Venetoclax, the first available bcl-2 antagonist for chronic lymphocytic leukaemia

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SUMMARY

Venetoclax, the first-in-class bcl-2 antagonist, has demonstrated deep and durable remissions as a single agent in relapse/refractory chronic lymphocytic leukaemia patients with a 17p deletion or chronic lymphocytic leukaemia refractory to B-cell receptor inhibitors or progressive after B-cell receptor inhibitor discontinuation. As reimbursement of venetoclax by the Belgian national public health insurance has been provided, this review describes mechanism of action, dosage and administration, efficacy and tolerability. As venetoclax can rapidly reduce the chronic lymphocytic leukaemia load, precautions to avoid tumour lysis syndrome depending on risk assessment is a sine qua non. Despite the convenience afforded by this oral, once daily formulation, treating physicians and patients must be aware of drug adherence and drug-drug interactions which can challenge treatment benefits and risks.

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INTRODUCTION

The introduction of the Bruton's tyrosine kinase (BTK) and phosphatidylinositol-3-kinase delta (PI3Kδ) inhibitors have revolutionised the treatment of chronic lymphocytic leukaemia (CLL) over the last years. Today we know that response to these B-cell receptor inhibitors (BCRi) is not infinite and that new treatment options are still needed.[1] The b-cell lymphoma 2 (bcl-2) protein was discovered in 1986 as the first of the anti-apoptotic proteins.[2] Deregulated expression of these anti-apoptotic proteins is a feature of many cancers, and especially of haematological malignancies. This deregulation is not only responsible for tumour development and maintenance but also for therapeutic resistance. Therapies that target these survival proteins are now making their way into the clinic, although the search began in the nineties. The first approaches used antisense molecules targeting bcl-2 translation or transcription. Later, small molecule inhibitors were developed thanks to the knowledge of the structural biology of the different bcl-2 proteins, their hydrophobic binding groove and their reciprocal interactions.[3]

After the development of weak pan-bcl-2 antagonists, dual bcl-2/bcl-extra large (xL) antagonists entered clinical trials. As a lot of patients developed dose-dependent thrombocytopenia due to the bcl-xL inhibition in the platelets, re-engineering occurred to generate a selective bcl-2 antagonist.[4] Venetoclax is the first orally available selective bcl-2 antagonist that entered clinical trials in CLL and Non Hodgkin lymphoma (NHL) in 2011.[2,3] In 2016, venetoclax was approved as monotherapy by the Food and Drug Administration (FDA) for the treatment of CLL in the presence of a 17p deletion who received at least one prior therapy. The European Medicines Agency (EMA) approved venetoclax at the end of 2016, not only for the treatment of adult CLL patients in the presence of a 17p deletion or p53 mutation who are unsuitable for or have failed a BCRi, but also for patients without p53 dysfunction who failed both chemo-immunotherapy (CIT) and a BCRi. As reimbursement of venetoclax in Belgium has been provided, we review mechanism of action, dosage and administration, efficacy, as well as adverse events (AEs) with a special interest for the prevention of tumour lysis syndrome (TLS).

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Keywords: bcl-2 inhibitor, chronic lymphocytic leukaemia, p53 mutation, treatment, tumour lysis syndrome, venetoclax, 17p deletion.

