnitude of clinical benefit (see figure) and to adapt this to the patient expectations in each and every economical context rather than to choose simply based on the medical reasoning and the efficacy and tolerability of the treatments.

Conflict-of-interest disclosure: A.C. reports honoraria for participation to speakers bureau and advisory board from AbbVie, AstraZeneca, Beigene, Janssen, and Lilly. P.G. reports research support from AbbVie, AstraZeneca, Bristol Myers Squibb (BMS), and Janssen, and honoraria from AbbVie, AstraZeneca, BeiGene, BMS, Galapagos, Janssen, Lilly/Loxo Oncology, Merck Sharp & Dohme, and Roche. ■

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https://doi.org/10.1182/blood.2023023758

MYELOID NEOPLASIA

Comment on Renga et al, page 1628

How lipid coating soothes the gut in AML therapy

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In this issue of *Blood*, Renga et al,[1] in elegant experimental mouse models, compared the impact on gut microbiota, fungal colonization, and intestinal mucosa integrity of 2 intensive induction acute myeloid leukemia (AML) therapies. A surrogate for the "7+3" regimen of cytarabine infused continuously over 7 days with an anthracycline (eg, daunorubicin) injected intravenously 3 days apart was compared with repeated administration of the recently approved CPX-351, a liposomal construction encapsulating these 2 pivotal anti-leukemia drugs at a fixed molar ratio.[1]

These experimental results are highly relevant clinically. As shown independently by several teams, intestinal microbiota of patients with AML is markedly disrupted during a classic 7+3 induction course.[2,3] This digestive microbial dysbiosis appeared to correlate with a higher risk of bloodstream infections and other microbiologically documented infections.[2] These changes seemed to be protracted and impact later phases of therapy.[3] They partly persisted when patients with AML are referred for allogeneic hematopoietic stem cell transplantation after achievement of a