Current Hematologic Malignancy Reports (2019) 14:469–476
https://doi.org/10.1007/s11899-019-00539-3

CHRONIC LYMPHOCYTIC LEUKEMIAS (N JAIN, SECTION EDITOR)

Venetoclax for the Treatment of Chronic Lymphocytic Leukemia

Herbert Eradat [1]

Published online: 11 September 2019

Abstract

Purpose of this Review This review summarizes the role of BCL-2 in the pathogenesis of CLL, and the clinical data evaluating safety and efficacy of venetoclax, in treatment of patients with CLL, in the context of other available targeted agents.

Recent Findings Venetoclax, alone or in combination with other targeted agents results in high rate of durable responses and undetectable measurable residual disease. Venetoclax maintains activity across all clinical and biologic subgroups, including those with high risk disease, including CLL with chromosome 17p deletion. TLS risk can be mitigated with risk stratification and five-week administration ramp-up schedule.

Summary Venetoclax, a novel, orally bioavailable inhibitor of BCL-2 has demonstrated substantial clinical activity in the treatment of CLL. In combination with other targeted agents it can induce high disease response rates and potentially lead to MRD-negative durable remissions.

Keywords CLL · Venetoclax · BCL-2

Abbreviations

BTK	Bruton's tyrosine kinase
CLL	Chronic lymphocytic leukemia
OS	Overall survival
PR	Partial remission
PD	Progressive disease
PFS	Progression free survival
R/R	Relapsed or refractory
IRC	Independent review committee
MRD	Minimal residual disease
PI3K	Phosphatidylinositol-3 kinase
IgVH	Immunoglobulin heavy chain variable region
TLS	Tumor lysis syndrome

Introduction

Evasion of apoptosis is a hallmark of many B cell malignancies. Overexpression of BCL-2 is one of the main mechanisms of this evasion of apoptosis, and is one of the key mechanisms of pathogenesis of chronic lymphocytic leukemia [1–4].

Chronic lymphocytic leukemia is the most common adult leukemia in Western countries. Annually, more than 20,000 new patients are diagnosed in the USA. Most patients are older than the age of 65 and the median age that diagnosis is 71 [5, 6].

The clinical course of patients with CLL is extremely heterogeneous and variable. Some patients have a very indolent course and may never require treatment for their disease while others have more aggressive disease requiring repeated course of therapy and ultimately relatively poor prognosis [7, 8].

A number of prognostic markers have been developed to better understand the pathophysiology of the disease and to better predict prognosis and response to therapy. Patients that have disease characterized by an un-mutated immunoglobulin heavy chain variable (IgVH) region have a more aggressive disease in comparison to those with mutated IgVH, leading to shortened survival after chemoimmunotherapy [9, 10]. CLL characterized by defective p53 function, via *TP53* mutation or deletion of 17p is generally rapidly progressive, and has a substantially lower response rate to conventional chemoimmunotherapy and novel, targeted therapies, and generally carries a poor prognosis [11].

The introduction of novel, targeted treatments, including inhibitors of Bruton's tyrosine kinase (BTK) and phosphatidylinositol-3 kinase (PI3K), have substantially changed the landscape of therapeutic options available for

This article is part of the Topical Collection on *Chronic Lymphocytic Leukemias*

✉ Herbert Eradat
HEradat@mednet.ucla.edu

[1] David Geffen School of Medicine at UCLA, University of California, Los Angeles, Los Angeles, CA, USA

patients with CLL, and have led to substantial and impressive improvement in long-term disease control and survival. These classes of compounds generally achieve rapid and durable disease control [12–14]. Despite their remarkable clinical efficacy, a number of limitations persist. As single agents, complete responses are less common and the substantial burden of residual disease remains. Both of these therapeutic classes are intended to be continued until disease progression or toxicity, and few studies have evaluated planned discontinuation of therapy or a defined course of therapy with these specific agents. Flare-up of CLL is a major concern after interruption or discontinuation of ibrutinib, even in those patients that have progressive disease while on ibrutinib therapy. Patients who discontinue therapy due to toxicity may need to initiate alternative treatments quickly, in order to control disease and avoid flareups. For patients who have progressive disease following discontinuation of ibrutinib, survival has been very short. This continuous long-term course of therapy is associated with risk of toxicity, very high financial burden, and compliance concerns. While these agents have better toxicity profiles than the conventional chemoimmunotherapy regimens, they have their own profile of toxicity and many patients may not be able to tolerate them. Finally, as these are not curative therapies, unfortunately most patients with CLL experience progression of their disease and will require therapy is beyond these classes of compounds.

Role of BCL-2 in the Development of CLL

Evasion of apoptosis is considered a hallmark of cancer and is a prominent feature of many B cell malignancies. The B cell Lymphoma-2 (BCL2) gene was discovered as a partner in the recurring 14;18 translocation abnormality that is the hallmark of follicular lymphoma [15]. In follicular lymphoma and in a fraction of diffuse large B cell lymphoma, the mechanism of BCL-2 activation is indeed this translocation of 14 and 18 which places the BCL-2 gene under the control of the immunoglobulin heavy chain enhancers, resulting in de-regulated expression of the gene [15–17]. In contrast, in CLL, the mechanism of BCL-2 overexpression is related to loss of 13q14, leading to down regulation of microRNA 15 and microRNA16, and consequent BCL-2 overexpression [16]. BCL-2 protein then mostly localizes in the mitochondria and promotes survival and inhibits apoptosis by preventing the release of cytochrome C from mitochondrial into the cytoplasm [16]. In this fashion, overexpression of BCL-2 thus protects cells from apoptosis, and is a fundamental step in the development of CLL.