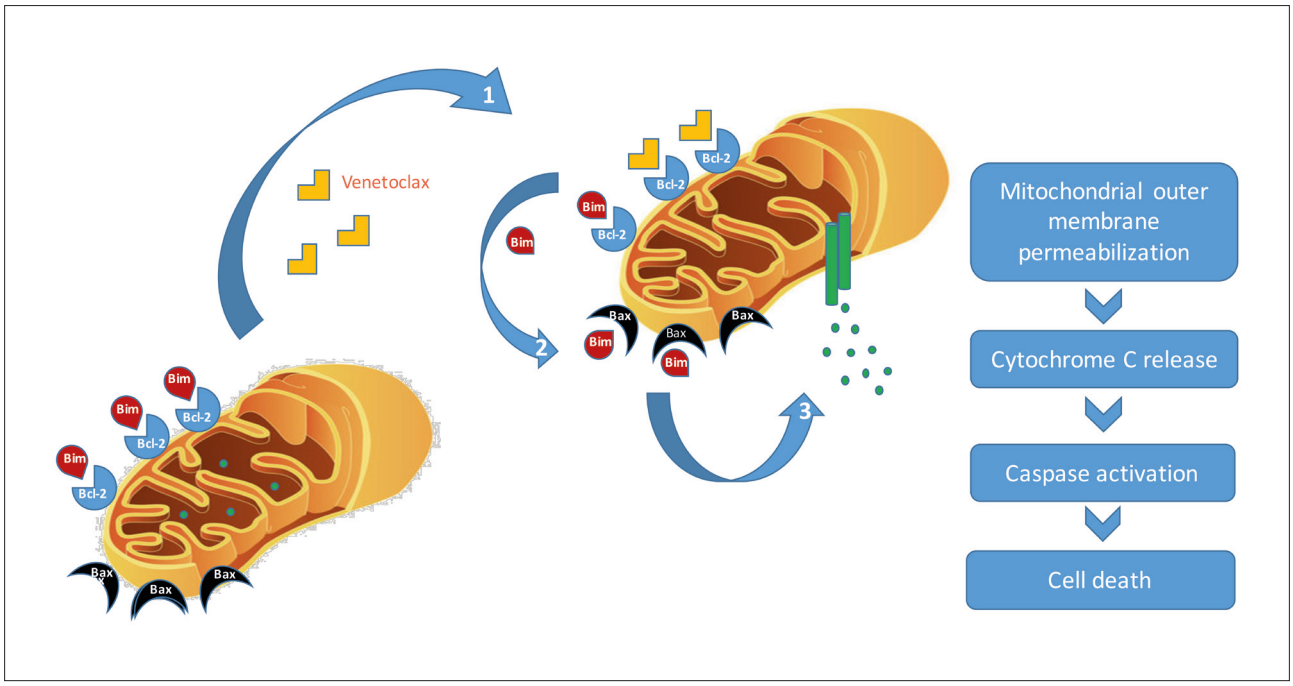

FIGURE 1. Venetoclax: mechanism of action. Venetoclax binds directly to the BH3-binding groove of bcl-2, releasing pro-apoptotic proteins (Bim) that can initiate mitochondrial outer membrane permeabilisation, caspase activation and cell death.[1-3]

MECHANISM OF ACTION

Venetoclax is a potent, selective inhibitor of bcl-2. Bcl-2 is one of the most important anti-apoptotic proteins. Over-expression of bcl-2 has been demonstrated in CLL where it mediates cell survival and chemoresistance.[5] Venetoclax binds directly to the BH3-binding groove of bcl-2, releasing pro-apoptotic proteins that can initiate mitochondrial outer membrane permeabilisation, caspase activation and cell death (*Figure 1*).[4] *In vivo* and *in vitro* experiments have shown that normal peripheral blood B-cells are also highly sensitive to venetoclax in contrast to T-cells and granulocytes.[6] In R/R CLL patients (n=57) treated with venetoclax (median time on study nineteen months (mo) (range 0.5-44mo)) no reductions were observed in the mean absolute counts of CD3+, CD4+, CD8+ T-cells or NK cells nor in the immunoglobulin levels.[7]

ADMINISTRATION AND DOSAGE

Venetoclax is orally administered, once daily, preferentially with a meal as this increases the maximum concentration and the area under the curve (AUC) by three to five times. Film-coated tablets should be swallowed with water at the same time each day. The tablets (10 mg, 50 mg or 100 mg) should not be broken or chewed. The recommended starting dose is 20 mg. This dose will be titrated to 50 mg, 100 mg, and 200 mg to the final dose of 400 mg in a five week period when no TLS alerts occur. If a dose of venetoclax is missed within eight hours of the time that it is usually taken, the dose can still be taken. If a patient misses a dose by more than eight hours or vomits following dosing, then the next dose will be postponed to the following day. Venetoclax is metabolised primarily by CYP3A and is eliminated mainly via faeces (99.9%) (unchanged 20.8%, metabolites 79%) and less via urine (<0.1%). The metabolite, M27, is totally inactive. Age, gender, and body weight do not affect the pharmacokinetics of venetoclax. The molecule is not recommended during pregnancy and should not be used during breast-feeding. As venetoclax has the potential of harmful effects on fertility, sexually active men and women of childbearing potential must use effective contraceptives for at least 30 days following completion of treatment.[8,9] In healthy animals venetoclax did not cross the blood brain barrier. Evaluation of penetration of the blood brain barrier in animals with CNS tumours and patients with CNS lymphoma has just been started (personal communication with Abbvie). For the moment treatment is continued till disease progression or unacceptable toxicity.[8,9] Randomised clinical trials have been started to investigate if patients reaching a minimal residual disease status (MRD) can stop treatment.

