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Leukemia (PH Wiernik, Section Editor)

BCL-2 Inhibition as Treatment for Chronic Lymphocytic Leukemia

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Opinion statement

At the end of the 1990s, with the advent of imatinib for chronic myeloid leukemia and rituximab for B cell lymphoproliferative diseases with CD20 expression, there was a great conceptual evolution in the treatment of onco-hematological diseases. Researchers from around the world and the pharmaceutical industry began to focus their efforts on the so-called target therapy used alone or associated with classic chemotherapeutic drugs. In chronic lymphocytic leukemia, the development of second-generation anti-CD20 antibodies, biosimilars, PI3K (phosphatidylinositol 3-kinases) inhibitors, BTK (Bruton's tyrosine kinase) inhibitors, and anti-bcl 2 drugs represented mainly by venetoclax brought new, broader, and more effective opportunities in the treatment of this disease. This breakthrough occurred mainly regarding patients with alteration in 17p or mutation of the p53 gene for whom selecting the new drugs that act on B cell signaling (BTK and PI3K inhibitors) in the first line is mandatory. In fit patients with immunoglobulin heavy chain mutation, it is still acceptable to use the chemotherapy regimen with fludarabine, cyclophosphamide, and rituximab (FCR) and, in those who do not fit or are not IgVH-mutated, bendamustine-rituximab regimen. However, the first-line use of ibrutinib or venetoclax associated with immunotherapy within the concepts of infinite (ibrutinib) or finite (venetoclax) treatment has been increasingly used. In the second line, venetoclax, ibrutinib, and idelalisib have become the preferred treatments. I believe that a process of instruction and decision shared with patients considering the risks–benefits–cost and

access to treatments should guide the choices within these concepts. Another fundamental aspect to discuss is the objective of the treatment for chronic lymphocytic leukemia (CLL) for a specific patient: the increase progression-free survival and overall survival and/or the achievement of minimal residual disease. CLL is the most common leukemia in adults with a median age at diagnosis of 72 years. The clinical course is heterogeneous, and outcomes are influenced by individual clinical presentation and disease biology. Molecular and genomic factors, including fluorescence in situ hybridization (FISH) testing, karyotype, and immunoglobulin heavy chain variable region gene (IGHV) mutational status, are important to treatment decisions and to predict the clinical course. However, despite disease biology, the presence of active disease is the most important criteria to initiate treatment. In the past decade, target therapies that inhibit B cell receptor signaling pathways and, more recently, BCL2 antagonists have emerged as a new treatment paradigm: chemo-free with fixed duration therapy. Bruton's tyrosine kinase inhibitors (BTK) are a class of oral medications approved for frontline and relapsed disease, effective for achieving lasting response and disease control with a good safety profile. BTK inhibitors are an attractive option for high-risk patients who are not candidates for an intensive regimen. However, it is a continuous therapy, and drug resistance or severe adverse events could lead to treatment suspension. BCL2 antagonists are an attractive alternative to BTK inhibitors. Anti-apoptotic BCL2 is associated with tumor genesis and chemotherapy resistance. The BCl2, an anti-apoptotic protein located in the mitochondrial membrane, is a major contributor to the pathogenesis of lymphoid malignancies and is overexpressed in CLL cells promoting clonal cell survival. Venetoclax is a potent and selective member of the BH3 mimetic drugs and a physiologic antagonist of BCL2. Venetoclax has demonstrated quick and durable responses in naïve and relapsed or refractory CLL (r/r CLL) patients, including high-risk patients. Furthermore, it has shown deeper responses, achieving a higher incidence of negative minimal residual disease (MRD) with a fixed duration therapy. In the past decade, there was a remarkable progress in CLL treatment. However, neither of the new target therapies is considered curative or free of toxicity. This article will focus on the treatment approach of CLL patients with BCl2 antagonists. Treatment strategy (combined versus monotherapy; continuous versus limited duration therapy), toxicity profile, and future directions will be exposed in this review.

Introduction

Chronic lymphocytic leukemia (CLL) is the most common leukemia in adults with a median age at diagnosis of 72 years [1]. Clinical presentation is heterogeneous, and outcomes are influenced by both individual clinical factors and disease biology. Molecular and genomic factors, including cytogenetic findings and IGHV mutational status, are important when choosing treatment and assessing prognosis [2, 3]. In recent years, the inhibition of the B cell receptor pathway and, more recently, the inhibition of the BCL-2 protein have emerged as new treatments for CLL.

