Venetoclax Based Treatments As Frontline Therapy For Chronic Lymphocytic Leukemia

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Venetoclax-based Treatment as Frontline Therapy for Chronic Lymphocytic Leukemia

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Abstract

The availability of novel targeted agents has revolutionized the management of chronic lymphocytic leukemia (CLL). Both B-cell lymphoma 2 (BCL2) and Bruton tyrosine kinase (BTK) inhibitors are highly effective agents for CLL treatment. Several clinical trials have demonstrated the efficacy and safety of these agents in the management of newly diagnosed and relapsed/refractory CLL. This has led to two broad approaches in the frontline management of CLL, namely venetoclax-based time-limited therapy versus BTK inhibitor-based continuous therapy. In this review, we discussed why we consider venetoclax-based therapy as a suitable frontline option for patients with CLL.

Keywords: Venetoclax, leukemia, lymphocytic, chronic

1. Introduction

The management of chronic lymphocytic leukemia (CLL) has significantly changed over the last decade with the availability of novel agents. Both B-cell lymphoma 2 (BCL2) and Bruton tyrosine kinase (BTK) inhibitors are highly effective for CLL treatment [1, 2]. Venetoclax is an oral BH3-mimetic drug that blocks the BCL-2 pathway linked to the survival of CLL cells and induces apoptosis [3]. As a single agent, venetoclax was initially studied in patients with relapsed/refractory CLL [4]. Subsequently, the combination of venetoclax and rituximab was compared against that of bendamustine and rituximab in the MURANO study, and the results indicated a significantly high progression-free survival with venetoclax-rituximab in patients with relapsed/refractory CLL [5].

The combination of venetoclax and obinutuzumab was studied in CLL-14 trial for the frontline management of patients with CLL [6]. This study included 432 patients with previously untreated CLL who had a cumulative illness rating score (CIRS) of greater than 6 or creatinine clearance of less than 70 ml/min and were randomized to receive venetoclax-obinutuzumab versus chlorambucil-obinutuzumab. The median age of the patients was 72 years with 13.8% having TP53 deletion and/or mutation and 59.8% with unmutated IGHV. The progression-free survival at 24 months was significantly higher with venetoclax-obinutuzumab than with chlorambucil-obinutuzumab (88.2% vs. 64.1%). Notably, venetoclax-obinutuzumab also resulted in higher rates of complete remission (49.5% vs. 23.1%) and minimal residual disease (MRD) negativity (75.5% vs. 35.2% in peripheral blood and 56.9% vs. 17.1% in bone marrow) compared with those of chlorambucil-obinutuzumab. The side-effect profile was manageable with common events being neutropenia (grade 3–4, 52.8%), febrile neutropenia (5.2%), infections (grade 3–4, 17.5%), and infusion reactions (9%). This study established venetoclax-obinutuzumab as a fixed duration therapy for frontline management of patients with CLL.

In this review, we will discuss why we consider venetoclax based therapy the best frontline therapy for patients with CLL. Of note, there have been no head-to-head trials comparing venetoclax based therapy to BTK inhibitors and the data discussed below will be an extrapolation from non-comparative studies.
2. Advantages with efficacy

Venetoclax-based first-line therapy is associated with high efficacy in patients with CLL. While the overall response rates remain high with both BTK inhibitors and venetoclax-based frontline therapy, the rates of complete remission are much higher with venetoclax-based therapy than with BTK inhibitors. As discussed earlier, nearly half of the patients treated with venetoclax-based therapy achieve complete remission at the end of the treatment [6]. In contrast, the rates of complete remission with BTK inhibitors are generally less than 10–30% [7–9]. MRD negativity has been demonstrated as a strong predictor of long-term outcomes in patients with CLL [10]. In this regard, venetoclax-based frontline therapy is associated with a high MRD negativity rate. Data from CLL-14 trial showed that nearly 75.5% achieved MRD negativity in peripheral blood 3 months after the completion of therapy, and most of this MRD negativity was also seen after cycle six of therapy [11,12]. Upon further follow-up, the rates of MRD negativity remained significantly high in patients treated with venetoclax [12]. In contrast, the therapy with BTK inhibitors as monotherapy produced very low rates of MRD negativity. The progression-free survival after a long follow-up was also significantly high with venetoclax-based therapy (74% at 4 years). This compares similarly to the rates of progression-free survival with ibrutinib therapy [7]. However, the time-limited nature of treatment and superior efficacy of venetoclax-based therapy offers better advantages to patients.