DOSE MODIFICATIONS

TOXICITY

Dose interruptions are necessary for any grade 3-4 non-haematological toxicity, a grade 3 neutropenia with infection

or fever and any grade 4 haematological toxicity. When the toxicities improve to grade 1, or completely recover, venetoclax can be restarted at full dose. When toxicities recur, it is advised to dose reduce venetoclax from 400 to 300 mg, from 300 to 200 mg, from 200 to 100 mg, from 100 to 50 mg, from 50 to 20 mg, and from 20 to 10 mg.[9]

HEPATIC IMPAIRMENT

As venetoclax is metabolised primarily by the liver, it is advised to closely monitor for toxicity in patients with mild or moderate impairment according to the Child Pugh classification. In patients with severe hepatic impairment venetoclax is not recommended.[9]

RENAL INSUFFICIENCY

As the clearance of venetoclax by the kidneys is negligible, the advised dosing of venetoclax must not be modified. However, good renal function is necessary to cope with TLS. Therefore, it is advised to monitor closely for toxicity in patients with a creatinine clearance (CrCl) between 30-80 ml/min. As venetoclax has not been studied in patients with a CrCl <30 ml/min or on dialysis, no dose recommendations in these situations exist.[9]

DRUG AND FOOD INTERACTIONS

Venetoclax is predominantly metabolised by CYP3A4. It is advised to avoid moderate inhibitors during the titration phase and thereafter or reduce the dose by at least 50%. As strong inhibitors of CYP3A4 (azoles, clarithromycin, telithromycin, etc.) increase the plasma concentration and the AUC of venetoclax by two to three and six to eight fold, respectively, it is contraindicated to use them concomitantly during the ramp-up. After completion of the titration phase it is advised to reduce the dose of venetoclax by at least 75% when the CYP 3A4 inhibitor is necessary. Grapefruit, Seville oranges and starfruit must be avoided for the same reasons. Co-administration of venetoclax with a CYP3A4 inducer (carbamazepine, phenytoin, rifampicine, and St. John's wort) decreases the plasma concentration and AUC two to three fold and should also be avoided. All gastric acid reducing agents seem not to affect the bioavailability of venetoclax. As bile acid sequestrants reduce the absorption of venetoclax, it is advised to administer venetoclax at least four to six hours after the sequestrant. When warfarin is given concomitantly with venetoclax it is advised to monitor INR closely as the concentration and AUC of warfarin could increase. Venetoclax by itself is a P-glycoprotein (P-gp), breast cancer resistance protein (BCRP) and organic anion transporting polypeptide 1B1 (OATP1B1) inhibitor *in vitro*. P-gp, BCRP and OATP1B1 substrates with a narrow therapeutic index must be used with caution and when orally given, separated from the venetoclax administration. Statins are OATP1B1 substrates and it is recommended to closely monitor statin related toxicity.[9] The help of a clinical pharmacist to review all drug-drug interactions and especially interactions with non prescribed products to reduce toxicity and enhance efficacy looks not redundant.

