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REVIEW

Venetoclax: evidence to date and clinical potential

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Abstract

The emergence of targeted therapy for patients with hematological diseases has permanently altered the therapeutic landscape. Immunochemotherapy regimes are now more and more being replaced by targeted therapies due to superior efficacy and better safety profiles. However, evolution and selection of subclones with continuous treatment leads to disease relapse and resistance toward these novel drugs. Venetoclax, the highly selective BCL-2 inhibitor (ABT-199), has an acceptable safety profile. To date, it has been approved for the treatment of first-line and relapsed/refractory chronic lymphocytic leukemia (CLL) and acute myeloid leukemia (AML). However, extension of indications can be expected in monotherapy and in combination regimens with promising outcomes in other hematological diseases. In this article, we describe the mechanism of action that stands behind the efficacy of venetoclax and provide a summary of available results from clinical trials.

Keywords: cancer drugs, leukemia, lymphoma, venetoclax.

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Introduction

Blood cancers, including non-Hodgkin lymphoma (NHL), acute leukemia, multiple myeloma, and Hodgkin lymphoma (HL), represent the 6.5% of all newly diagnosed cancer patients.[1] Although many therapies have been developed for the treatment of hematological malignancies, there is still a need for improvement.

Targeted anticancer therapies with small-molecule inhibitors and antibodies have become an important strategy to treat hematological cancers. These agents have demonstrated good effects in treatment, often independently of genetic features.

Venetoclax, a novel, orally bioavailable small-molecule inhibitor for selective targeting of B-cell lymphoma-2 (BCL-2), has proven high efficacy and safety in different hematological diseases, particularly in chronic lymphocytic leukemia (CLL), and also in AML.

In 2016, the US Food and Drug Administration (FDA) approved venetoclax for the treatment of patients with CLL with 17p deletion who have been previously treated with at least one other therapy. In June 2018, the approval was extended to patients with CLL or small lymphocytic lymphoma (SLL) regardless of 17p deletion, who have received at least one prior therapy. In November 2018, the FDA approved venetoclax in combination with azacitidine or decitabine or low-dose cytarabine (LDAC) for the treatment of newly diagnosed AML in adults who are 75 years of age or older and for the treatment of patients with comorbidities and no intensive induction chemotherapy indicated. In May 2019, the treatment was expanded to all adult patients with CLL or SLL.[2]

In addition, the European Medicines Agency (EMA) approved venetoclax for the treatment of patients with CLL in combination with rituximab as a second line of treatment. It also could be used as a single agent for the treatment of patients unsuitable for chemoimmunotherapy when pathway inhibitors (ibrutinib and idelalisib) are not suitable or have failed.[3]

The unique properties of venetoclax, specifically its high selectivity for the BCL-2 protein and lower hematological toxicity compared to other drugs in its class, make it a promising agent for treatment of B-cell malignancies in the future.[4] The drug has been shown to be clinically effective in many hematological malignancies as a single agent, especially CLL, follicular lymphoma (FL), and mantle cell

lymphoma (MCL),[5] which have high levels of BCL-2. Further trials involving the use of venetoclax in combination therapies are also still being conducted in other malignancies (e.g. acute lymphoblastic leukemia [ALL], diffuse large B-cell lymphoma [DLBCL]).

This paper is a review of venetoclax as an agent for the treatment of pathologies with accepted treatment indication (CLL and AML), as well as a review of the new evidence of venetoclax as treatment of other pathologies. A search was done on PubMed, American Society of Hematology meeting abstracts, European Society of Hematology meeting abstracts, American Society of Clinical Oncology meeting abstracts, and also the package insert of venetoclax for the most up-to-date information about clinical trials and indications for the medication. In this review there will first be a discussion of the unique pharmacology of the drug, including mechanism of action, dosing, toxicities, and drug interactions. Data for past, ongoing, and future clinical trials, in addition to information about off-label indications, will follow.

Pharmacology

Mechanism of action

Venetoclax is orally bioavailable and part of a class of antineoplastic agents called BH3-mimetics.[6] In general, BH3-mimetics inhibit antiapoptotic proteins such as BCL-2, BCL-w, and BCL-X_L.[7,8] Venetoclax specifically copies the actions of the physiological antagonists of BCL-2 and binds directly to the protein. This reinstates programmed cell death with displacement of proapoptotic proteins (e.g. BIM) and caspase activation.[9]

It should be noted that navitoclax was the first member of the BH3-mimetics class with BCL-2 inhibition that was studied in clinical trials.[10] Navitoclax was proven in these trials to be active against refractory CLL. However, the drug also targeted the antiapoptotic protein BCL-X_L, which is very important in platelet survival, leading to dose-limiting thrombocytopenia.[11] Venetoclax is a novel BH3 mimetic because it has significantly reduced activity against the BCL-X_L protein (a 200-fold decrease compared to navitoclax). This allows it to have minimal effect on platelet counts. Additionally, venetoclax binds and inhibits BCL-2 with great affinity, as seen by its very small Ki value (<0.010).[10]

Table 1a. Ramp-up dosing of venetoclax in the first 5 weeks in patients with chronic lymphocytic leukemia.

Week	Recommended Dosage Level
1	20 mg once daily
2	50 mg once daily
3	100 mg once daily
4	200 mg once daily
5	400 mg once daily

Dosing

General information

Venetoclax is an oral medication that is taken once daily with food and water. The dosing schedule for venetoclax depends on the pathology to be treated. In CLL cases, it involves a progressive increase over 5 weeks (Table 1a). And in AML cases, the dose increase is daily over 4 days, associated with azacitidine, decitabine, or low doses of cytarabine on day 1 (Table 1b).[5]

For CLL patients, after week 5, venetoclax is recommended to be continued at 400 mg q.d. until there is unacceptable toxicity or progression of the malignancy. The purpose of the weekly dose ramp-up is to debulk and decrease the risk of tumor lysis syndrome (TLS). Dosing of venetoclax was determined by studies that showed the steady state AUC (area under the curve) of venetoclax increased proportionally from 150 to 800 mg. Tablets come in three strengths (10, 50, and 100 mg) and are advised to be taken with water and a meal at approximately the same time each day. Studies have shown that taking venetoclax with a low-fat or high-fat meal increased exposure of the drug by 3.4-fold to 5.3-fold, respectively.[5]

Dose reductions for toxicities

Dose reductions are sometimes needed when venetoclax-related toxicities (e.g. TLS, hematologic toxicities such as grade 3 neutropenia, and/or grade 3/4 non-hematologic toxicities) are present.[12] Table 2 details the recommended dose reduction corresponding to the dose during time of toxicity.[5]

Tumor lysis syndrome

For any occurrence of TLS (blood chemistry changes or concerning symptoms), the following day's dose may be withheld. If TLS resolves within 24–48 hours of the last dose, treatment should be resumed at the same dosage level. Should the blood chemistries of TLS take longer than 48 hours to

Table 1b. Ramp-up dosing of venetoclax in the first 4 days in patients with acute myeloid leukemia.

Day	Daily dose
1	100 mg
2	200 mg
3	400 mg
4 and beyond	400 mg when dosing in combination with azacitidine or decitabine. 600 mg when dosing in combination with low-dose cytarabine.

resolve, treatment should resume at a reduced dosage level (see Table 2). Lastly, in any cases of clinical TLS (defined as TLS indicated by lab values plus acute renal failure, seizures, and/or cardiac arrhythmias), treatment should be resumed at the reduced dose after resolution.[5,13] To aid in what premedications should be used in CLL patients being treated with venetoclax, Table 3 shows the manufacturers guidelines for tumor lysis premedication based on risk of TLS.

Table 2. Reduced dosage level for toxicities during venetoclax administration.

Dose during time of toxicity (mg)	Recommended reduced dosage level (mg)
400	300
300	200
200	100
100	50
50	20
20	10

Non-hematologic toxicity

For any grade 3/4 non-hematologic toxicities related to venetoclax, treatment should be interrupted during the first occurrence. Treatment may continue at the same dosage level after the toxicity becomes grade 1 or baseline level. For the second or later occurrence of grade 3/4 non-hematologic toxicity, dosing should be interrupted as well. Following resolution, treatment may resume at a reduced dose, as outlined in Table 2, or at an even larger reduction if the physician believes this would be safer for the patient.[5]

Hematologic toxicity

For grade 3 neutropenia with fever or infection, or grade 4 hematologic toxicities (with the exception of lymphopenia) following venetoclax administration, the same recommendations for dosage interruption and resumption of treatment are made as the non-hematologic toxicities. In addition, granulocyte-colony stimulating factor (G-CSF) may be given if clinically indicated during either the first or

Table 3. Premedication for venetoclax patients based on TLS risk.

Risk level	Criteria	Premedication	Monitoring (uric acid, calcium, creatinine, phosphorus, and potassium levels)
Low	ALC <25,000/mm^3 AND all lymph nodes <5 cm	Can be done outpatient: 1.5–2 L of oral hydration (starting 2 days before and day of first dose; IV if unable to tolerate oral) and allopurinol 2–3 days before starting venetoclax	Monitor levels at pre-dose, 6–8 hours, and 24 hours for first 20 and 50 mg dose; thereafter, monitor pre-dose levels for each of the following ramp-up dosages: 100, 200, 400 mg
Medium	ALC ≥25,000/mm^3 OR any lymph node 5 to <10 cm	Outpatient: 1.5–2 L of oral hydration (starting 2 days before and day of first dose; IV if unable to tolerate oral) and allopurinol Inpatient: preferred for patients with creatinine clearance <80 mL/min for IV fluid supplementation and frequent lab monitoring; allopurinol given as hypouricemic agent 2–3 days before starting venetoclax	Monitor levels at pre-dose, 6–8 hours, and 24 hours for first 20 and 50 mg dose; thereafter, monitor pre-dose levels for each of the following ramp-up dosages: 100, 200, 400 mg
High	ALC ≥25,000/mm^3 OR any lymph node ≥10 cm	Inpatient: patients should be hospitalized for 2–3 days during each of the first 2 weeks of venetoclax administration (20 and 50 mg doses); oral (1.5–2 L) and IV (150–200 mL/h as tolerated) fluids are administered, and there is frequent lab monitoring (pre-dose and at 4, 8, 12, and 24 hours after administration of venetoclax); allopurinol is given 2–3 days before venetoclax administration; rasburicase is the preferred hypouricemic agent if there is baseline elevation of uric acid (Note: rasburicase should only be administered if patient has confirmed sufficient levels of glucose-6-phosphate-dehydrogenase [G6PD])	For first 20 and 50 mg dose (inpatient), monitor levels at pre-dose, 4, 8, 12, and 24 hours Thereafter, for the following 100, 200, and 400 mg ramp-up doses, monitor levels at pre-dose, 6–8, and 24 hours (can be done outpatient)

ALC, absolute lymphocyte count; IV, intravenous; TLS, tumor lysis syndrome.

any subsequent occurrence to attempt to reduce the risk of infection.[5,14]

Drug interactions

As will also be discussed later, venetoclax is metabolized by the CYP3A4/5 system. It is additionally a substrate of P-glycoprotein (P-gp). Concurrent use of a strong CYP3A inhibitor (e.g. ketoconazole) is therefore contraindicated during the start of venetoclax treatment and the 5-week dose increase. If use of the strong CYP3A inhibitor cannot be avoided with venetoclax after the dose escalation, it is recommended that the venetoclax dose be reduced by 75% or more. It is also advised that venetoclax not be used along with moderate CYP3A, P-gp inhibitors, CYP3A inducers, or narrow therapeutic index P-gp substrates. If there needs to be continued use of moderate CYP3A and P-gp inhibitors along with venetoclax, it is recommended that the venetoclax dose be reduced by 50% or more. If a narrow-spectrum P-gp substrate needs to be taken concurrently, administration should be at least 6 hours before taking the daily dose of venetoclax.[5,10,11,15]

Furthermore, fruits such as grapefruit, star fruit, and Seville oranges have the potential to increase venetoclax plasma concentrations if taken concurrently. This is due to these fruits causing moderate inhibition of CYP3A4. Therefore, it is recommended that these fruits be avoided during administration of venetoclax.[15]

Other dosing considerations and precautions

In patients with hepatic impairment, close monitoring of liver function tests (LFTs) is recommended to check for toxicities. These patients, especially with moderate or greater impairment, are at increased risk for adverse events (AEs) with venetoclax administration. Treatment should be temporarily stopped if serum aminotransferase levels increase to 5 times the upper limit of normal and resumed when levels decreased to 1.5 times the upper limit of normal or less.[10]

Additionally, venetoclax administration may lead to embryo-fetal toxicity in pregnant women. Prior to starting venetoclax treatment, all women of reproductive potential should have a pregnancy test. They are also advised to use effective contraception while receiving treatment and continue for 30 or more days following the final dose. Patients should also not breastfeed while on venetoclax, as it not known whether the drug is present in breast milk.[5,15] In men, venetoclax treatment may lead to infertility. This is based on a study that showed testicular toxicity in dogs following venetoclax exposure. Men of reproductive potential should therefore be informed of this potential side effect and about possible use of sperm banking.[5,11]

No antidote currently exists for venetoclax. Due to its large volume of distribution and great amount of protein binding, dialysis is not believed to be effective in removing the drug from circulation. In those who do experience overdose, supportive treatment and close, frequent monitoring are recommended.[5]

Lastly, live vaccines should not be given before, during, or after treatment with venetoclax until there is B-cell recovery. This is because the vaccine may either not work as well or could potentially be unsafe during this time.[5,11,16]

Metabolism and elimination

Venetoclax is primarily metabolized by CYP3A4/5 and predominantly cleared by the liver, as shown by *in vitro* studies. It has also been demonstrated that almost all (99.9%) of an administered dose of venetoclax is eliminated through feces, whereas a minimal amount (<0.1%) is through urinary excretion.[17]

Preclinical studies

Many preclinical trials reported the effectiveness of venetoclax in *in vitro* studies. Venetoclax activates BAK and BAX and, later, mitochondrial cytochrome C release, leading to apoptosis. This model of action has been confirmed in various cellular models validating its mechanism of action. Vogler and colleagues in 2013 described that T cells lacking BAX showed no response to treatment with venetoclax in different concentrations.[9]

During preclinical development, the utility of a proapoptotic single agent was probed in different pathologies (NHL, including DLBCL, MCL, and FL). NHL cell lines expressing the t(14:18) showed higher sensitivity toward ABT-199 treatment than cells without that translocation.[18] Multiple myeloma cell line with the expression of BCL-X_L and MCL1 showed sensitivity to venetoclax, which were predictive for treatment response. The expression of both BCL-2 and BCL-X_L, derived from resistance to venetoclax monotherapy, still showed response to BCL-X_L inhibitors.[19]

Better results have been obtained in the treatment of AML and pediatric ALL cell lines.[20] New studies using xenografts of AML, ALL, and B-cell lymphomas with venetoclax in monotherapy or in combination with rituximab and bendamustine emphasized the efficacy of venetoclax as well as its safety in combination treatments.

In CLL, patients treated with ibrutinib (inhibitor of BTK) showed remarkable complete and durable responses[15]; however, a subset did not achieve deep remission or cure. In order to probe a possible synergism between venetoclax and ibrutinib, *ex vivo* serial samples of CLL patients under ibrutinib treatment were treated with venetoclax. The combined treatment resulted in high cytotoxicity *in vitro* and confirmed the synergism between these two drugs. The explanation of the synergism lies in the decrease of MCL1 and BCL-X_L mediated by ibrutinib and how this augmented the response to inhibition of BCL-2 through venetoclax.[16]

Clinical efficacy in hematological malignancies

Chronic lymphocytic leukemia

CLL is the most common adult leukemia in the Western world. This disease arises from clonal mature B-lymphocytes with a distinctive immunophenotype.[21] Characteristically it is an indolent malignancy with a variable clinical course, and the prognosis is predicted according to present genetic lesions. More than 80% of CLL cases have presented genomic aberrations; the most frequent aberrations are del13q (55%), del11q (18%), del 17p (8%), and trisomy 12 (12–16%).[22]

New studies have revealed that nearly all patients have increased BCL-2 expression in CLL cells.[23] Other genetic alterations such as t(14;18)(q32;q21), t(2;18)(p11;q21.3), and t(18;22)(q21.3;q11) are rarely detected.[24]

The loss of the tumor suppressor genes *microRNA15* (*miR15*) and *miR16* (located on the 13q14 chromosome region) leads to BCL-2 overexpression. These genes interact directly with and inhibit BCL-2 and several other oncogenes (i.e. *MCL1* and *MB11*). Therefore, del 13q14 results in the loss of these two genes and the increase of BCL-2 protein in 50% of CLL patients.[25]

A 17p mutation is associated with resistance to chemotherapy and a poor prognosis.[26–28] In patients who are refractory to one or more of these initial therapies or present with relapsed CLL, venetoclax is indicated.[29,30] On April 11, 2016, the FDA approved venetoclax for patients with CLL who have a chromosome 17p deletion and received at least one prior therapy. Thereafter, on June 8, 2018, the FDA expanded approval for venetoclax to include CLL or SLL patients, with or without a 17p deletion, who have received at least one prior therapy.[5,31,32] And, in May 2019, venetoclax was approved as a chemotherapy-free combination regimen for previously untreated patients with CLL or SLL.[7]

The aim of the first phase I and II studies with venetoclax as single agent in CLL was to achieve the most effective dose but with the lowest percentage of adverse effects. A phase I clinical trial for dose escalation was initiated to determine the dosing of venetoclax in patients with relapsed/refractory (RR) CLL, SLL, or B-NHL.[33] The first group was treated with an escalating dose, receiving eight different doses of treatment between 20 and 50 mg venetoclax with a weekly dose escalation to 1200 mg per day. A second group of patients were treated in a stepwise weekly ramp-up of up to 400 mg per day. The overall response rate (ORR) was 79% in RR poor prognosis CLL, with an ORR of 77% in the dose escalation group and an ORR of 82% in the expansion cohort.[39] A rapid absolute lymphocyte count reduction was reported within 6–24 hours after a single dose of 20 mg, with observation of apoptotic CLL cells in a peripheral blood smear. Reduction in tumor burden was observed in blood, lymph nodes, and bone marrow; however, in only three patients with lymphadenopathy, TLS was observed. Complete remission was achieved in 20% of total patients, and 5% were negative for minimal residual disease (MRD) by flow cytometry. Almost no differences were detected in the subgroup of patients with del17p (ORR was 71%, and complete response [CR] was 16%). The progression-free survival (PFS) at 15 months was around 66% (CLL patients with del17p presented a PFS of 16 months, and for CLL patients with unmuted chromosome 17, the median PFS was not reached), and the 2-year overall survival (OS) for all cohorts was 84%. The first data published presented TLS as a dose-limiting toxicity; for that reason, different strategies were implemented to diminish its presentation, including the gradual increase of the dose and the prophylactic measures to allow the treatment. Other most common serious AEs (grade 3/4) were neutropenia, immune thrombocytopenia, febrile neutropenia, pneumonia, and upper respiratory tract infection.

Due to the results in poor-risk CLL, a pivotal phase II clinical trial was initiated. In this multicenter, open-label study, 107 patients with RR del17p CLL were enrolled and treated with venetoclax with a weekly dose escalation from 20 to 400 mg over 4 weeks and continued until disease progression. Response occurred in 79% of patients, with 8% achieving CR. One-year PFS and OS were 72 and 87%, respectively.[6] The response was stable in time, and the majority of the patients showed a reduction in absolute lymphocyte count, lymph node lesion diameter, and bone marrow infiltrate. The most frequent adverse effect was neutropenia, which occurred in 40% of patients. The management of this adverse effect included the administration of G-CSF or the prophylactic regimens of antibiotics.

Another phase II study assessed the efficacy of venetoclax monotherapy in the treatment of CLL patients relapsed or refractory to ibrutinib and idelalisib. In the first group (prior treatment with ibrutinib for a median of 17 months), 70% of patients responded to venetoclax, and 2% achieved CR. In the second group, 57% of patients (prior idelalisib for a median of 8 months) responded with partial remission (PR) as the best response. One-year PFS was 72% and OS was 90%, for all patients. The majority of both arms were refractory to ibrutinib (91%) or idelalisib (67%). The most common AEs were hematological toxicity (cytopenias), febrile neutropenia, and pneumonia.[19] The results of these trials led to the FDA approval of venetoclax in April 2016, as monotherapy for the treatment of RR CLL with del17p.[10]

Impact of venetoclax on MRD status

The concept of MRD status is becoming an increasingly important topic in CLL. Undetectable MRD status is achieved when there is less than 1 CLL cell per 10,000 lymphocytes (10^{-4}) detected in the bone marrow or blood. Low-level MRD status is achieved when the range is between 1 CLL cell per 100 lymphocytes and 1 CLL cell per 10,000 lymphocytes ($\geq 10^{-4}$ to $<10^{-2}$). There is increased OS and greater PFS in both CLL patients who have undetectable MRD-negative status and low-level MRD status. There are several promising current and

future trials focusing on the MRD status of patients who are on venetoclax monotherapy and combination regimens.[34] The results of these studies are increasingly favoring the use of targeted agents such as venetoclax over chemotherapy for the treatment of CLL.

Past studies

There have been multiple studies done to evaluate MRD status in CLL patients, with either venetoclax monotherapy or a venetoclax combination regimen. In a phase II pivotal trial, CLL patients with 17p deletions (n=158) were given venetoclax 400 mg per day after an initial dose ramp-up with MRD status evaluated. The median time for which venetoclax was administered was 23.1 months, and 30% of the patients achieved undetectable MRD status in the peripheral blood.[7]

Additionally, MRD status was evaluated in a pooled analysis from two phase 2 clinical trials of RR CLL patients on venetoclax monotherapy (n=176). The study showed that venetoclax monotherapy was associated with a high rate of undetectable MRD and low-level MRD in the peripheral blood in patients with CR or partial response (PR). Moreover, this analysis showed the association of undetectable MRD or low-level MRD with a longer PFS and superior outcomes using venetoclax monotherapy. PFS rates were 92.8% in those with undetectable MRD and 84.3% in those with a low-level MRD status, measured 24 months from the start of venetoclax monotherapy. This is important as prior to this analysis, due to the infrequent occurrence of undetectable MRD with B-cell receptor pathway inhibitors, the prognostic significance of undetectable MRD using targeted agents had not been established.[35]

In the MURANO phase III study, 398 patients with RR CLL were enrolled to either randomly receive six 28-day cycles of venetoclax–rituximab and thereafter venetoclax 400 mg once a day for 2 years or six cycles of bendamustine–rituximab. It was shown that fixed-duration venetoclax–rituximab led to significantly higher PFS compared to a fixed-duration bendamustine–rituximab combination regimen for CLL over the course of 2 years of treatment. Further analysis showed that there was higher undetectable MRD rates at the end of combination therapy in patients who received venetoclax–rituximab (62%) compared to those who received bendamustine–rituximab (13%). In patients on venetoclax–rituximab, there was additionally a low conversion rate (12%) to a detectable MRD. Higher clearance rates of MRD were seen in the venetoclax–rituximab combination compared to other agents used in the past. This suggests that using venetoclax instead of chemotherapy, rather than adding another targeted treatment to chemoimmunotherapy, could achieve better clinical results.[36]

Current/future studies

One of the components of an ongoing phase 2 study called CAPTIVATE evaluates undetectable MRD status in patients who are on a combination ibrutinib–venetoclax regimen: 164 treatment naive patients, who are all less than 70 years old, initially received three 28-day cycles of single-agent ibrutinib lead-in treatment followed by 1 year of combination with venetoclax ramp-up dosing up to 400 mg once a day. Of the 30 patients out of 164 total who completed six cycles of the combination treatment, 77% had undetectable MRD and 13% had a low-level MRD in the peripheral blood. Additionally, there were 14 patients out of 164 total who completed 12 cycles of combination treatment, of which 93% achieved undetectable MRD in the peripheral blood and 86% achieved undetectable MRD in the bone marrow. The completion date of this study is estimated to be in December 2020.[37]

Lastly, one of the components of a phase 1b study (GP28331) evaluated the undetectable MRD status of previously treatment naive patients (n=32) receiving a combination venetoclax–obinutuzumab (VEN+G) treatment. Obinutuzumab is an anti-CD20 monoclonal antibody. Patients were initially given six cycles of VEN+G, followed by six additional cycles of venetoclax monotherapy. The latter could be administered after 1 year if there was still MRD positivity or PR. Median time for the study was 11.3 months. Results showed that 100% of patients achieved undetectable MRD in the peripheral blood, and of the samples available, 74% achieved undetectable MRD in the bone marrow. Additionally, 72% of patients achieved CR or CR with incomplete blood count recovery (CRi), and there was 100% PFS at 1 year. With this data, VEN+G treatment may be a promising treatment option for treatment naive CLL patients, and this combination is currently being further tested in a phase 3 trial.[38]

Another ongoing clinical trial (GLOW/CLL3011) is a phase 3 study assessing PFS in previously treatment naive CLL patients receiving ibrutinib–venetoclax *versus* an obinutuzumab–chlorambucil (G-Clb) combination regimen. One of the components is evaluating the percentage of participants with undetectable MRD status over the course of 6 years. This study's completion date is estimated to be in April 2024.[39]

In Table 4, we show the studies' features that led to the current indication of the use of venetoclax in the treatment of CLL.

Acute myeloid leukemia

AML is an aggressive malignancy of myeloid progenitor cells. Important characteristics of AML cases include the enormous clinical and molecular heterogeneity, which is related to the variable outcomes after chemotherapy. For a long time, cytotoxic induction therapy combining anthracycline and cytarabine has been the gold-standard treatment with little increase in survival, despite the addition of novel agents.

AML cells depend on the expression of BCL-2 for survival.[40] Overexpression of this antiapoptotic protein is also implicated in chemotherapy resistance, even though this mechanism has not yet been fully described.[41]

Pan and colleagues published the first evidence of venetoclax efficacy, demonstrating selective blast killing in AML cell lines,

Table 4. Selected venetoclax clinical trials in CLL.

ClinicalTrials.gov number	Author	Phase	Study design	Follow-up
NCT02141282	Coutre S.	2	Relapsed/refractory CLL	14 months (1–29)
NCT02141282	Jones J.	2	Relapsed/refractory CLL	14 months (8–18)
NCT01889186	Stilgenbauer S.	2	Relapsed/refractory CLL	12.1 months (10.1–14)
NCT01328626	Roberts A.	1	Relapsed/refractory CLL	17 months (1–44)
NCT01682616	Seymur J.	1b	Relapsed/refractory CLL	28 months (19–32)
NCT02427451	Rogers K.	1b	Relapsed/refractory CLL	24.4 months
NCT01685892	Flinn I.	1b	CLL	29.3 months (1–29)
NCT02401503	Cramer	2	CLL	16 months (15–18)
NCT02005471	Kater A.	3	Relapsed/refractory CLL	9.9 months (1.4–22.5)

CLL, chronic lymphocytic leukemia.

primary patient samples, and murine primary xenografts by this agent.[42]

Primary studies have published that patients with mutated isocitrate dehydrogenase proteins 1 and 2 (IDH 1/2) are more likely to respond to BCL-2 inhibition by venetoclax.[43] In the first clinical trial using venetoclax monotherapy (800 mg daily) in 32 high-risk RR AML patients, the ORR was 19%. However, 38% had IDH 1/2 mutation, of whom 33% reached CR or CRi. The AEs grade 3/4 presented included nausea, vomiting, diarrhea, febrile neutropenia, and hypokalemia.[44] The low response rates with short response duration motivate further studies of regimens combining venetoclax with other agents that had demonstrated synergy in preclinical studies. These trials were conducted in older patients, with previously untreated AML unfit for intensive induction chemotherapy.

Wei and colleagues in 2018 published the results of a phase Ib/II clinical study of venetoclax with LDAC in newly diagnosed unfit older patients with AML with no indication for intensive regimens.[45] A total of 82 patients were enrolled to receive cytarabine 20 mg/m^2/daily for a total of 10 days associated with venetoclax 600 mg once daily for 28 days. Venetoclax was given in a 5-day ramp-up for the first cycle. Patients with poor-risk cytogenetics represented a 32% of the total, and 49% had secondary AML. The combination treatment was well tolerated, with cytopenias and infections as the most common grade 3 AEs and only three cases of high-grade TLS. The CR/CRi rate was 54%, with a median time to response of 1.4 cycles. The higher response rate was achieved in patients with *de novo* AML (CR/CRi of 71%), and CR/CRi of 35% in secondary AML. The median OS was 10.1 months with an estimated 1-year OS of 27%.

In a multicenter phase Ib study, venetoclax was tested in combination with hypomethylating agents (HMAs), decitabine or azacitidine, in elderly patients with newly diagnosed AML unable to receive intensive therapy.[46] A total of 174 patients with a median age of 74 years were classified into three groups (comparing 400, 800 and 1200 mg doses of venetoclax), and the 400 and 800 mg cohorts were tested further in a dose expansion cohort due to optimal safety and efficacy profiles. Mutations present in this cohort included TP53 (25% of patients), FLT3 (12%), IDH 1/2 (24%), and NPM1 (16%). Adverse cytogenetics was observed in 49% of the patients. During the expansion phase, patients were randomized to receive venetoclax 400 or 800 mg with either decitabine 20 mg/m^2 for 5 days or azacitidine 75 mg/m^2 for 7 days every 28 days. Grade 3/4 AEs were infections (45% of cases), pneumonia (18%), fungal infections (8%), and sepsis (10%). The CR/Cri rate was 68% with a median time to response of 1.2 cycles. No difference in response rate was observed between the venetoclax 400 and 800 mg groups (p=0.35).

Based on these results, in November 2018, the FDA approved venetoclax in combination with an HMA or LDAC for newly diagnosed AML patients or unfit-for-intensive-therapy AML patients aged 75 years and older.[47]

Other studies have published results of venetoclax in combination with an HMA in different dosage (decitabine for 10 days) with an overall CR/Cri rate of 53% after a median of 2 cycles, with a 64% rate of MRD negativity by flow cytometry.[48]

Today, some clinical trials are evaluating the use of venetoclax as a frontline therapy for fit older patients with indication of intensive chemotherapy. The phase Ib study (CAVEAT) enrolled 44 patients to receive venetoclax with dose-reduced intensive chemotherapy (5+2).[49] Of the total of patients, 41% had secondary AML and 38% previous exposure to an HMA. The median age was 72 years. A dose escalation of venetoclax of 50–600 mg daily for 14 days with a 7-day dose ramp-up was performed, followed by cytarabine 100 mg/m^2 for 5 days and idarubicin 12 mg/m^2 for 2 days during induction. In case of achieving CR, 4 cycles of consolidation regimen comprising venetoclax for 14 days, cytarabine for 2 days, and idarubicin for 1 day are indicated, followed by maintenance therapy with single-agent venetoclax for 14 days every 28 days for 7 cycles. The overall CR/CRi rate was 69%: 95% in patients with newly

Table 5. Selected venetoclax clinical trials in AML.

ClinicalTrials.gov number	Author	Phase	Study design	Follow-up
NCT01994837	Konopleva M.	2	Relapsed/refractory AML	Not given
NCT02203773	DiNardo C.	1b	Untreated AML	12.4 months (8.3–15)
NCT02287233	Wei A.	1b/2	Untreated AML	4.2 months (0.2–29)

AML, acute myeloid leukemia.

diagnosed AML and 42% in those with secondary AML. No TLS was reported.

The combination of FLAG-IDA (fludarabine 30 mg/m^2 days 2–6, cytarabine 2 g/m^2 days 2–6, idarubicin 6 mg/m^2 days 4–6, G-CSF 5 mcg/kg daily for 7 days) with venetoclax is currently being evaluated in 11 patients with R/R AML eligible for intensive therapy in a phase Ib/II clinical trial.[50] The venetoclax dose was of 200 mg, with a 2-day ramp-up, on a 28-day cycle. Due to high responses but increased AEs (neutropenic fever, bacteremia, and sepsis), the clinical trial protocol was amended to reduce the duration of venetoclax to 14 days and reduce the dose of cytarabine to 1.5 g/m^2. After induction and consolidation therapy, non HSCT patients patients could continue maintenance therapy with venetoclax 400 mg daily. Patients with CR/CRi represented 73%, all but one occurring within the first cycle. Currently, a phase II trial is ongoing.

A summary of the main studies conducted in AML is shown in Table 5.

Use in other hematological malignancies

Clinical data are available regarding the sequential use of this novel drug in other hematological pathologies. In the case of lymphomas, there is no great sensitivity to venetoclax, but promising results have been achieved in patients with MCL and DLBCL. In multiple myeloma patients, venetoclax is especially active in those with translocation t(11;14), even if high-risk features such as del17p are also present (Table 6).

Mantle cell lymphoma

MCL is an aggressive B-cell lymphoma developing from naive B cells.[51] The most common translocation associated with this pathology is t(11:14)(q13;q32), resulting in overexpression of cyclin D1 in 70–95% of cases.[52] However, additional genetic changes (loss of tumor suppressor genes *TP53*, *ATM*, and *CDKN2A* or gain of oncogenes *BCL-2*, *c-MYC*, and *SYK*) are usually necessary for malignant transformation.[53] Almost 95% of clonal cells in MCL are BCL-2 positive.[43] The presence of *c-MYC*, which participates in the oncogenesis process, might contribute to BCL-2 overexpression as well.[54]

A phase I study with RR NHL included 106 patients; the group of RR MCL patients (median of three previous therapies) was one of the best responding groups, with an ORR in 75% and CR in 21% of patients. One-year OS was achieved in 82%, and median PFS was 14 months. The most common grade 3/4 toxicity was hematological (cytopenias), and secondary hyponatremia and infections (lower respiratory tract infection and influenza) were present. No clinical TLS was observed.[55]

A phase II study published results of treatment combination with venetoclax and ibrutinib in two groups of patients: the first group of RR MCL patients (95% of total) with median of two previous therapies and of which 30% failed autologous stem cell transplantation (SCT) and a second group of untreated MCL patients (5%). The ORR of 71% and CR were achieved in 63% of all patients, and estimates of PFS and OS at 8 months were 74 and 81%, respectively. Two cases presented with TLS, with high tumor burden, leading to a revision of the protocol.[56] A phase III trial comparing venetoclax plus ibrutinib with ibrutinib or venetoclax monotherapy is ongoing (NCT03112174).

Diffuse large B-cell lymphoma

DLBCL represents the most common of the aggressive lymphomas. Morphologically it is characterized by the diffuse growth of mature neoplastic large B lymphoid cells.[44] It comprises several distinct histologic, immunophenotype, and genetic subgroups. Mutations of the *BCL6* (30%), *BCL-2* (20–30%), and *c-MYC* (5–22%) genes are the most common genetic alterations.[57] BCL-2 overexpression is the result of the translocation t(14;18)(q32;q21) presented in 20–30% of patients and the amplification of 18q21-23 presented in 21% of DLBCL patients.[58] Double-hit DLBCL is a subgroup with a poor clinical outcome that harbors concurrent gene rearrangement of *c-MYC* and the *BCL-2*, *BCL-6*, or *BCL-3* proto-oncogene. This group represents less than 10% of DLBCL, with the most frequent MYC/BCL-2 subtype carrying translocation of *c-MYC* and t(14;18)(q32;q21).[59]

Davids and colleagues presented the results of a phase I study in 34 patients with RR DLBCL (median of three previous therapies) treated with venetoclax in monotherapy. The response rate for patients with DLBCL was 18%, and four patients achieved CRs, including two patients who

Table 6. Selected venetoclax malignancy trials.

ClinicalTrials.gov number	Author	Phase	Study design	Follow-up
NCT01794520	Kumar S.	1	Relapsed/refractory t(11;14) multiple myeloma	Ongoing
NCT01328626	Davids M.	1	Relapsed/refractory non-Hodgkin lymphoma, follicular lymphoma, diffuse large B-cell lymphoma, Richter transformation, Waldenström macroglobulinemia, and marginal zone lymphoma.	5.3 months (0.2–46)
NCT01794507	Moreau P	1b	Relapsed/refractory multiple myeloma	5.9 months (0.3–29)
NCT02055820	Zelenetz A.	1b/2	Non-Hodgkin lymphoma	22 months (11.4–36)

went on to undergo allogeneic SCT and remain in CR after transplantation. B-cell receptor pathway antagonists have shown limited efficacy in DLBCL, and therefore, novel agents such as venetoclax are urgently needed for combination regimens.[44]

At the American Society of Hematology (ASH) 2016 annual meeting, preliminary data using combination therapy, venetoclax plus R-CHOP/G-CHOP (rituximab/obinutuzumab, cyclophosphamide, doxorubicin, vincristine, and prednisone), were presented. Patients with different types of lymphoma (marginal zone lymphoma [MZL], MCL, FL, DLBCL) with untreated disease or RR disease were enrolled. Results were presented for all NHL types together, and they were nearly the same in cohorts. Patients treated with venetoclax and R-CHOP achieved ORR in 86% of patients and CR in 67% of patients, and in the group of venetoclax and G-CHOP, ORR and CR were 81 and 62%, respectively. Toxicity seemed to be higher than venetoclax in monotherapy.[60] Further studies are needed prior to considering venetoclax in DLBCL.

Follicular Lymphoma

FL is an indolent lymphoproliferative disease. It originates from the malignant germinal center B cells (centrocytes and centroblasts). Almost 30–40% of cases undergo histologic transformation typically to DLBCL.[61] The most frequent translocation presented in 80–90% cases is t(14;18)(q32;q21),[62] but other aberrations might be caused by various genes, including *c-MYC* and *TP53*.[63]

Davids and colleagues presented the results of their phase I study of RR NHL using venetoclax in monotherapy in 29 patients with RR FL. Treatment was successful in 38% cases, and 14% of CRs were observed. No deaths were reported. The estimated median PFS was 11 months. Toxicity was acceptable and similar to all groups/types of NHL.[47]

Another phase I study of 24 patients with untreated RR FL using the combination of venetoclax plus standard immunochemotherapy (R-CHOP/G-CHOP) was published. Preliminary results were published for the whole cohort of NHL together. ORR and CR were 86% (18/21) and 67% (14/21) *versus* 81% (17/21) and 62% (13/21), respectively, in venetoclax plus R-CHOP *versus* venetoclax plus G-CHOP.[44]

Acute lymphoblastic leukemia

Over the past decades, treatment of pediatric B-cell precursor ALL (BCP-ALL) has evolved to be more and more successful, improving survival rates to more than 80%[64]. However, decreased tolerance to therapy due to toxicity and minimal residual positivity with subsequent relapse remain issues associated with poor outcome. The current treatment regimen includes chemotherapy associated with kinase inhibitors (imatinib or dasatinib) in the particular case of Philadelphia chromosome-positive ALL. A preclinical trial in mice demonstrated that the combination of dasatinib and venetoclax is synergistic and tolerable *in vivo* and that the antileukemic effects were markedly improved.[65]

Two clinical trials will study the efficacy of venetoclax in monotherapy in RR ALL. A phase I study is recruiting pediatric patients and young adults with RR ALL to address the safety and pharmacokinetics of venetoclax monotherapy (NCT03236857). Another phase 1 study with dose escalation is underway and recruiting participants and will analyze the safety and pharmacokinetics of venetoclax, navitoclax, and chemotherapy in recurrent ALL (NCT03181126).

Multiple myeloma

Multiple myeloma (MM) is a heterogeneous disease due to the dependence on antiapoptotic proteins such as

BCL-2, BCL-X_L, or MCL-1. Nowadays, the proportion of MM patients BCL-2 dependent is unknown.[66] Nevertheless, it has been demonstrated in MM lines that venetoclax is highly effective in a specific subset of t(11;14) MM, mainly due to the higher BCL-2/MCL-1 ratio. Interestingly, in this subgroup of MM patients, even if high-risk 17p deletion is present, venetoclax has shown an active response. Moreover, it has been shown that venetoclax works synergistically with dexamethasone and is able to increase the expression of BCL-2 and BIM, so the MM cells become more sensitive to venetoclax.[67]

In the monotherapy approach, a phase I trial recruited 66 RR MM patients with a median of five previous therapies. Overall, 21% of patients responded to venetoclax treatment (ORR), with 15% reaching a very good partial response (VGPR) or better. Almost 40% of patients carried the t(11;14) and were refractory to bortezomib and lenalidomide, and they were treated with at least four prior regimens.[68]

Venetoclax alone or in combination had an acceptable safety profile in all the phase I trials; the most common grade 3/4 AEs were thrombocytopenia, anemia, neutropenia, and infectious complications.[69]

In RR patients, the combination of venetoclax and standard therapy with dexamethasone and bortezomib is currently being studied (NCT02755597; NCT01794507). Other trials combining venetoclax with daratumumab, a CD38 antibody (NCT033141810), are recruiting patients right now.

Conclusions

Deregulation of the intrinsic apoptotic pathway due to overexpression of antiapoptotic proteins is found in a variety of tumor types. The blockade of these proteins might restart the process of cell suicide in malignant cells. Venetoclax is the first selective BCL-2 inhibitor molecule and BH-3-only mimetic. Numerous studies have been conducted to show venetoclax's therapeutic use. Although this drug has been approved for the treatment of CLL, SLL, and AML, new indications are expanding rapidly, and many studies suggest that the therapeutic potential is not yet exploited.

At present, there are many clinical trials recruiting patients for the treatment of hematological pathologies using venetoclax in monotherapy or in combination. Taking all the efficacy data and its low toxicity into consideration, venetoclax might become an important part of the therapeutic arsenal against a substantial number of blood disorders. But despite promising results in clinical tests, there are already signs of resistance; thus, it is important to establish additional prognosis markers that can predict the sensitivity to this drug and explore potential resistant mechanisms.

What is clear is that the use of targeted therapy, like venetoclax, as single agent or in combination, will improve the landscape of treatment options for patients not eligible for conventional therapies, helping in the route toward the cure of hematological malignancies.

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