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EDITORIAL COMMENT

Bridging the Knowledge Gap for Older Patients With CLL on Ibrutinib*

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Over the past 10 years, the treatment landscape for chronic lymphocytic leukemia (CLL) has drastically changed with the use of targeted therapies in place of traditional cytotoxic chemotherapy for the majority of patients. Bruton's tyrosine kinase (BTK) inhibitors are 1 such class of targeted therapies that not only offer a generally more favorable side effect profile but also have partially overcome the negative prognostic impact of high-risk molecular features in CLL compared with traditional fixed-duration chemotherapy.[1,2] However, the current Food and Drug Administration–approved BTK inhibitor–containing regimens are all used continuously until disease progression or toxicity. Therefore, the discussion of these agents with patients requires close review of patient lifestyles, comorbidities, and concomitant medications.

Ibrutinib was the first-in-class approved BTK inhibitor, with-well described toxicities including atrial fibrillation, bleeding, cytopenia, and infection. Second-generation BTK inhibitor therapies (acalabrutinib and zanubrutinib) have less off-target effects compared with first-generation ibrutinib and appear to be as effective or superior in terms of survival outcomes.[3,4] Second-generation BTK inhibitors have lower rates of atrial fibrillation compared with ibrutinib. In separate head-to-head comparisons with ibrutinib, the risks with acalabrutinib (9% vs 16%) and zanubrutinib (5% vs 12%) were less. The risk of major hemorrhage was similar for all 3 agents (~4%).[3,4]

Major limitations of the prospective randomized controlled studies on CLL is that the population of patients enrolled in the studies were of younger age, and they excluded patients with major cardiovascular risk factors and/or those on warfarin anticoagulation.[3-7] The median age of the clinical trial participants was 66 to 68 years,[2-4] whereas the median age of diagnosis is 70 years of age in the general population with over one-third of patients being diagnosed at 75 years or older. In a pooled secondary analysis of several clinical trials evaluating ibrutinib, the rate of major hemorrhage was 4%. Only 15% of patients had a prior history of bleeding events, 20% were treated with anticoagulant, 39% were treated with antiplatelet therapy, and 10% received both.[8]

In their well-conducted population study in this issue of *JACC: CardioOncology*, Diamond et al[9] used the Surveillance, Epidemiology, and End Results-Medicare database to bridge the knowledge gap and add to the growing body of real-world evidence regarding older patients with CLL who were not represented in the majority of prospective clinical trials.[3-7,9] The median age was 78 years with approximately two-thirds of patients aged 75 years or older. A history of stroke, atrial fibrillation, and bleeding were reported in 18% to 21%, 20% to 25%, and 26% to 34% of treated patients, respectively. Of the 299 patients who received ibrutinib, 49% had previously been prescribed anticoagulation, and 19% required anticoagulant therapy within 12 months before starting ibrutinib.

Although this study did expectedly confirm the increased risk of atrial fibrillation and cardiovascular complications among patients treated with ibrutinib, the rate of bleeding complications appears to be much higher than previously described in this older

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population of patients. This study revealed a 4.9-fold increase in the rate of bleeding and a 7.5-fold increase in the rate of major bleeding.

These results highlight a key challenge in managing older patients with CLL requiring therapy and should prompt clinicians to have a more nuanced approach in selecting agents for this population. A collaborative approach with cardio-oncology to ensure proper risk assessment and mitigation pre- and post-treatment is necessary. This also allows for frank discussion on the necessity of anticoagulant, antiplatelet, and nonsteroidal anti-inflammatory therapies in advance. Often, a fixed duration of venetoclax plus obinutuzumab is the preferred regimen in this older population with cardiac comorbidities if they are able to tolerate the increased hydration necessary for preventing tumor lysis syndrome and the risk of infusion reactions associated with obinutuzumab. Among patients with high-risk cytogenetics such as del17p and TP53 mutations, continuous BTK inhibitor therapy appears to have longer progression-free survival rates than fixed-duration therapy. However, this benefit may not outweigh the risks in older patients with cardiovascular risk factors and an increased risk of bleeding. In patients who do elect to start BTK inhibitor, a second-generation BTK inhibitor is preferred because of a more favorable side effect profile compared with ibrutinib.

A key future area of research is real-world data evaluating differences in bleeding and cardiac complications between a second-generation BTK inhibitor in older patients and novel combination regimens that use a fixed-duration BTK inhibitor. Lastly, phase 3 studies evaluating novel non-covalent BTK inhibitors such as pirtobrutinib are underway. Early clinical data have shown a more favorable toxicity profile compared with a covalent BTK inhibitor in non-Hodgkin lymphoma, which may translate into safer administration in older patients with CLL.[10]

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