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Cross Fire: BTK Inhibitors Alone or in Combination are the Best Frontline Therapy for CLL

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Abstract

BTK (Bruton’s tyrosine kinase) inhibitors are highly effective front-line therapy for CLL (chronic lymphocytic leukemia) due to high response rates and prolonged progression-free survival, even in patients with high-risk disease features. They are also generally well tolerated, with the newer BTK inhibitors demonstrating better tolerability than ibrutinib while maintaining efficacy. Adverse effects such as bleeding or infections are usually manageable with supportive care or dose adjustments. Orally administered BTK inhibitors do not require intensive or inpatient monitoring and improve quality-of-life outcomes. Moreover, the established activity of venetoclax in the setting of BTK inhibitor failure is also reassuring as a salvage option. Nevertheless, the advantage of venetoclax as a time-limited treatment option is substantial, despite its inferior progression-free survival, since these patients can get another challenge with a reasonable chance of success. BTK inhibitors after venetoclax may be effective, but long-term data is limited. Given these reasons, BTK inhibitors remain the preferred treatment option as initial therapy for patients with CLL, especially those with del17p or TP53 mutations.

Keywords: Chronic lymphocytic leukemia, BTK inhibitors, bcl2 inhibitors

1. Introduction

Therapeutic advances in the management of patients with chronic lymphocytic leukemia (CLL) over the last decade have significantly improved clinical outcomes. Patients now experience prolonged disease-free intervals with generally well-tolerated agents. One of the major advances in the frontline treatment of CLL has been the development and approval of selective inhibitors of Bruton’s tyrosine kinase (BTK). BTK signaling is essential for B cell development and function. In addition, the inhibition of its downstream signaling has been shown to induce apoptosis in these cells. Ibrutinib was the first approved BTK inhibitor in CLL. Since then, more selective inhibitors of BTK have been developed such as acalabrutinib and zanubrutinib, which may help to alleviate some of the off-target side effects of ibrutinib [1]. These next-generation inhibitors also offer an additional therapeutic option for those patients who are unable to tolerate ibrutinib therapy. These therapeutics, either as a single agent or in combination with anti-CD20 monoclonal antibodies, have already demonstrated improved clinical outcomes as compared to historically utilized chemoimmunotherapeutic regimens. Similarly, the approval of bcl-2 antagonist, venetoclax, was based on promising activity and deep responses seen both as a single agent and in combination with anti-CD20 monoclonal antibodies. Moreover, combinations of BTK inhibitors and bcl-2 antagonists are being combined to further enhance the activity of these therapeutic approaches.

Despite the multitude of options available, the decision to initiate therapy is still dependent on progressive, symptomatic disease as defined by the International Workshop on Chronic Lymphocytic Leukemia (iwCLL) 2018 criteria [2]. Subgroups of patients with CLL who have worse prognoses include those with advanced age, multiple comorbid conditions, TP53 mutation and/or deletion, and those with unmutated immunoglobulin heavy chain.

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variable region gene (IgHV). Notably, patients with CLL who harbor mutations in TP53 or deletions of 17p (del(17p)) consistently experience a worse prognosis with shorter disease-free and overall survival, despite the use of novel therapies [3].

2. Why choose BTK inhibitors as the preferred frontline therapeutic option

2.1. Ibrutinib

Ibrutinib's approval for patients with treatment-naive CLL followed the results of the RESONATE-2 trial. The trial randomized patients aged 65 or older without del(17p) to continuous once daily oral ibrutinib vs. time-limited chlorambucil therapy. The trial demonstrated an 84% relative risk reduction in progression or death. This benefit of risk reduction seemed sustainable and with 7 years of follow up, nearly half of the patients on the ibrutinib arm remain on therapy. Progression free survival (PFS) benefit remains robust overall (61% for ibrutinib vs. 9% for chlorambucil) and across all subgroups studied, including those with high risk features (unmutated IgHV, del(11q)) [4]. Similarly, the iLLUMINATE trial compared the combination therapy of ibrutinib with the anti-CD20 monoclonal antibody, obinutuzumab, against chlorambucil with obinutuzumab in a group of patients over 65 years old or with comorbidities. Estimated PFS at 30 months was 79% in the ibrutinib arm vs. 31% in the chlorambucil arm. Although more serious adverse events were reported in the ibrutinib-containing arm, the number of fatalities (one in each arm) was the same [5].