EFFICACY

Venetoclax as single agent has been approved for the treatment of CLL due to the results of the following two trials. The M13-982 trial consisted of 107 R/R CLL patients with a 17p deletion, who received at least one prior treatment.[10] Fifty one more patients were added in the expansion cohort.[9] The median age of the patients was 67 years (y), 65% was male and the median number of prior treatments was two (range 1-10). The overall response (ORR) achieved was 79% by independent review committee assessment. A complete remission (CR) or complete remission with incomplete recovery of blood counts (CRi) and nodular partial remission (nPR) was reported in eleven patients (10%). The time to response was very short (median of 0.8 mo). The twelve mo PFS and overall survival (OS) were 72% and 87%, respectively.[10] In an investigator-assessed analysis, including all 158 patients, the ORR was 77% (18% CR/CRi and 6% nPR). The mDOR was 27.5 mo, with a mPFS of 27.2 mo. Using a cut-off of one CLL cell per 10^{-4} leukocytes, 27% of patients (42/158) were shown to have no MRD in the peripheral blood (fifteen were also MRD-negative in bone marrow).[9] In the M14-032 trial, 64 CLL patients who were refractory while on treatment with ibrutinib (n=43) or idelalisib (n=21) or progressed after ibrutinib/idelalisib discontinuation were treated with venetoclax. The median age in this study was 67 y and 75% of patients were male. The median number of prior treatments was four (range 1-12). A 17p deletion was found in 36% (23/61), an 11q deletion and a TP53 mutation in respectively 26% (19/62) and 26% (16/61) of patients. In the total study cohort, the ORR was 64%, with a CR/CRi in 9% and a nPR in 3%. The six and twelve mo PFS were 89% and 72%. Venetoclax could induce MRD negativity in 25% (16/64) of tested patients in the peripheral blood (one also in bone marrow).[11]

TOLERABILITY OF VENETOCLAX MONOTHERAPY (*Table 1*)

The following treatment emergent AEs (all grades in ≥10% and grades 3-4 ≥2% of subjects) were seen in patients treated with venetoclax monotherapy in the CLL/SLL studies (n=410): gastro-intestinal complaints (75.4%; 9.3%) (diarrhoea (42.2%; 2.7%), nausea (40.2%), constipation (16.3%),

TABLE 1. Treatment emergent adverse events in patients treated with venetoclax monotherapy in CLL/SLL studies (n=410).

		all grades >10% of subjects	Grade 3-4 >2% of subjects
Gastro-intestinal toxicity		75.4%	9.3%
	diarrhoea	42.2%	2.7%
	nausea	40.2%	
	constipation	16.3%	
	vomiting	15.6%	
	abdominal pain	10.5%	2%
Infections		70.7%	21.2%
	pneumonia	10.7%	6.3%
	upper respiratory tract infections	27.3%	
Haematological toxicity		62.7%	49%
	anaemia	28.8%	15.6%
	neutropenia	41%	36.8%
	thrombocytopenia	20.7%	13.4%
Fatigue		30.5%	2.4%
Peripheral oedema		12.9%	
Pyrexia		18.3%	
Arthralgia		10.7%	0.1%
Cough		19.5%	
Dyspnea		10%	
Headache		17.8%	
Dizziness		10.5%	
Tumour lysis syndrome			4.6%

vomiting (15.6%), abdominal pain (10.5%; 2%)), infections (70.7%; 21.2%) (pneumonia (10.7%, 6.3%), upper respiratory tract infection (27.3%)), cytopaenias (62.7%; 49%) (anaemia (28.8%; 15.6%), neutropenia (41%; 36.8%), thrombocytopenia (20.7%; 13.4%)), fatigue (30.5%; 2.4%), peripheral oedema (12.9%), pyrexia (18.3%), arthralgia (10.7%), 0.1%), cough (19.5%), dyspnea (10%), headache (17.8%), dizziness (10.5%).[12] Although gastro-intestinal complaints were the most frequently noticed AEs, they were mostly grade 1-2. Colitis as observed with the use of PI3Kd inhibitors has not been seen. Complaints were most prevalent the first months after starting treatment and decreased significantly thereafter.

Neutropenia was the most common observed haematological toxicity. Grade 3-4 neutropenia has been reported in 36.8% of patients. Although the frequency of neutropenia decreased with time, some patients showed a persistent neutropenia. Myeloid growth factors can be used to deal with the neutropenia and to continue with venetoclax. We only can speculate on the mechanism of neutropenia. Apoptosis and survival of myeloid precursors and neutrophils is highly dependent on the ratio pro- versus anti-apoptotic bcl-2 like proteins. It seems that bcl-2 is more important in myeloid precursors than in mature neutrophils which only have a life span of a few hours. If in some patients bcl-2 is the most important pro-apoptotic protein, we can expect that these patients can develop neutropenia on treatment with venetolax.[13] Grade ≥3 infections were noticed in 21% of patients. Autoimmune cytopaenia (haemolytic anaemia and thrombocytopenia) has been reported during venetoclax treatment (AIC) (1.5%).

MEDICAL EVENT OF SPECIAL INTEREST WITH VENETOCLAX: TUMOUR LYSIS SYNDROME (TLS) (*Figure 2*)

As venetoclax can cause a deep reduction in tumour cells as early as six to eight hours (h) following the first dose, clinical or laboratory TLS can occur. The first measure to prevent TLS is to use the recommended ramp-up, meaning that the dose will be titrated from 20 mg to respectively 50 mg, 100 mg, and 200 mg to the final dose of 400 mg in a five week period when no TLS alerts occur. Next to titrating the dose, preventive measures according to risk group assessment is also mandatory to avoid TLS. Tumour burden, renal function and other comorbidities define three risk groups (high, median and low risk). Tumour mass is assessed by lymphocyte count (< or ≥25000/μl) and measurement of single lymph nodes on CT-scan (< 5 cm, between 5 and 10 cm, ≥10 cm). A 'low tumour burden' is defined as single nodes <5 cm 'and' a lymphocyte count of <25000/μl. A 'median tumour burden' is defined as any single node between 5 and 10 cm 'or' a lymphocyte count ≥25000/μl. A 'high tumour burden' is defined as a single node ≥10 cm 'or' a single node ≥5 cm with a lymphocyte count ≥25000/μl. The risk score is upgraded by the presence of a huge splenomegaly and/or a reduced renal function (CrCl <80 ml/min). Additional comorbidities and pre-existing electrolyte or uric acid abnormalities can increase the risk further. Oral or intravenous hydration, anti-hyperuricemic drugs, laboratory assessments and eventually hospitalisation are part of the TLS preventive measures. All patients, independent of risk group, should be adequately hydrated during the dose-titration phase. Patients should be instructed to drink ± 2.0 L of water daily, two to three days prior to initial dosing and the days of each subsequent dose increase. Intravenous fluids should be administered to high risk patients or for those who cannot maintain an adequate level of oral hydration. All patients, independent of risk group, should receive antihyperuricemic agents (allopurinol) two to three days prior to the start of treatment which has to be continued through the titration phase. When the baseline uric acid is still too high at the start of venetoclax or at a dose elevation rasburicase has to be considered according to the local policy guidelines. For all patients, blood chemistries should be assessed prior to the initial dose to evaluate kidney function, uric acid and electrolyte (potassium, calcium, phosphorus) abnormalities. Blood chemistries should be reassessed prior to each subsequent dose increase during the titration phase. Blood chemistries should be monitored at six to eight hours and at 24 h after the first 20 and 50 mg of venetoclax. The next venetoclax dose (d2 or d9) should not be administered until the 24 h blood chemistry results have been evaluated. Electrolyte abnormalities should be corrected promptly. The same monitoring schedule should be followed at the start of the 100 mg dose or higher for patients who continue to be at TLS risk or have shown problems before. Hospitalisation is recommended for patients with a high tumour burden or intermediate tumour burden with additional risk factors as a huge splenomegaly, a reduced renal function (CrCl <80 ml/min), relevant comorbidities, uric acid elevation or electrolyte abnormalities especially at the start of 20 and 50 mg. Following the above mentioned preventive TLS measures laboratory TLS was reported in five patients without clinical TLS in the M13-982 study and laboratory TLS was seen in only one patient in the M14-032 trial.[10,11]

The medical events of special interest seen with the BCRi such as redistribution lymphocytosis, increased bleeding tendency, atrial fibrillation, transaminitis, non-infectious pneumonitis and colitis have not been observed with venetoclax.