Mechanism of BCL-2 Overexpression in CLL

In more than half of the cases of CLL, there is hemizygotes and or homozygous loss of 13q14. This constitutes the most frequent chromosomal abnormality in CLL. This suggested that one or more tumor suppressor genes at this 13q14 region may be involved in the pathogenesis of CLL [1–3, 18]. Carlo Croce's group demonstrated that two small non-coding RNAs, miR15 and miR16 are localized in this 13q14 deleted region. In addition, they found that 68% of CLL patients indeed showed a significant reduction in expression of miR15 and miR16, in comparison to normal tissue counterparts. These findings suggested that miR15 and miR16 are downregulated in the majority of the CLL cases [1]. By analyzing complementarity between microRNA 15 and 16 and the BCL-2 messenger RNA, Croce and colleagues demonstrated that the first nine nucleotides from the 5′ end of both microRNAs are complementary to the BCL-2 DNA. BCL-2 overexpression, by microRNAs 15a and 16 down regulation seems to be the main regulatory mechanism involved in the pathogenesis of the major fraction of CLL [16].

The BCL-2 family of proteins integrates diverse pro-survival or proapoptotic intracellular signals generated within the cell, in order to regulate apoptosis [4]. Cellular stress signals such as DNA damage induced TP53 activation, trigger pro-apoptotic BH3-only proteins to neutralize the pro-survival BCL-2 proteins. There is indeed a multilayered regulatory network that allows exquisite control of apoptosis such that it can be triggered for any cell type, in the appropriate physiological context. This tight control is achieved through specificity of interactions between pro-survival and BH3-only proteins, differential induction and post-translational modulation of BH3-only protein expression, and cell type dependent expression of family members [19].

There are two major pathways to apoptosis. An extrinsic pathway that is triggered by ligation of a so-called death receptor on the cell surface and an intrinsic pathway that is triggered by diverse cellular stresses such as loss of survival signals, DNA damage, or uncontrolled cellular proliferation. The intrinsic pathway is regulated by a large family of proteins, all of which contain at least one of four BCL-2 homology (BH) domains, and fall into three functional subfamilies. Death effector proteins (BAX, BAK) homodimerize or heterodimerize to permeabilize the mitochondria. The pro-survival proteins (e.g., BCL-2, MCL-1, BCLxL) hold these death effector proteins in an inactive mode. The pro-apopototic BH-3 only proteins (e.g., BIM, BID, NOXA, p53 upregulated modulator of apoptosis, BAD, HRK) antagonize the function of the pro-survival proteins. This mitochondrial pathway to apoptosis involves a series of protein-protein interactions in the cytosol and predominantly on the outer mitochondrial membrane, which culminates in the permanent position of the outer mitochondrial membrane leading to mitochondrial depolarization, release of cytochrome C, and activation of caspases that drive cellular demolition [19].

Therapeutic Targeting of BCL-2 in CLL

Considering the function of BCL-2 as the major promoter of cell survival, it has long been considered an attractive target for cancer therapy. Navitoclax, a selective inhibitor of both BCL-2 and BCLxL demonstrated therapeutic potential of directly inhibiting these pro-survival proteins, with demonstration of clinical efficacy in CLL and other hematologic malignancies. The overall response rate was 35% in patients with relapsed refractory CLL, all of which was a partial remission, with a median progression free survival of 25 months. However, thrombocytopenia caused by BCLxL on target inhibition limited its efficacy and safety [20]. Obatoclax, a pan BCL-2 family inhibitor, binds BCL-2 as well as BCLxL, BCLw, and MCL1. Its mechanism of action however was thought to be caspase independent. Its clinical activity in CLL was limited and neurologic toxicity was dose limiting.

Venetoclax, also known as ABT199 is an orally bioavailable inhibitor of BCL-2. It was rationally designed via structure-informed reverse engineering of the navitoclax, with high affinity for BCL-2 but not BCLxL or BCLw, thus leading to its most, it is more potent effect against the CLL, but less platelet toxicity.

Clinical Data on Venetoclax for the Treatment of CLL

In pharmacokinetic and metabolic studies, venetoclax exhibits a profile that allows once daily dosing, with food, regardless of fat content. Peak concentrations of the drug were achieved at about 5 to 8 h and the mean terminal phase elimination half-life ranges between 14 and 18 h [21, 22]. At steady-state, venetoclax exposure showed minimal accumulation and is approximately proportional to the dose. In the phase 1 studies, a maximum tolerated dose was not identified. The overall response rate in CLL appeared to be similar among patients receiving doses ranging between 400 and 1200 mg. In an effort to minimize toxicity while maintaining efficacy, dose of 400 mg/day was subsequently selected for ongoing evaluation in CLL [21]. The pharmacokinetic profile of venetoclax in CLL patients with 17p deletion is comparable to the overall CLL as well as non-Hodgkin's lymphoma patient population [23].

Tumor Lysis Syndrome Associated with Venetoclax-Based Therapy

CLL patients treated with venetoclax are at risk of tumor lysis syndrome (TLS). Within 24 h of single dose of venetoclax, laboratory evidence of TLS can be observed, and indeed, in initial phase 1 studies, tumor lysis-related deaths have occurred. A new TLS assessment tool was then designed and validated based on a small cohort of patients in the phase 1 studies to mitigate the risk of TLS. This tool has been used in all subsequent venetoclax trials, and is strongly recommended to be used in clinical practice.

Patients are categorized into low, intermediate, and high risk groups for tumor lysis, based on clinical and laboratory criteria. Patients with any mass ≥ 10 cm, or any mass ≥ 5 cm with absolute lymphocyte count ≥ 25,000, are considered at high risk for TLS. Patients with lymphadenopathy between 5 and 10 cm or absolute lymphocyte count ≥ 25,000 are at moderate risk. Others are at lower risk of TLS. Patients with high risk of TLS are admitted to the hospital for aggressive hydration and close monitoring for tumor lysis syndrome. All patients started venetoclax at 20 mg/day and a gradual dose ramp-up schedule is used with weekly dose increases from 20, 50, 100, 200 mg, to a final recommended dose of 400 mg daily. Uric acid reducing agents should be initiated 72 h prior to therapy and treatment with rasburicase is mandatory for all patients at high risk of tumor lysis syndrome. Following these risk stratification and ramp-up modifications, there has been substantial reduction in the frequency of laboratory TLS, and no clinical tumor lysis syndrome have been observed in clinical trials [24].

Clinical Data for Previously Untreated CLL

Published clinical data relating to efficacy and safety of single-agent venetoclax in treatment-naïve CLL patients is limited. A number of ongoing clinical trials are utilizing rational combinations of venetoclax with anti-CD20 monoclonal antibodies, B cell receptor inhibitors, cytotoxic chemotherapy, in the frontline setting. The ultimate goal is not only improvement in clinical outcomes by achieving higher overall response rates, higher rates of undetectable measurable residual disease, improvement in progression free- and overall survival, but also strategies to overcome stromal–mediated resistance.

Preclinical studies have suggested synergy between inhibitors of B cell receptor and BCL2. Ibrutinib mediated over expression of BCL-2 has been described, suggesting a possible mechanism by which CLL cells may counteract ibrutinib therapy [25]. In addition, stromal protection of CLL cells may result from inhibition of the proapoptotic factors and up regulation of several anti-apoptotic factors in the BCL-2 family of proteins. These data suggest that treatment with B cell receptor inhibitors selectively increases the dependence of CLL cells on BCL-2, thus lending further support to rational behind the ibrutinib-venetoclax combination therapy [26]. In addition, the combination of other therapies, including anti-CD20 monoclonal antibodies, with complementary mechanisms of action are being evaluated, with the ultimate goal of improved clinical outcomes in patients with CLL.

Obinutuzumab has established clinical activity in patients with CLL. In the phase 3 CLL 14 trial, patients with previously untreated CLL and coexisting medical conditions, as assessed by a CIRS score > 6 or estimated creatinine clearance

less than 70 mL/min were randomized to receive either six cycles of chlorambucil with obinutuxumab followed by 6 months of chlorambucil monotherapy, or 6 months of venetoclax plus obinutuxumab followed by 6 months of venetoclax monotherapy. Venetoclax was initiated 22 days after initiation of obinutuzumab, and the dose was gradually ramped up each week, in standard fashion, to the dose of 400 mg, which was continued throughout the remainder of treatment. Safety and efficacy results from the run-in phase of the trial have been reported [27]. Three months after the end of treatment the overall response rate was 100%. Complete responses were achieved in 58% of the patients. Adverse events included grade ¾ neutropenia, successfully treated with granulocyte colony stimulating factor as well as 25% grade 3/4 febrile neutropenia, 16.7% grade ¾ infections, and 16.7% of patients experienced laboratory tumor lysis syndrome with no clinical sequelae. The data suggested that the venetoclax can be safely administered in combination with obinutuzumab, in patients with coexisting medical conditions. Long-term follow-up data is anticipated to be released in upcoming meetings.

The HOVON CLL study group also evaluated the combination of obinutuzumab, and venetoclax, in the context of a novel MRD-driven trial design. Treatment consisted of 4 treatment phases, preinduction with 2 cycles of obinutuzumab, induction I with 6 cycles of obinutuzumab and venetoclax, induction II with 6 cycles of venetoclax, and a randomization for maintenance venetoclax. A planned interim safety analysis of the first 30 patients has been reported. Pre-induction led to downgrading of TLS risk in 25 patients, and none of the patients remained at high risk of TLS. Eighty-seven percent of the patients had undetectable measurable residual disease in peripheral blood at the end of induction II. This combination was well tolerated in unfit patients and results in abrogating high TLS risk in all patients [28].

The combination of obinutuzumab, ibrutinib (IBR), and venetoclax for a fixed duration of treatment has also been evaluated in the frontline setting [29]. Treatment was given at the established doses and schedule for 14 28-day cycles, with obinutuzumab, ibrutinib and venetoclax starting sequentially over the first 3 cycles. The toxicity profile was consistent with the known toxicities of the included individual agents. Hematologic toxicity was the most frequent, with the majority of patients experiencing thrombocytopenia or neutropenia. The most frequent non-hematologic toxicities were hypertension, infusion related reactions, bruising, myalgia and nausea. No patients had progressive disease, but otherwise responses have not been publicized. The study established tolerable safety profile of this in three drug regimen for treatment naïve CLL patients.

In CLL2-BAG, trial investigated the combination of bendamustine, obinutuzumab, and venetoclax. Patients received sequential treatment of with two cycles of bendamustine (70 mg/m^2 on days 1 and 2 of each of the two 28-day cycles), followed by induction and maintenance with obinutuzumab (1000 mg intravenously on days 1–2, 8, and 15 of the first induction cycle, every 4 weeks in induction cycles 2–6, and every 12 weeks in the maintenance phase, and oral venetoclax starting in induction cycle 2 with 20 mg/day, with a weekly standard dose escalation over 5 weeks to the target dose of 400 mg/day. ORR of 95% was reported including all 34 patients in the treatment-naive cohort. The most common grade 3/4 adverse events were cytopenias during the debulking phase (11%), infection (6%). The serious adverse events were infections and cytopenia. This sequential application of bendamustine and obinutuzumab combined with venetoclax caused no unexpected or cumulative toxicities, and a high proportion of patients achieved responses [30].

Treatment of Relapsed or Refractory CLL

Venetoclax has been extensively evaluated in treatment of R/R CLL. Initial studies established safety and efficacy of single agent therapy with indefinite duration, in patients with R/R disease, as well as those with high risk disease. Similar to the strategy in the frontline setting, more recent studies are utilizing combinations of venetoclax with other targeted agents with the ultimate goal of improvement in clinical outcomes and overcoming resistance.

The phase I dose escalation study of daily oral venetoclax in patients with R/R CLL/SLL documented significant clinical activity of this BCL-2 targeted agent [24]. Majority of the patients had multiple previous treatments, and 89% with poor prognostic clinical or genetic features. Venetoclax was active in all dose levels, and a maximum tolerated dose was not defined. The ORR was 79%, and CR occurred in 20% of the patients, including five patients that had no measurable residual disease by flow cytometry. The 15-month PFS for the 400 mg cohort was 69%. As previously noted, prior to implementation of the TLS risk stratification and dose ramp-up schedule, TLS occurred in three out of 56 patients in the dose escalation cohort, with one death. After adjustments for the dose escalation schedule, clinical tumor lysis syndrome did not occur in any of the 60 patients in the expansion cohort. Other toxicity included grade ¾ neutropenia, mild diarrhea, upper respiratory tract infection, nausea.

Venetoclax provides rapid disease control as a single agent therapy. The median time to achieve peripheral blood minimal residual disease negativity was 8.8 months. The median time to first response by IRC was 0.8 months, and the median time to complete remission or complete remission with incomplete recovery of blood counts was 8.2 months [31]. In addition, responses with venetoclax appeared durable. The greatest proportion of ongoing responses are seen in patients with the deepest response, i.e., those achieving a complete remission

or complete remission with incomplete recovery, nodular partial remission, or MRD negative remission [31].

Venetoclax in combination with rituximab was evaluated in treatment of R/R disease [32••]. Rituximab has modest single agent activity in CLL, but when combined with traditional cytotoxic chemotherapy, it improves the proportion of patients who achieve overall response, improvement of PFS and OS. A similar combination of rituximab with Navitoclax proved tolerable and highly active in patients with R/R lymphoid malignancies including CLL [20, 33]. Forty-nine patients were treated, more than 50% of the patients had Rai stage III/IV disease, 51% had disease refractory to the most recent therapy, 57% had received prior fludarabine based therapy, and 18% were thought to be refractory to fludarabine. Ninety percent of the patients had received previous rituximab containing therapy and 43% were considered refractory to rituximab. Forty-five percent of the patients had bulky lymph nodes greater than 5 cm, and 70% of the patients had unmutated IgVH, 63% had either 17p deletion, 11q deletion. Thirty-one percent had a mutated p53 gene. Overall, 86% of the patients achieved a response including a CR and 51%. Two-year estimates for PFS were 82%, and ongoing responses were reported in 89% of patients. Undetectable measurable residual disease was noted in 80% of patients whose disease had a CR, and 50% of the overall patient population. Overall a substantial portion of the patients achieved an overall response with this combination. The most common adverse grade 3/4 adverse events, occurring in 76% of patients included neutropenia, thrombocytopenia, anemia, febrile neutropenia. Serious adverse events included febrile neutropenia and pyrexia, lower respiratory tract infection, and pneumonia. Clinical tumor lysis syndrome occurred in two patients on this protocol, who initiated venetoclax at 50 mg level, one resulting in death. Thereafter, as previously noted, significant TLS prophylaxis measures were instituted there was no evidence of clinical tumor lysis. A maximum tolerated dose of venetoclax was not identified in this study [33].

The MURANO study compared the combination of venetoclax with rituximab to bendamustine and rituximab in a randomized, open-label, phase 3 trial. Three hundred eighty-nine patients received venetoclax for a defined course of therapy of up to 2 years, with rituximab for the first 6 months. Bendamustine (70 mg/m^2 on days 1 and 2) plus rituximab was administered per standard practice for 6 months. After a median follow-up period of 23.8 months, the PFS was significantly higher in the venetoclax–rituximab group than in the bendamustine–rituximab group, and the 2-year rates of PFS were 84.9% and 36.3%, respectively, with hazard ratio for progression or death, 0.17. The benefit was maintained across all clinical and biologic subgroups, including the subgroup of patients with chromosome 17p deletion. Specifically, among patients with chromosome 17p deletion, the 2-year PFS was 81.5% in the venetoclax–rituximab group versus 27.8% in the bendamustine–rituximab group. For those without chromosome 17p deletion, the 2-year PFS was 85.9% versus 41.0%. Modest toxicity was notable with the venetoclax– rituximab group having a higher rate of grade 3 or 4 neutropenia, but grade 3 or 4 febrile neutropenia and infections were lower with venetoclax than with bendamustine. TLS (grade 3 or 4) was noted in 3.1% of the venetoclax–rituximab group. The MURANO data thus established superior safety and efficacy of a defined 2-year course of therapy with venetoclax and rituximab for patients with R/R CLL [32••].

CLL characterized by deletion of chromosome 17p confers a very poor prognosis when treated with chemoimmunotherapy approaches. Allogeneic stem cell transplantation is potentially curative, but applicable only to a few patients and is associated with substantial limitations and toxic effects. Monotherapy with ibrutinib and a combination of idelalisib and rituximab are potentially effective treatments for these patients. Venetoclax induces rapid onset apoptosis of CLL cells in patients via a TP53 independent mechanism [34]. Venetoclax was evaluated in patients with R/R CLL characterized by 17p deletion. A standard weekly dose ramp-up schedule was utilized, and treatment was continued until disease progression or toxicity. The median number of prior treatment was two, ranging from 1 to 4, including 58% of patients that had disease refractory to bendamustine or fludarabine. Fifty-three percent of patients had bulky disease with one or more lymph nodes greater than 5 cm, and 40% of patients were categorized into the medium TLS risk category and 42% of patients had high TLS risk. In addition to 17p deletion, 72% of the patients had a p53 mutation [31]. With a median follow-up of 12 months, the overall response rate was 79.4%, as assessed by an IRC, with the majority the patients achieving a partial remission, 8% complete remission. 20.5% of the patients had progressive disease including 10% with Richter's transformation. The median duration of overall response, event-free survival, time to progression, PFS, or OS had not been reached [31]. This study demonstrated that the venetoclax monotherapy was active and well-tolerated patients with R/R CLL carrying the 17p deletion. More importantly, it documented that the mechanism by which venetoclax kills CLL cells right overcome dysfunctional p53. The overall response rate remains high in subgroups with additional risk features including fludarabine refractory disease, bulky disease, p53 mutation.

Ibrutinib in combination with venetoclax and obinutuzumab has also been evaluated for RR CLL [35]. Patients with R/R CLL received a fixed-duration regimen using sequentially administered obinutuzumab followed by ibrutinib (cycle 2) and venetoclax (cycle 3), for a total of fourteen 28-day cycles. They evaluated 3 dose levels of venetoclax. The side effect profile was consistent with known toxicities of the individual agents, with hematologic adverse events being most frequent. No clinically significant tumor lysis syndrome occurred. The overall response rate was 92%

with 42% achieving a complete remission or complete remission with incomplete marrow recovery. Fifty percent of the patients had undetectable measurable residual disease in peripheral blood and bone marrow at the end of treatment.

Venetoclax therapy was evaluated in patients with R/R CLL after failure or intolerance of ibrutinib or idelalisib therapy in a multicenter, open-label, non-randomized, phase 2 trial [36•, 37]. Patients were stratified into two cohorts, based on the last B cell receptor inhibitor therapy they had received (ibrutinib versus idelalisib), prior to enrollment on this trial. Venetoclax was administered per the described standard 5-week dose ramp-up schedule, and then continued daily at 400 mg until PD or toxicity. Ninety-nine patients had received ibrutinib as the last B cell receptor inhibitor before enrolment. With a median follow-up was 14 months, the ORR was 65% in this cohort, and median PFS had not been reached [36•]. The group of patients who had received idelalisib just prior to their enrollment on this protocol included 36 patients. The ORR was 67% with 3 patients achieving CR/CRi. Median PFS had not been reached and the estimated 12-month PFS was 79% [37]. Grade 3/4 adverse events were primarily hematologic in both cohorts of patients. There were no treatment-related deaths in either cohort. Venetoclax demonstrated significant and promising clinical activity and favorable tolerability in patients with R/R CLL whose disease progressed during or after ibrutinib or idelalisib therapy.

The optimal sequencing of novel therapeutic modalities including B cell receptor inhibitors and venetoclax has not been evaluated and prospective randomized trials [38]. A large multicenter, retrospective analysis of CLL patients treated with kinase inhibitors or venetoclax suggested that ibrutinib appeared superior to idelalisib as first kinase inhibitor. Furthermore, in the setting of failure of kinase inhibitor, alternate kinase inhibitor or venetoclax therapy appeared superior to chemoimmunotherapy combinations. Venetoclax upon ibrutinib failure may be superior to idelalisib [38].

Risk Factors and Outcome of Progression on Venetoclax

The clinical and pathological features and outcome of progression of CLL on venetoclax have been evaluated in in order to define risk factors for progression and the clinical and pathologic features of PD, and the outcomes for patients after venetoclax failure [39]. Data on 67 heavily pretreated patients on three early phase clinical trials were evaluated. Investigations at the time progression included positron emission tomography scan and biopsy. Thirty-seven percent of the patients manifested progressive disease on therapy, 17 of which had Richter's transformation and eight with progression of CLL. Richter's transformation occurred significantly earlier, at a median of 7.9 months, then PD with CLL, median of 23.4 months. Disease refractory to fludarabine and characterized by complex karyotype was associated with progression, with a hazard ratio of 7.01 and 6.6 respectively. On the other hand, deletion 17p and/or TP53 mutation were not associated with progression. The median survival after progression was 13 months. From clinical perspective, the time to progression varied according to the pathology at progression. Time to progression with Richter's transformation was significantly shorter than for PD with CLL, with a median of 7.9 months versus 23.4 months respectively. The short time frames for presentation with Richter's transformation suggested that, perhaps, some patients entered the trials with pre-existing Richter's transformation, especially as patients had not been screened specifically for transformation prior to enrollment on those trials. Earlier progression of any kind indeed appeared to be related to the receipt of less than the recommended phase 2 dose of venetoclax [39].

In evaluation of outcome of patients, following progression on venetoclax, six of the eight patients with progressive CLL/SLL on venetoclax were treated with ibrutinib. Five achieved a partial remission, and at the time of reporting of the publication, three remained alive on therapy, with two patients dying of toxicity, and one dying of PD. Treatment for Richter's transformation was variable and included salvage with high-dose chemotherapy followed by autologous or allogeneic stem cell transplantation, radiotherapy, as well as multiagent salvage chemotherapy alone. Responses were variable in patients with transformed disease with 30% of the patients achieving a CR, 17% PR, and 50% of patients had no response. Following PD, the median follow-up was 11.4 months. Refractoriness of CLL to fludarabine-based strategies and complex karyotype were dominant risk factors for progression, despite ongoing treatment with BCL-2 inhibitor. Overall, complex karyotype may hold greater prognostic significance than aberrations involving the p53 gene, in heavily treated patients receiving novel agents. Complex karyotype may indeed reflect greater genomic instability among this group [39].

Clinical features of PD on venetoclax in, in addition to progressive lymphadenopathy and B symptoms, included potential Richter's transformation characterized by the presence of cytopenia and mixed nodal response, especially in heavily treated patients and those with markers of genomic instability [40]. In the population of less heavily treated patients with R/R CLL, the development of Richter's transformation during venetoclax therapy was less common, observed in 12% of patients [41].

Duration of Therapy with Venetoclax

A number of ongoing studies are evaluating the optimal duration of therapy with venetoclax-based combinations. Ability of therapeutic modality to achieve undetectable measurable residual disease is indeed a surrogate measure of substantial

reduction in disease burden, and is associated with prolonged progression free survival [42–44]. As previously discussed, the HOVON CLL study group evaluated the optimal duration of venetoclax treatment. They evaluated an MRD-guided duration of venetoclax treatment. Following the second phase of induction, a randomization phase was planned with one group receiving maintenance with 12 additional cycles of venetoclax irrespective of MRD and a second group where the MRD guided venetoclax maintenance with a maximum of 12 cycles. They reported a planned interim safety analysis of the first 30 patients. Eighty-seven percent of the patients had undetectable measurable residual disease in peripheral blood at the end of induction II. A high proportion of the patients responded with undetectable measurable residual disease, after the combination treatment. Long-term data will elucidate whether the role of MRD guided duration of venetoclax therapy [28].

Conclusion

Overexpression of BCL-2 is one of the main mechanisms of evasion of apoptosis, and is one of the key mechanisms of pathogenesis of chronic lymphocytic leukemia. Venetoclax, alone or in combination with anti CD-20 monoclonal antibodies, induces rapid disease control, with durable responses. The MURANO data established superior safety and efficacy of a defined two-year course of therapy with venetoclax and rituximab for patients with R/R CLL. Venetoclax maintains activity across all clinical and biologic subgroups, including those with high risk disease, including CLL with chromosome 17p deletion. In the context of other highly active targeted agents, including BTK and PI3Kinase inhibitors that are traditionally continued until disease progression or toxicity, this defined course of therapy represents a paradigm shift for management of patients with CLL. Patients treated with venetoclax are at risk for risk of tumor lysis syndrome (TLS). Multiple studies have now demonstrated that with TLS risk stratification and five-week ramp-up schedule, there is substantial reduction in the frequency and severity of TLS. Studies with venetoclax in combination with next generation of BTK and PI3Kinase inhibitors, antiCD20 monoclonal antibodies, ROR-1 inhibitors are ongoing to evaluate safety and efficacy of these new combinations, with the goal of inducing a high rate of MRD-negative durable remissions with curative potential.