The Alliance A041202 study compared chemo-immunotherapy (bendamustine plus rituximab) to ibrutinib, with or without rituximab in a similar, previously untreated, patient cohort aged 65 years or older. This trial demonstrated that the estimated 2-year PFS was significantly higher in the ibrutinib and ibrutinib plus rituximab arms (87% and 88%, respectively) than in the chemoimmunotherapy arm (74%). In addition, the chemoimmunotherapy arm had higher rates of grade 3−5 hematologic adverse events while ibrutinib-containing regimens had higher rates of grade 3−5 non-hematologic adverse events [6]. The complementary ECOG E1912 trial assessed standards of care for chemo-immunotherapy with fludarabine, cyclophosphamide, and rituximab (FCR) with ibrutinib-rituximab combination therapy in patients under the age of 70 years. The study reached its primary endpoint of a significantly higher 3-year PFS at a median follow up of 33 months of 89% in the ibrutinib-containing arm as compared with 73% in the FCR arm. In addition, there was also an increase in the overall survival at 3 years with 99% in the ibrutinib-containing arm compared with 92% in patients receiving standard of care. On subgroup analysis, this was most pronounced in patients with an unmutated IgHV with a 3-year PFS of 91% in the ibrutinib-containing arm compared with 63% in patients receiving standard of care [7].

These studies clearly establish the efficacy and utility of ibrutinib in the frontline setting. Furthermore, while toxicity is a concern, especially in the older age groups, aggressive intervention and management can afford patients a prolonged disease control state with chronic therapy. In addition, long-term data demonstrates durability of response and minimal discontinuation for adverse events beyond the initial 1−2 years of therapy [1].

2.2. Acalabrutinib

Similar to ibrutinib, acalabrutinib was the second in class molecule that received FDA approval for the management of CLL [8,9]. The important ELEVATE-TN trial evaluated acalabrutinib with or without obinutuzumab, against chlorambucil plus obinutuzumab in patients over 18 years of age with significant comorbid conditions [10]. The primary endpoint was PFS, which, at 24 months, was 93% in the acalabrutinib-obinutuzumab group and 87% in the acalabrutinib monotherapy group compared with 47% in the chlorambucil-obinutuzumab group. Long-term results with a median follow up of 47 months, demonstrated excellent durability of response. Moreover, patients with high-risk features of unmutated IgHV and del(17p) had median PFS of 22 months and 18 months in the chlorambucil-obinutuzumab arm, whereas median PFS was not reached in the acalabrutinib monotherapy and combination arms. The 4-year PFS was 87% and 78% for acalabrutinib with obinutuzumab and acalabrutinib monotherapy, respectively. While the study was not designed to evaluate the impact of the addition of a monoclonal antibody to BTK inhibitor, it did provide important evidence for the feasibility and benefit of this approach [10]. Importantly, acalabrutinib was also shown to be well tolerated in patients who were forced to discontinue ibrutinib because of adverse events [11], thus providing an alternate treatment option within the same class.

BTK inhibitors are now clearly recognized as an important therapeutic option for patients with CLL. Furthermore, BTK inhibitors have proven superior effectiveness when compared to conventional chemoimmunotherapeutic options. However, BTK
inhibitors have established durable efficacy with overall manageable toxicities especially with long-term use. An argument can still be made about the need to stop therapy and utilize time-limited therapeutic options. One such important option is the bcl-2 antagonist, venetoclax.

2.3. Venetoclax

The development of venetoclax has provided another extremely effective option for patients with CLL. While early development was marred by the incidence of tumor lysis syndrome (TLS), subsequent efforts using gradual dose ramp up with risk stratification and aggressive management has essentially eliminated the risk of clinical TLS for the vast majority of patients. It was initially utilized predominantly for the management of patients with disease relapse following treatment with BTK inhibitors and del(17p) disease and demonstrated impressive results [12]. However, the data for venetoclax as a frontline treatment of CLL is more recent, with a smaller number of large-scale trials demonstrating its effectiveness in combination. The CLL14 trial explored the role of venetoclax- obinutuzumab as upfront therapy for CLL in patients with comorbidities compared with chlorambucil-obinutuzumab. The primary endpoint of disease progression or death was reached with an estimated 24-month PFS of 88% in the venetoclax combination arm as compared with 64% in the chlorambucil combination arm. This benefit of increased PFS was seen in subgroups with TP53 mutation or deletion as well as those with unmutated IgHV [13]. However, one concern is that there was an elevated rate of fatal grade 5 adverse events in the venetoclax-obinutuzumab group occurring in 7.6% of patients vs. 3.8% in the chlorambucil-obinutuzumab group. Most of the adverse events occurred after the completion of therapy. These were generally infections or cardiac disorders, and the difference was not statistically significant. In addition, the estimated 4-year PFS was 74% in the venetoclax arm which was similar to long-term results with single-agent ibrutinib and/or acalabrutinib. In addition, the estimated 4-year PFS was inferior to the combination of BTK inhibitors with monoclonal antibodies in trials evaluating similar patient populations. Moreover, the 2-year PFS in patients with high-risk del(17p) was inadequate at 65%, despite the deep responses seen in the majority of patients treated with venetoclax. However, most patients who improve after initial treatment with venetoclax are shown to respond to repeat treatment with venetoclax albeit with inferior outcomes as compared with its initial use [14,15].

2.4. Combinations of BTK inhibitors and bcl-2 antagonists

BTK inhibitors have also been combined with venetoclax in an effort to utilize different classes of drugs to enhance response depth and duration, and to allow for time-limited therapy. The CAPTIVATE trial was a multi-center phase II trial assessing the ability of time-limited ibrutinib followed by venetoclax to achieve deep remissions in upfront CLL. Patients achieved undetectable Minimal Residual Disease (uMRD) at increasingly higher rates with additional cycles of ibrutinib: 57% after 6 months, 68% after 9 months, and 73% after 12 months. One of the benefits of ibrutinib lead-in therapy compared to venetoclax in these patients is a lower risk of laboratory TLS. Two-year PFS was 95% for all patients and 84% in patients with del(17p) [16]. The GLOW study utilized a similar combination of venetoclax with ibrutinib and demonstrated a 2-year PFS of 96% in patients without del(17p) [17].

3. Conclusion

BTK inhibitors have been established as the leading therapeutic option for frontline treatment for patients with CLL. The benefits of BTK inhibitor therapies are particularly salient for patients at risk of TLS due to heavy disease burden, patients with del(17p), and those who prefer to avoid intensive inpatient or outpatient monitoring with treatment initiation. In addition, the overall impressive, sustained disease control and manageable toxicity, especially with the use of acalabrutinib, make a compelling argument for their use. Furthermore, data from comparable patient cohorts suggest a better PFS with the use of BTK inhibitors as compared to venetoclax (Table 1). Nevertheless, an argument can be made that retreatment with venetoclax in an on-off manner might result in similar outcomes.
long-term outcomes. Moreover, venetoclax has established activity in patients failing BTK inhibitors and that can be reassuring for patients and clinicians as a salvage option.

In order to minimize the risk of adverse events in patients that will receive BTK inhibitors, care providers should evaluate patients’ medication lists for potential drug interactions that could lead to toxic accumulation. The care providers should attempt to modify unnecessary therapies that may put patients at risk for bleeding. Moreover, the care providers should monitor cardiovascular function and the development of infectious symptoms.

Sustained novel biomarker identification will continue to clarify the ideal patient populations for these targeted therapies and lead to continued improvement in patient outcomes. The eventual utilization of these agents will depend on patient and physician preference, comorbid conditions, and resource availability.

Conflict of interest

TS has no disclosures. FTA has provided consultancy to: Genentech, Astrazeneca, Abbvie, Janssen, Pharmacyclics, Gilead sciences, Kite pharma, Celgene, Karyopharm, MEI Pharma, Verastem, Incyte, Beigene, Johnson and Johnson, Dava Oncology, BMS, Merck, Cardinal Health, ADCT therapeutics, Epizyme, Caribou Biosciences, Cellecter Biosciences, Luxo Oncology, Adaptive Biotechnologies, Genmab, and received research funding from Pharmacyclics.

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