3. High-risk subgroups

Venetoclax-based therapy showed responses in patients with high-risk features such as deletion 17p, TP53 mutation, complex karyotype, or unmutated IGHV. In the CLL-14 trial, the distribution of genomic features at baseline included deletion 17p (7%), deletion 11q (18%), complex karyotype (17%), unmutated IGHV (60%), ATM (13%) and TP53 (10%) [13]. The progression-free survival was noted to be significantly high with venetoclax-based therapy, and none of the high-risk abnormalities such as deletion 17p, deletion 11q, mutated TP53, ATM, and BIRC3 reduced response rates with venetoclax-obi-nutuzumab. However, the presence of deletion 17p and mutated TP53 were the only abnormalities with an effect on progression-free survival (HR, 4.4 [P < 0.01]; HR, 3.1 [P < 0.01], respectively). In patients with complex karyotypes, venetoclax-obi-nutuzumab was associated with high responses (with or without complex karyotype—overall response of 82.4% and 87.3%, complete response of 50.0% and 51.8%, respectively) with no impact of complex karyotype on the progression-free survival [14]. However, an adverse impact of complex karyotype was previously noted with ibrutinib therapy [15]. While a continuous BTK inhibitor therapy is often considered for patients with deletion 17p/TP53 mutation to minimize the risk of relapse and progression, the right approach in this patient population remains unclear due to the lack of prospective comparative studies that address the question of time-limited versus continuous therapy in patients with high-risk features. Additionally, evidence suggests that patients with deletion 17p who were not included in the original landmark clinical trial had inferior survival with frontline ibrutinib therapy [16]. Nevertheless, venetoclax therapy still offers the advantage of completing treatment in one year in patients with high-risk features, especially if they achieve MRD negativity at the end of therapy.

4. Advantages with safety

From a safety standpoint, the adverse events associated with venetoclax-based therapy are viewed favorably as compared with that of BTK inhibitor therapy. While toxicity is the most common reason for discontinuation of ibrutinib therapy, patients on venetoclax therapy are mostly able to stay on the therapy [17–19]. Importantly, the limited duration of treatment with venetoclax provides a platform for the temporary nature of most adverse events as compared with that of continuous therapy with BTK inhibitors, which can lead to long-term side effects. The most common adverse event noted with venetoclax therapy is cytopenia, particularly neutropenia. The incidence of grade 3–4 neutropenia was nearly 50% in the CLL-14 trial. However, this is manageable with growth factor support and often improves after dose modification or interruption of therapy in case of recurrent or prolonged cytopenia. Although the risk of tumor lysis syndrome is a possibility with venetoclax, initial therapy with obinutuzumab significantly reduces this risk in most patients. In addition, the weekly dose ramp-up of venetoclax also lowers the risk of developing tumor lysis syndrome. In the CLL-14 study, only three patients indicated lab evidence of TLS with no clinical TLS. In contrast, long-term BTK inhibitor therapy is associated with significantly high risk of adverse events such as hypertension, atrial fibrillation, and bleeding, and studies indicate that adverse events are the most common cause of treatment discontinuation with ibrutinib [17–19].
While the incidence of these adverse events is relatively low with acalabrutinib, the risk of hypertension, atrial fibrillation, and bleeding are present with this agent. Hence, venetoclax-based initial therapy offers greater advantages to patients in terms of safety, with no long-term adverse events.

5. Advantages with quality of life

Health-related quality of life is an important consideration in patients with CLL given the prolonged natural history of the disease and ability of symptoms to significantly affect the patient's well-being and quality of life. In the CLL-14 study, patient-reported outcomes suggest that the baseline levels of physical and role functioning were maintained throughout the treatment and follow-up [20]. Moreover, venetoclax-treated patients experienced meaningful improvement in the quality of life during treatment and follow-up by at least eight points in cycle three. In contrast, those improvements were much delayed in patients treated with chlorambucil therapy. While improvement in the health-related quality of life was also demonstrated with BTK inhibitors [7], the need for long-term therapy and risk of side-effects could add considerable anxiety to patients. While it is currently unclear whether venetoclax-based therapy cures patients with CLL, the advantage of limited-duration treatment with venetoclax as first-line therapy provides a subjective sense of relief to patients as they still have the opportunity of stopping treatment at some point in time and potentially experience reasonable duration of remission while off therapy.