RESISTANCE

Approximately 20% of CLL patients in the registration trials do not respond to venetoclax and +/- 40% show disease progression after initial response. The mechanisms responsible for primary or acquired resistance to venetoclax remain to be elucidated. Tumour escape via upregulation of other anti-apoptotic proteins not targeted by venetoclax (myeloid cell leukemia-1 (Mcl-1), bcl-xL, etc.) and/or decrease in one or more pro-apoptotic proteins or acquired changes in bcl-2 (mutations in the bcl-2 BH3 binding groove, bcl-2 phosphorylation).[14,15] *In vitro* studies have already shown that anti-apoptotic molecules as Mcl-1, bcl-xL and bcl-2 related protein A1(bfl-1)) can be upregulated in CLL cells residing in the lymph node through protective signalling from the micro-

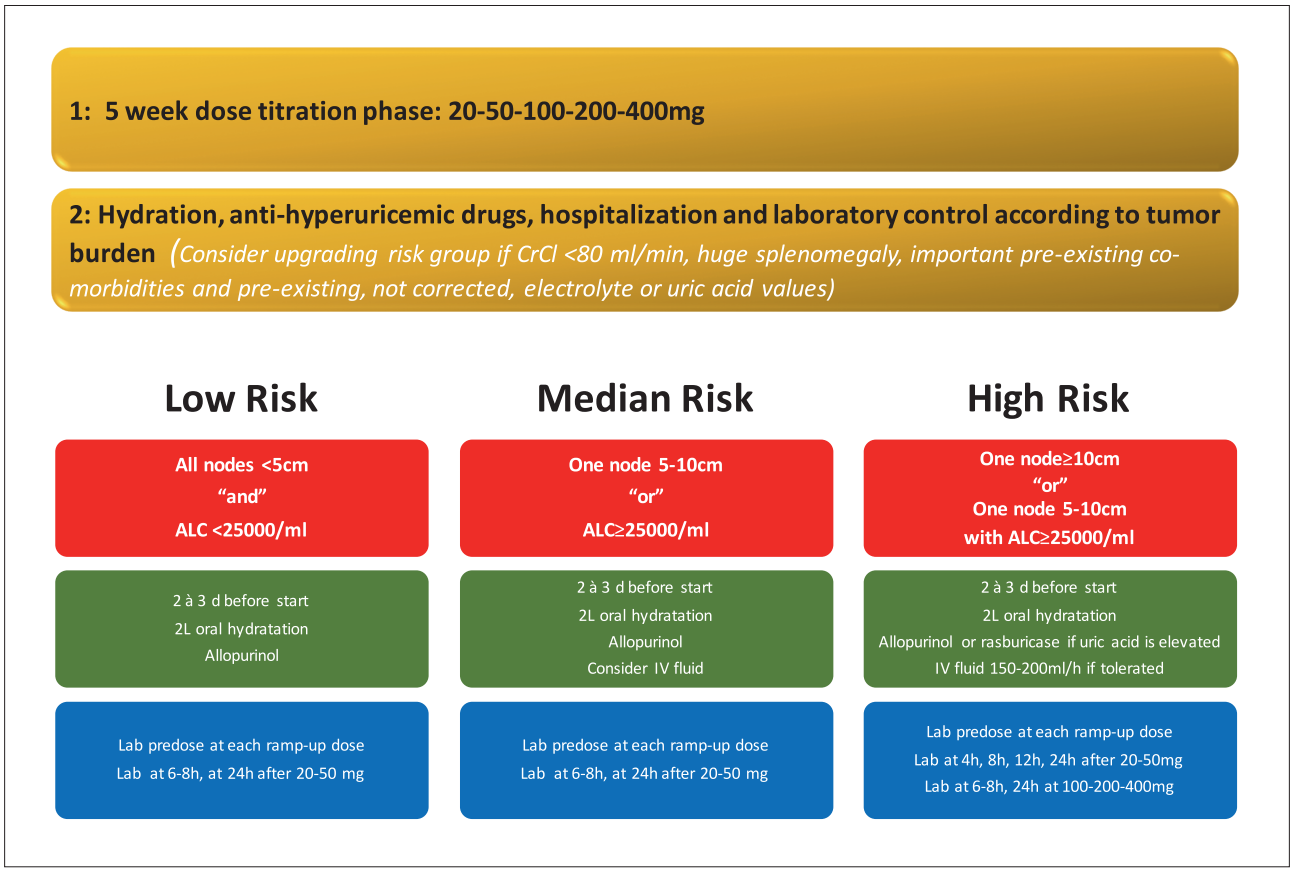

FIGURE 2. Prevention of tumour lysis syndrome by venetoclax.
Abbreviations: ALC: absolute lymphocyte count, L: litre, IV: intravenous, h: hour, CrCL: creatinine clearance.

environment.[16] It can be anticipated that multiple causes are responsible for the acquired resistance to venetoclax.[14-16]

FUTURE DIRECTIONS

Although the efficacy of venetoclax as a single agent is high in CLL, combination with anti-CD20 molecules (rituximab, obinutuzumab) and/or BCRi (ibrutinib, idelalisib, duvelisib) and chemotherapy (bendamustine) are being explored to see if response rates and MRD can be increased.[17-19] In Waldenström macroglobulinemia venetoclax is tested as a single agent and in combination with ibrutinib. Venetoclax also shows efficacy in other types of NHL (follicular lymphoma, mantle cell lymphoma and diffuse large B-cell lymphoma) although not as impressive as in CLL. Clinical trials in combination with anti-CD20 molecules (rituximab, obinutuzumab), anti-CD79 molecule (polatuzumab vedotin), chemotherapy (bendamustine, CHOP, DA-EPOCH), BCRi (ibrutinib, duvelisib) and immunomodulatory agents (lenalidomide) are ongoing.[20] In multiple myeloma (MM) responses seem highest in patients with the translocation (11;14) where the bcl-2/Mcl-1 ratio is high. Combination trials in MM with dexamethasone, proteasome inhibitors (bortezomib, carfilzomib) and the anti-CS-1 molecule are ongoing. Trials are also running in acute myeloid leukaemia (AML) in combination with hypomethylating agents (azacitidine, decitabine) or cytarabine low-dose as synergy with the combination drug has been shown. Patients with isocitrate dehydrogenase (IDH) 1/2 mutations in AML appear to have higher responses to venetoclax as a single agent.[3]