Compliance with Ethical Standards

Conflict of Interest Herbert Eradat declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Calin GA, Dumitru CD, Shimizu M, Bichi R, Zupo S, Noch E, et al. Frequent deletions and down-regulation of micro- RNA genes miR15 and miR16 at 13q14 in chronic lymphocytic leukemia. Proceedings of the National Academy of Sciences USA. 2002;99:15524–9.
2. Bullrich F, Fujii H, Calin G, Mabuchi H, et al. Characterization of the 13q14 tumor suppressor locus in CLL: identification of ALT1, an alternative splice variant of the LEU2 gene. Cancer Research. 2001;61(18):6640–8.
3. Liu Y, Corcoran M, Rasool O, Ivanova G, Ibbotson R, Grandér D, et al. Cloning of two candidate tumor suppressor genes within a 10 kb region on chromosome 13q14, frequently deleted in chronic lymphocytic leukemia. Oncogene. 1997;15:2463–73.
4. Strasser A, Cory SA, Adams JM. Deciphering the rules of programmed cell death to improve therapy of cancer and other disease. EMBO J. 2011;30:3667–83.
5. Nabhan C, Rosen ST. Chronic lymphocytic leukemia: a clinical review. JAMA. 2014;312(21):2276.
6. Institute, National Cancer. Surveillance epidemiology and end results cancer statistics review (SEER) database. 2016.
7. Guieze R, Wu CJ. Genomic and epigenomic heterogeneity in chronic lymphocytic leukemia. Blood. 2015;126:445–53.
8. Bron JR, Halleck MJ, Pagel JM. Chemoimmunotherapy versus targeted treatment in chronic lymphocytic leukemia: when, how long, how much, and in which combination? American Society of Clinical Oncology Education Book. 2016;35:387–98.
9. Hamblin TJ, Davis Z, Gardiner A, Oscier DG, Stevenson FK. Unmutated Ig V(H) genes are associated with a more aggressive form of chronic lymphocytic leukemia. Blood. 1999;94:1848–54.
10. The International CLL-IPI working group. An international prognostic index for patients with chronic lymphocytic leukaemia (CLL-IPI): a meta-analysis of individual patient data. Lancet Oncology. 2016;17:779–90.
11. Zenz T, Kroeber A, Schere K, Habe S, et al. Monoallelic TP53 inactivation is associated with poor prognosis in chronic lymphocytic leukemia: results from a detailed genetic characterization with long-term follow-up. Blood. 2008;112:3322–9.
12. Byrd JC, Furman RR, Coutre SE, Flinn IW, Burger JA, Blum KA, et al. Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia. N Engl J Med. 2013;369:32–42.
13. Byrd JC, Furman RR, Coutre SE, Burger JA, et al. Three-year follow-up of treatment-naïve and previously treated patients with CLL and SLL receiving single-agent ibrutinib. Blood. 2015;125(16):2497–506.
14. Farooqui MZ, Valdez J, Martyr S, Aue G, et al. Ibrutinib for previously untreated and relapsed or refractory chronic lymphocytic leukaemia with TP53 aberrations: a phase 2, single-arm trial. Lancet Oncology. 2015;16(2):169–76.
15. Tsujimoto Y, Cossman J, Jaffe E, Croce CM. Involvement of the bcl-2 gene in human follicular lymphoma. Science. 1985;228:1440–3.
16. Cimmino A, Calin GA, Fabbri M, Iorio MV, et al. miR-15 and miR-16 induce apoptosis by targeting BCL2. Proceedings of the National Academy of Sciences USA. 2005;102:13944–9.
17. Tsujimoto Y, Finger LR, Yunis J, Nowell PC, Croce CM. Cloning of the chromosome breakpoint of neoplastic B cells with the t(14;18) chromosome translocation. Science. 1984;226:1097–9.