6. Advantages with cost of therapy

Given the chronic nature of CLL, the economic burden in terms of patient-per-month cost with systemic therapy is estimated to be approximately $17,442 [21]. Similarly, due to longer and continuous duration of therapy, the cost associated with BTK inhibitors is also high over time [22]. In contrast, time-limited therapy with venetoclax costs lesser over time. A study by Cho Sk et al. analyzed this aspect in a modeling design where the budget impact of fixed duration of venetoclax-obinutuzumab treatment was compared against that ofibrutinib-based therapy or chemoimmunotherapy in patients with CLL [23]. The costs analyzed included those for therapy, adverse events, routine care, and monitoring. They found that venetoclax-obinutuzumab as first-line therapy resulted in cost savings of $1,550,663, and the cumulative difference in 3-year costs favored venetoclax-obinutuzumab (versus ibrutinib: $300,942, ibrutinib-obinutuzumab: $367,001, and ibrutinib-rituximab: $369,784). Hence, time-limited therapy with venetoclax-obinutuzumab results in significant cost savings as compared with that of continuous BTK inhibitor-based therapy.

7. Future directions

While the current argument focuses on venetoclax-based therapy versus BTK inhibitors as first-line treatment options for patients with CLL, it is important to note that both venetoclax and BTK inhibitors are very effective options. A summary of efficacy from studies with venetoclax-based novel frontline combination therapy is summarized in Table 1. However, the real question in future would be the choice between fixed-duration versus continuous therapy. BTK inhibitors produce durable overall response when given as continuous agents. However, they are associated with lower rates of complete remission, compared with that of venetoclax, and the need for long-term continuous therapy.

<table>
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<tr>
<th>Study</th>
<th>Regimen</th>
<th>Key outcomes</th>
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| Fischer et al. [6] (CLL-14) | Venetoclax-obinutuzumab | PFS: 88.1% at 24 months  
CR: 49.5%  
MRD negativity: 75.5% (PB), 56.9% (BM) (3-months post treatment) |
| Jain et al. [26] | Ibrutinib-venetoclax | PFS: 93% at 3 years  
CR/CRi: 69% at 24 cycles  
MRD negativity: 66% (BM) (cycle 24)  
DFS: 95% (1 year)  
CR/CRi: 46% |
| Weirda et al. [25] (Captivate study) | Ibrutinib-venetoclax | MRD negativity: 75% (PB), 68% (BM) (12 cycles)  
CR: 46% |
| Davids et al. [28] | Acalabrutinib-venetoclax-obinutuzumab | MRD negativity: 92% (PB), 86% (BM) |
| Soumerai et al. [27] | Zanubrutinib-venetoclax-obinutuzumab | MRD negativity: 89% (PB and BM) with 25.8 months median follow-up |

PFS = progression-free survival; DFS = disease-free survival; MRD = minimal residual disease; CR = complete remission; PB = peripheral blood; BM = bone marrow.
therapy. In contrast, venetoclax-based treatment leads to high rates of complete remission and gives an opportunity to stop the therapy after a finite period. Currently, clinical trials are focusing on combining BCL2-inhibitors with BTK-inhibitors to identify whether this combination would lead to high response rate in a fixed duration. The additional benefit of this combination strategy would be a fully oral treatment regimen without and logistical issues associated with obinutuzumab. For example, recent updates from the ibrutinib–venetoclax studies show high rates of complete remission and MRD negativity at the end of therapy [24,25]. In addition, the role of adding obinutuzumab to ibrutinib and venetoclax is being evaluated in larger clinical trials [NCT03701282- ECOG 9161 (Ibrutinib-obinutuzumab vs. obinutuzumab-ibrutinib-venetoclax in younger patients), NCT03737981- Alliance 041702 (Ibrutinib-obinutuzumab vs. obinutuzumab-ibrutinib-venetoclax in older adults), NCT04608318- CLL17 (Ibrutinib vs. venetoclax-obinutuzumab vs. ibrutinib-venetoclax)]. A list of ongoing clinical trials investigating venetoclax-based frontline therapy is also summarized in Table 2. Hence, the optimal combination strategy for frontline therapy and duration of treatment are currently being explored.

8. Conclusions

The treatment landscape for CLL has significantly changed with the availability of novel agents that target BCL-2 and BTK pathways (Fig. 1). BCL-2-targeted therapies such as venetoclax in combination with obinutuzumab can produce high rates of complete remission with a manageable side-effect profile and offer the ability to provide fixed-duration treatment. This leads to cost savings and improved acceptance of such therapies from patient perspective. In contrast, BTK inhibitor-based therapies have lower rates of complete remission, and continuous long-term therapies could lead to toxicity and financial burdens. Hence, venetoclax-based frontline therapy for CLL offers more advantages as a potent regimen. In future, to know whether the choice for the initial management of CLL should be time-limited
therapy or continuous long-term therapy is important as current clinical trials are testing the combination of upfront BTK inhibitor and BCL2 inhibitor, which is likely be a standard of care in future.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnesp.2022.09.004.

References: