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COMMENTARY

Front-line chronic lymphocytic leukemia: The role of chemoimmunotherapy

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The frontline therapy for chronic lymphocytic leukemia (CLL) has changed in the past 10 years. Chemoimmunotherapy (CIT) was the only available option with different regimens based on age and fitness. The current treatment for first-line therapy includes Bruton tyrosine kinase (BTK) inhibitors until progression of disease or venetoclax combined with obinutuzumab for fixed duration therapy. For patients without 17p/*TP53* mutations only, chemoimmunotherapy is considered a possible option. However, it is not a category 1 option in the NCCN guidelines unlike the other two therapies.

The relevant question facing both TP53 mutated and TP53 wild type patients is: what is the optimal sequence of agents to maximize my survival and quality of life? And, more practically, is it preferable to begin with a BTK inhibitor or venetoclax-obinutuzumab followed by the other, or chemoimmunotherapy, or is it preferable to begin with bendamustine-rituximab or fludarabine-cyclophosphamide-rituximab and reserve these agents in the salvage setting? Current trials have leveraged the initial PFS as a stand-in for these debates, but this endpoint neither captures survival nor quality of life. Here we argue that our evolution in first-line CLL therapy is not firmly evidence based and chemoimmunotherapy remains a reasonable option in most patients.

RESONATE-2 was the first trial to establish the role of ibrutinib in first-line CLL. Treatment naïve patients that were 65 and older were randomized to ibrutinib until disease progression or chlorambucil with improvement in progression free survival (PFS) in the ibrutinib arm. Yet, the use of chlorambucil, a weak control arm, limited the persuasiveness of the data. The standard of care did not change immediately as bendamustine was shown to have greater efficacy compared to chlorambucil.[1] It was not until the Alliance trial A041202 showed improvement in PFS with ibrutinib compared to bendamustine-rituximab in previously untreated CLL that the standard changed.

First, the survival benefit of BTK inhibitors compared to CIT has not been established. Long-term results of A041202 were reported in 2021 with no difference in overall survival (OS) between ibrutinib and bendamustine-rituximab.[2] E1912 did show a survival benefit of ibrutinib-rituximab (IR) compared to fludarabine, cyclophosphamide, and rituximab at long-term follow up.[3] However, the median age of patients was 58 with only 7.9% older than 65 which is not representative of the majority of CLL patients where the average age of diagnosis is 70. There were only 14 deaths in total, and rates of post-progression ibrutinib were not provided. In the FLAIR study that compared the IR and FCR in an older population with 33.6% older than 65, there was no difference in overall survival.[4]

Even in clinical trials that compared BTK inhibitors with a chlorambucil-based regimens there is no established overall survival benefit. The iLLUMINATE trial compared ibrutinib-obinutuzumab to chlorambucil-obinutuzumab in previously untreated CLL patients that were 65 or older or younger than 65 with comorbidities. In the final analysis reported in 2022 there was no overall survival benefit.[5] RESONATE-2 showed a survival benefit of ibrutinib compared to chlorambucil. These results are not relevant to current practice as chlorambucil is a substandard control arm compared to bendamustine-rituximab. Other BTK inhibitors have not demonstrated OS benefit. There was no difference in OS between acalabrutinib and chlorambucil-obinutuzumab after 4 years of follow-up in ELEVATE-TN.[6] In the SEQUOIA trial, zanabrutinib showed only PFS improvement compared to bendamustine-rituximab.[7]

Second, there is no evidence that BTK inhibitors improve health-related quality of life (HRQoL) in the first-line setting. Comparing the adverse event burden of BTK inhibitors and chemoimmunotherapy is complicated by distinct side effect profiles and differences in duration of adverse events. In A041202, grade 3 or higher hematologic adverse events were more frequent with bendamustine-rituximab at 61% compared to 41% with ibrutinib. Non-hematologic adverse events were more frequent with ibrutinib at 74% and bendamustine-rituximab at 63%. HRQoL was not reported. The burden of adverse events in A041202 was

reported by Ruppert et al by introducing an adverse event burden score (AE score) that measured the cumulative toxicity of all grades over time divided by the period of reporting.[8] Wile the AE score was higher in the bendamustine-rituximab group for the first 6 cycles, it was lower when comparing the entire duration of assessment. The SEQUOIA trial collected data on HRQoL which has not been reported. To date, it is not established that BTK inhibitors improve quality of life compared to standard chemoimmunotherapy regimens. Considering that, real world patients are older and less fit than clinical trial patients and thus more susceptible to side effects, long term adverse events such as hypertension or atrial fibrillation and daily side effects such as myalgia, diarrhea or rash are likely to have a greater impact, thus favoring limited duration therapy.

Thirds, the use of BTK inhibitors over chemoimmunotherapy, despite lack of improvement in overall survival or quality of life, may lead to treatment of patients that otherwise would not have received treatment. The preference for BTK inhibitors over chemoimmunotherapy is that oral regimens avoid intravenous infusions and patients may be more willing to start treatment. Treatment is indicated in CLL for active disease which is defined by the International Workshop on Chronic Lymphocytic Leukemia (iwCLL). Some indications are based on objective laboratory values such as anemia and thrombocytopenia. Other indications or subjective such as symptomatic splenomegaly or significant fatigue. With a lower bar for starting oral therapy, patients that previously would not have started treatment may start BTK inhibitors at an earlier stage of disease with borderline active disease or inactive disease with asymptomatic splenomegaly or lymphocytosis. Treatment of early stage CLL even in high-risk patients has not demonstrated survival benefit with either chemoimmunotherapy or BTK inhibitor.[9,10] Patients that start treatment with asymptomatic disease will experience toxicity without benefit.

The case for bendamustine-rituximab in previously untreated CLL is strongest for patient without 17p deletion and/or TP53 mutation. The clinical trials that established the role of BTK inhibitors in the first-line included patients with 17p del/TP53 mutations. Although not demonstrated in randomized clinical trials, if these high-risk patients derived an overall survival benefit, the remained patients may have a survival benefit with chemoimmunotherapy. The majority of CLL patients starting treatment are older individuals and clinical equipoise is needed when deciding first-line therapy.

Our analysis of the data suggests there is no strong basis to support the routine upfront use of BTK inhibitors over chemoimmunotherapy in the average CLL patient. Providers should be open to a frank discussion about the benefits, harms and uncertainties. Patients should not be deprived of the opportunity to receive limited duration therapy and avoid daily side effects without clear evidence of OS benefit. Future trials should include overall survival as the primary endpoint and have better reporting of quality-of-life metrics over meaningful durations of time to guide optimal clinical decisions.

AUTHOR CONTRIBUTIONS

Vinay Prasad contributed to conception and design of the work and provided critical revision. Myung Sun Kim wrote the article.

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All authors have no conflict of interest to disclose.

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