18. Migliazza, A, Bosch, F, Komatsu, H, Cayanis, E, et al. Nucleotide sequence, transcription map, and mutation analysis of the 13q14 chromosomal region deleted in B-cell chronic lymphocytic leukemia. 2001, Vol. 97, pp. 2098–2104.
19. Roberts, AW, Huang, DCS. Targeting BCL 2 with the BH3 mimetics: Basic science and clinical application of Venetoclax in chronic lymphocytic leukemia and related B cell malignancies. 2017, Vol. 101, pp. 89–98.
20. Kipps TJ, Eradat H, Grosicki S, et al. A phase 2 study of BH three my medic BCL-2 inhibitor Nvidia clocks ABT 263 with or without rituximab, in previously untreated B cell chronic lymphocytic leukemia. Leukemia and Lymphoma. 2015;56:2826–33.
21. Salem AH, Agarwal SK, Dunbar M, Enschede SL, et al. Pharmacokinetics of venetoclax, a novel BCL-2 inhibitor, in patients with relapsed or refractory chronic lymphocytic leukemia or non-hodgkin lymphoma. Journal of Clinical Pharmacology. 2017;57(4):484–92.
22. Salem AH, Dunbar M, Agarwal SK. Pharmacokinetics of venetoclax in patients with 17p deletion chronic lymphocytic leukemia. Anticancer Drugs. 2017;28(8):911–4.
23. Salem AH, Dunbar M, Agarwa SK. Pharmacokinetics of venetoclax and patient with 17p deletion chronic lymphocytic leukemia. Anti-Cancer Drugs. 2017;28:911–4.
24. Roberts AW, Davids MS, Pagel JM, Kahl BS, Puvvada SD, Gerecitano JF, et al. Targeting BCL-2 with venetoclax in relapsed chronic lymphocytic leukemia. The New England Journal of Medicine. 2016;374:311–22.
25. Cervantes-Gomez F, Lamothe B, Woyach JA, Wierda WG, et al. Pharmacological and protein profiling suggests venetoclax (ABT-199) as optimal partner with Ibrutinib in chronic lymphocytic leukemia. Clinical Cancer Research. 2015;21(16):3705–15.
26. Aw A, Brown JR. The potential combination of BCL-2 inhibitors and ibrutinib as frontline therapy in chronic lymphocytic leukemia. Leukemia and Lymphoma. 2017;10:2287–97.
27. Fischer K, Al-Sawaf O, Fink AM, Dixon M, et al. Venetoclax and obinutuzumab in chronic lymphocytic leukemia. Blood. 2017;129(19):2702–5.
28. Kater AP, Kersting S, van Norden Y, Dubois J, et al. Obinutuzumab pretreatment abrogates tumor lysis risk while maintaining undetectable MRD for venetoclax + obinutuzumab in CLL. Blood Adnavces. 2018;2(24):3566–71.
29. Rogers KA, Huang Y, Ruppert AS, Awan FT, et al. Phase 2 study of combination obinutuzumab, ibrutinib, and venetoclax in treatment-naive and relapsed/refractory chronic lymphocytic leukemia. Blood. 2018;132(15):1568–72.
30. Cramer P, von Tresckow J, Bahlo J, et al. Bendamustine followed by obinutuzumab and venetoclax in chronic lymphocytic leukaemia (CLL2-BAG): primary endpoint analysis of a multicentre, open-label, phase 2 trial. Lancet Oncol. 2018;19:1215–28.
31. Stilgenbauer S, Eichhorst B, Schetelig J, Coutre S, Seymour JF, Munir T, et al. Venetoclax in relapsed or refractory chronic lymphocytic leukaemia with 17p deletion: a multicentre, open-label, phase 2 study. Lancet Oncol. 2016;17:768–78.
32.•• Seymour JF, Ma S, Brander DM, Choi M, et al. Venetoclax plus rituximab in relapsed or refractory chronic lymphocytic leukaemia: a phase 1b study. The Lancet oncology. 2017;18:230–40. **Findings from this study established superior safety and efficacy of therapy with venetoclax and rituximab for patients with relapsed or refractory CLL, in comparison to cytotoxic chemoimmunotherapy with bendamustine and rituximab. For the first time, these MURANO data findings can lead to a paradigm shift in the treatment of patients with relapsed disease, utilizing a defined 2-year course of therapy that induces high response rates, with durable disease control.**
33. Roberts AW, Advani RH, Kahl BS, Persky D, Sweetenham JW, Carney DA, et al. Phase 1 study of the safety, pharmacokinetics, and antitumour activity of the BCL2 inhibitor navitoclax in combination with rituximab in patients with relapsed or refractory CD20+ lymphoid malignancies. British Journal of Hematology. 2015;170:669–78.
34. Anderson MA, Deng J, Seymour JF, Tam C, Kim SY, Fein J, et al. The BCL2 selective inhibitor venetoclax induces rapid onset apoptosis of CLL cells in patients via a TP53-independent mechanism. Blood. 2016;127(25):3215–24.
35. Rogers KA, Huang Y, Ruppert AS, Awan FT, et al. Phase 1b study of obinutuzumab, ibrutinib, and venetoclax in relapsed and refractory chronic lymphocytic leukemia. Blood. 2018;132(15):1568–72.
36.• Jones JA, Mato AR, Wierda WG, Davids MS, et al. Venetoclax for chronic lymphocytic leukaemia progressing after ibrutinib: an interim analysis of a multicentre, open-label, phase 2 trial. Lancet Oncology. 2018;19(1):65–75. **Findings in this study established the efficacy and safety of venetoclax after BTK inhibition, and provide clinical guidance on optimal sequencing of these agents.**
37. Coutre S, Choi M, Furman RR, Eradat H, et al. Venetoclax for patients with chronic lymphocytic leukemia who progressed during or after idelalisib therapy. Blood. 2018;131(15):1704–11.
38. Mato AR, Hill BT, Lamanna N, Barr PM, et al. Optimal sequencing of ibrutinib, idelalisib, and venetoclax in chronic lymphocytic leukemia: results from a multicenter study of 683 patients. Annals of Oncology. 2017;28(5):1050–6.
39. Anderson MA, Tam C, Lew T, Juneja S, Juneja M, Westerman D, et al. Clinical and pathological features and outcomes of progression of CLL on BCL-2 inhibitor venetoclax. Blood. 2017;129:3362–70.
40. Parikh SA, Kay NE, Shanafelt TD. How we treat Richter's syndrome. Blood. 2014;123(11):1647–57.
41. Roberts AW, Seymour JF, Eichhorst B, et al. Pulled multi-trial analysis of venetoclax efficacy in patients with relapsed or refractory chronic lymphocytic leukemia [abstract]. ASH Annual Meeting Abstacts, Blood. 2016;128(22):3230.
42. Badoux XC, Keating MJ, Wang X, et al. Fludarabine, cyclophosphamide, and rituximab chemoimmunotherapy is highly effective treatment for relapsed patients with CLL. Blood. 2011;117(11):3016–24.
43. Strati P, Keating MJ, O'Brien SM, Burger J, Ferrajoli A, Jain N, et al. Eradication of bone marrow minimal residual disease may prompt early treatment discontinuation in CLL. Blood. 2014;123:3727–32.
44. Böttcher S, Ritgen M, Fischer K, Stilgenbauer S, Busch RM, Fingerle-Rowson G, et al. Minimal residual disease quantification is an independent predictor of progression-free and overall survival in chronic lymphocytic leukemia: a multivariate analysis from the randomized GCLLSG CLL8 trial. J Clin Oncol. 2012;30:980–8.