Bruton's tyrosine kinase inhibitors (BTK) have now been approved for both frontline and relapsed CLL patients. It has shown to be effective on longer follow-up with a good safety profile. BTK inhibitors are now considered the standard of care for patients not eligible for fludarabine-based therapy, including patients with comorbidities and high-risk molecular findings [4]. However, as continuous treatment, there is concern about long-term toxicities, including financial toxicity.

BCL-2 inhibitors are also approved for the treatment of newly diagnosed and relapsed CLL. The anti-apoptotic BCL-2 protein is overexpressed in CLL and

other hematological malignancies, promoting disease resistance and clonal cell survival [5]. Venetoclax, a potent and selective BH3-mimetic, has demonstrated fast, deep, and durable responses in treatment-naïve and relapsed/refractory CLL patients including high-risk patients [6, 7]. Moreover, achieving deep responses, even among patients with undetectable minimal residual disease, enabled venetoclax to be tested as a fixed duration therapy [7].

Overview of the BCL2 antagonists: mechanism of action, pharmacokinetics, safety profile, and cost

Mechanism of action

The BCL-2 family comprises both pro-apoptotic and anti-apoptotic members. The anti-apoptotic subfamily includes the proteins BCL-2, BCL-XL, BCL-w, BCL-2-related protein A1 (Bfl-1/A1), myeloid cell leukemia 1 (MCL-1), and BCLB/Boo. The pro-apoptotic family includes the multi-domain pro-apoptotic "effectors" (BAK and BAX) and the "BH3-only proteins" (BAD, BID, BIK, BIM, BMF, HRK, PUMA, and NOXA). By binding and sequestration of active forms of BAK and BAX, the anti-apoptotic members of the BCL-2 family prevent mitochondrial outer membrane permeabilization (MOMP), a crucial step in the apoptosis intrinsic pathway. MOMP allows the release of proteins, including caspases in the cytosol, leading to cell death. The direct sequestration of BH3-only proteins by the BCL-2 family is also important since BH3-only proteins can initiate apoptosis by inhibiting the anti-apoptotic BCL-2 family members or by directly activating pro-apoptotic family proteins [8].

The first-in-class BCL-2 inhibitor, ABT-737, showed in vitro cytotoxicity in lymphoid malignancies cell lines [9] and multiple myeloma [10] and acute myeloid leukemia [11] cell lines. However, due to low aqueous solubility and low bioavailability, the clinical development of ABT-737 was abandoned. The second-generation navitoclax (ABT-263) showed superior bioavailability and was the first BCL-2 inhibitor tested in clinical trials [12]. Like its predecessor, navitoclax showed high affinity and inhibition of BCL-2, BCL-XL, and BCL-w. Based on promising results in vitro, a phase 1 trial enrolling patients with R/R lymphoid malignancies showed responses in different tumor histologies, including CLL. However, the clinical use of navitoclax was restrained by thrombocytopenia related to the inhibition of BCL-XL [13].

Using reverse engineering, venetoclax, a selective and potent inhibitor of BCL-2, was developed. Venetoclax is able to bind and neutralize BCL-2 with a subnanomolar affinity (Ki < 0.010nM) and interacts weakly with BCL-XL and BCL-W, keeping its anti-tumor activity with little effect on platelet survival. In vitro studies showed activity against a variety of cell lines, including acute lymphoblastic leukemia (ALL), non-Hodgkin's lymphoma, and acute myeloid leukemia. Interestingly, venetoclax-induced cytotoxicity was different between cell lines from different diseases. In ALL, for example, activity against most xenografts required simultaneous inhibition of BCL-2 and BCL-XL, and a strong correlation between poor venetoclax response and expression of BCL-XL was observed. In contrast, in CLL, BCL-2 inhibition alone was able to induce cytotoxicity [14].

Pharmacokinetics

Venetoclax is a once-daily oral medication with hepatic metabolism and a half-life elimination between 14 and 18 h. Based on a phase 1 study in 116 patients with relapsed or refractory CLL, the dose of 400 mg per day was selected. The initial three patients received single doses of 200 mg followed by a 72-h washout period and subsequent daily doses. Unfortunately, all three patients developed tumor lysis syndrome (TLS). This finding led to a protocol change to include a ramp-up period. In the expansion cohort, patients received weekly dose increases from 20, 50, 100, 200, and finally the targeted dose of 400 mg. Combined with other TLS prophylaxis such as allopurinol and hydration, no patients showed clinical TLS [5, 13].

A pharmacokinetic analysis combining 116 patients from the phase 1 r/r CLL study and 106 patients with NH [5, 15] demonstrated that the peak venetoclax concentrations were observed 5–8 h post-dose and a terminal half-life of 14–18 h. Food increased the bioavailability of venetoclax and was dependent on the fat content of the meal. When administered with food, the maximum concentrations were observed approximately 2 h later and were higher than when given during fast. Based on these data, venetoclax is recommended to be administered during meals [15].

Venetoclax is a substrate for both CYP3A4 and P-glycoproteins (p-gp), and p-gp inhibitors, such as rifampin, can influence venetoclax levels [16]. In a study with healthy females, a 78% higher area under the curve (AUC) was observed after a single dose of rifampin because of an acute inhibition of p-gp. Within the same trial, a 71% lower venetoclax AUC was observed after multiple doses of rifampin due to induction of CYP3A with multiple doses [17].

Clinical development of venetoclax in CLL

Relapsed/refractory CLL

Venetoclax was initially tested in a phase 1, open-label, multicenter dose-escalation trial in 116 patients with R/R CLL. The median age of patients was 66 years, and patients were highly pretreated, with a median of 3 previous lines of therapy. Moreover, 89% of patients presented with high-risk R/R CLL, defined as the presence of del17p, unmutated IGHV, and resistance to fludarabine. In this trial, an overall response rate (ORR) of 79% was observed, including 20% complete responses (CR), CR with incomplete marrow recovery (CRi), and 5% of MRD negativity. The estimated 2-year overall survival for all patients was 84% [13]. Moreover, a high response rate in patients with deletion 17p (82% in the expansion cohort) led to the development of a phase 2 trial in this specific population.

In this phase 2 trial, with 107 patients with R/R CLL harboring del17p, the median age was 67 years, and patients had a median of 2 prior lines of therapy, including 3% of patients receiving ibrutinib. The ORR was 79%, with 8% of patients achieving CR/CRi. Of 85 responding patients, MRD negativity was observed in the peripheral blood in 18 and in the bone marrow in 6 patients. These findings led to the approval of venetoclax by the Food and Drug Administration (FDA) in patients with R/R CLL [5, 18].

The addition of anti-CD20 monoclonal antibody rituximab to venetoclax was initially tested in a phase 1b clinical trial for r/r CLL. In this trial, 49 patients

with R/R CLL were enrolled, with a median age of 68 years and a median of 2 prior lines. ORR was 86%, and 51% of patients achieved CR, leading to a 2-year PFS of 82%. Moreover, rituximab's addition led to a higher percentage of MRD negativity, including 80% of marrow negativity in complete responders and 57% in all patients. Interestingly, this phase 1b study showed durable responses in patients who stopped therapy, including 11 patients with MRD negativity [19]. The concept of a finite therapy with venetoclax was established, leading to the phase 3 MURANO trial.

The MURANO trial was an international, randomized, open-label, phase 3 trial evaluating a 2-year fixed duration venetoclax in combination with rituximab compared with bendamustine with rituximab in patients with R/R CLL, with investigator-assessed PFS as the primary outcome. A total of 389 patients were enrolled. The median follow-up was 23.8 months. There was a clear benefit from the venetoclax-based therapy, including a superior ORR (92.3% versus 72.3%) and a superior PFS, with a 2-year PFS of 84.9% versus 36.3%. The benefit was observed across all subgroups, including patients with del17p. With a median follow-up of 4 years, the superiority of venetoclax plus rituximab over BR was sustained and particularly durable in patients who achieved uMRD [6, 20]. In conclusion, a fixed duration therapy combining venetoclax with rituximab showed durable and deep responses in patients with R/R CLL and is now considered the standard of care in this population.

Treatment-naïve CLL

The phase 3 CLL 14 trial evaluated venetoclax and obinutuzumab as a 1-year fixed duration therapy compared with chlorambucil and obinutuzumab in 432 previously untreated CLL patients with cumulative illness rating scale (CIRS) total score > 6 and/or creatinine clearance < 70ml/min, including patients with high-risk genomic features (del17p or *TP53* mutation). Patients were randomized to receive either 6 cycles of chlorambucil plus obinutuzumab plus 6 cycles of chlorambucil or 6 cycles of venetoclax plus obinutuzumab plus 6 cycles of venetoclax. With a median follow-up of 28.1 months, the estimated 2-year PFS was 88.2% compared with 64.1% in the chlorambucil arm, although no overall survival difference was observed in both arms. Furthermore, deep remissions with higher rates of uMRD were seen in patients in the venetoclax arm. Peripheral blood MRD negativity was superior in the venetoclax–obinutuzumab group (75.5% vs. 35.2%, $P < 0.001$) and in the bone marrow (56.9% vs. 17.1%) [7].

These findings have been updated recently, with a 40-month follow-up: the combination of venetoclax–obinutuzumab continued to show superiority over chlorambucil-obinutuzumab, with a 3-year PFS of 81.9% versus 49.5%. Moreover, CLL-14 has rehabilitated MRD as a surrogate endpoint, and critical information has been shown in clonal dynamics of patients off therapy [21]. Based on the results, both the European Medicines Agency and the US FDA have approved venetoclax–obinutuzumab in the first-line treatment of CLL.

Toxicity

Serious adverse events have been observed in patients treated with venetoclax, and TLS remains the most important and life-threatening event. However,

protocol changes, including a 5-week ramp-up, associated with TLS risk stratification and prophylaxis, have mitigated the risk of clinical TLS. However, caution should be taken in patients with high tumor burden and patients with renal insufficiency [13, 22].

Hematological toxicities, including neutropenia, anemia, and thrombocytopenia, can be observed in patients treated with venetoclax. Neutropenia is the most common hematological toxicity, and grade 3–4 neutropenia has been observed in 40% of patients receiving venetoclax monotherapy [18, 23] and up to 60% when venetoclax is combined with an anti-CD20 monoclonal antibody [24, 25]. Despite the high rate of neutropenia, febrile neutropenia and opportunistic infections are unusual complications [18, 25]. The rates of all grade infections associated with venetoclax appear consistent with rates seen in CLL patients with relapsed and refractory disease [26]. Anemia and thrombocytopenia also can occur in 25% and 20%, respectively, as described in a phase 2 study [24].

The most frequent nonhematological toxicities include nausea, diarrhea, and fatigue. In most cases, these adverse events are mild and do not lead to venetoclax discontinuation [27].

Costs

The recent approval of new oral drugs for CLL treatment has dramatically improved the treatment landscape of CLL patients but substantially increased the cost compared to former chemoimmunotherapy. The estimated cost of chemotherapy protocols in the USA, including bendamustine-rituximab, fludarabine and rituximab, and chlorambucil plus rituximab, ranges from $57,000 to $101,000 per patient. As a comparison, ibrutinib annual cost may reach $169,000, and patients tend to stay on treatment for a few years [28, 29].

The need for a chemotherapy-free, finite therapy is also important regarding cost. Venetoclax plus obinutuzumab, in a 12-month fixed therapy, costs around $181,000 [30]. Despite the high cost of therapy, most patients will be off therapy for few years before progression and need for a new treatment.

The addition of venetoclax plus obinutuzumab for first-line CLL was estimated in a 3-year analysis of the total budget impact considering drug cost protocol, adverse event management, drug administration, and PFS/OS, and cost savings were observed in 3-year time with venetoclax plus obinutuzumab protocol [30].

Future directions

Venetoclax has dramatically changed the treatment of CLL patients, especially by showing that a chemotherapy-free treatment can have a fixed duration, in opposite to BTK inhibitors. Venetoclax, in combination with anti-CD20 monoclonal antibodies, was capable of inducing a high rate of MRD negativity, allowing patients to be off therapy for longer periods [20]. Moreover, venetoclax treatment has shown an excellent safety profile when TLS prophylaxis measures are taken [22].

Venetoclax has shown in vitro synergy with different drug classes, and the combination of venetoclax with BTK inhibitors is now being tested in clinical

trials. In the R/R setting, CLARITY is a phase 2 trial combining venetoclax and ibrutinib and has shown promising results: ORR of 89%, with 51% achieving complete responses, including 53% and 36% MRD negativity in the peripheral blood and bone marrow, respectively. In a follow-up of 21.1 months, only one patient has progressed, and all patients are alive. Frontline therapy combining venetoclax and ibrutinib has also shown promising results [31]. In the phase 2 CAPTIVATE study, 164 patients with CLL were enrolled, and results are unprecedented, with 30-month PFS > 95% in all randomized trials [32].

Finally, trials comparing venetoclax-based therapy with standard of care regimens are ongoing. CLL17 trial compares continuous treatment with ibrutinib with fixed duration treatment with venetoclax and obinutuzumab or ibrutinib and venetoclax (NCT03701282). Another trial investigating FCR vs ibrutinib plus venetoclax versus ibrutinib and rituximab (ISRCTN01844152) is ongoing.

Declarations

Conflict of interest

None of the authors has any potential conflicts of interest to disclose.

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