CONCLUSION

Venetoclax, the first-in-class bcl-2 antagonist, has demonstrated deep and durable remissions as a single agent in R/R CLL patients with a 17p deletion or CLL refractory to BCRi or progressive after BCRi discontinuation. The FDA and EMA approved venetoclax monotherapy in 2016 for one or both of these indications. Neutropenia and infections are the most important adverse events to deal with. As venetoclax can rapidly reduce the CLL load, precautions to avoid TLS depending on risk assessment is a sine qua non. Clinical trials exploring venetoclax in combination with monoclonal antibodies, BCRi and/or chemotherapy are ongoing in naive and R/R CLL. The hope is that combination treatment overcomes primary or acquired resistance and can induce MRD

KEY MESSAGES FOR CLINICAL PRACTICE

1. **Venetoclax, a selective bcl-2 antagonist, can induce deep and durable remissions in R/R CLL with a 17p deletion or CLL refractory to BCRi or progressive after BCRi discontinuation.**
2. **With the initial five week dose (20 to 400 mg) titration phase and TLS preventive measures depending on tumour burden assessment, renal function, comorbidities, uric acid and electrolyte values, laboratory and clinical TLS are seldom observed.**
3. **Neutropenia and infections are the most frequently observed toxicities in R/R CLL patients treated with venetoclax. Myeloid growth factors can be used in patients with persistent neutropenia.**
4. **Venetoclax is given as an oral, once daily formulation and continued till disease progression or unacceptable toxicity. Clinicians and patients must be aware that drug adherence and drug-drug interactions can challenge treatment benefits and risks.**

in a higher percentage of patients so that the continuous treatment can be stopped.

Despite the convenience afforded by this oral, once daily formulation, treating physicians and patients must be aware of drug adherence and drug-drug interactions which can challenge treatment benefits and risks.

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