Article published online: 2021-05-17

Venetoclax – The Game-changer in Hematology

Abstract

The introduction of small molecule inhibitors in many hematological malignancies made a landmark achievement in this field with a dramatic change in the survival outcome. Venetoclax is a B-cell lymphoma-2 inhibitor which has become the game-changer molecule in chronic lymphocytic leukemia and acute myeloid leukemia. This review is intended to summarize the mechanism of action, side effects, dosage, and different phases of clinical trials of this drug with review of literature.

Keywords: *Acute myeloid leukemia, B-cell lymphoma-2 inhibitor, chronic lymphocytic leukemia, venetoclax*

Tanmoy Kumar Mandal, Somnath Roy, Lingaraj Nayak, B K Mishra

Department of Medical Oncology, Tata Memorial Centre, Homi Bhabha Cancer Hospital, Varanasi, Uttar Pradesh, India

Introduction

Hematological malignancies such as lymphoma, acute leukemia, and multiple myeloma comprise 6.5% of all malignancies.[1] The emergence of various targeted therapies has altered the therapeutic landscape of these diseases. Chemotherapy, the backbone of hematological malignancies, is now being gradually replaced by various targeted therapies with a better safety profile. The discovery of a new class of pro-apoptotic agents has become an important inclusion in the armamentarium to treat these cancers, irrespective of genetic diversities.[2]

Venetoclax, formerly known as ABT-199, a novel B-cell lymphoma-2 (BCL-2) inhibitor, has proven its therapeutic safety and efficacy, particularly in chronic lymphocytic leukemia (CLL) and also in acute myeloid leukemia (AML).[3] Venetoclax is unique for its specificity for BCL-2 protein coupled with minimal hematological toxicities, making its widespread use in other low-grade BCLs.[4] Combination therapy with this drug has also being tested in acute leukemia such as acute lymphoblastic leukemia (ALL) and aggressive lymphomas.[5]

Discovery

Professor Andrew Roberts, a hematologist from the Walter and Eliza Hall Institute of Australia, in 1988, found that BCL-2 protein had a role in cancer progression.[6] His team then noticed that venetoclax had shown a remarkable response in the killing of leukemic cells in animal models. This led to the development of venetoclax as a potential cure for CLL and other hematological malignancies.

Mechanism of Action

Venetoclax is a BH-3 mimetic group of oral agents. It is a BCL-2 and BCL-XL inhibitor which promotes apoptosis.[7] After binding with BCL-2 protein, it activates caspase with displacement of apoptotic inducers such as BIM and BAX, thereby leading to initiation of apoptotic pathway and cell killing. It has a greater affinity with BCL-2 with significantly reduced activity against BCL-XL protein which is responsible for thrombocytopenia.[8]

Approved Indications with Food and Drug Administration Approval Status

1. 17p deleted CLL post first-line failure – Food and Drug Administration (FDA) approval in 2016
2. CLL irrespective of the p53 status post first-line failure in 2018 gained FDA approval
3. Elderly AML in combination with hypomethylating agents – FDA approval in 2018
4. All patients with CLL in first line – FDA approval in 2019.

How to cite this article: Mandal TK, Roy S, Nayak L, Mishra BK. Venetoclax – The game-changer in hematology. Indian J Med Paediatr Oncol 2020;41:555-8.

Submitted: 26-May-2020
Revised: 06-Aug-2020
Accepted: 11-Aug-2020
Published: 29-Aug-2020

Address for correspondence:
Dr. Somnath Roy, Department of Medical Oncology, Tata Memorial Centre, Homi Bhabha Cancer Hospital, Varanasi, Uttar Pradesh, India.
E-mail: sroysskm1980@gmail.com

Access this article online

Website: www.ijmpo.org

DOI: 10.4103/ijmpo.ijmpo_260_20

Quick Response Code:

Pharmacokinetics

- Distribution: Volume of distribution – 256–321 L
- Protein binding: Highly bound to plasma protein
- Metabolism: Hepatic, predominantly via CYP3A
- Half-life (elimination): 26 h (approximately)
- Time to peak: 5–8 h
- Excretion: Predominantly via feces (>99.9%).

Dosage and Administration Instructions

Tablets are available in three strengths (10 mg, 50 mg, and 100 mg), and it should be taken with meal and water. The dosing depends as per disease site. In CLL, an escalating dose schedule over the first 5 weeks [Table 1a] and 400 mg once daily until unacceptable toxicity or disease progression thereafter is recommended, whereas in AML, the dose is escalated in the first 4 days along with azacitidine or decitabine or low-dose cytarabine [Table 1b]. Such kind of dose escalation strategy is adopted to debulk the tumor burden, reduce the chance of developing tumor lysis syndrome (TLS), and to check the tolerance of the drug. Venetoclax has significant drug interactions with concomitant use of CYP3A inhibitors such as imatinib, crizotinib, aprepitant, spironolactone, and various azoles (except posaconazole). Drug interactions have also been seen with P-glycoprotein inhibitors such as amiodarone, statins, and proton-pump inhibitors. The dose of venetoclax needs to be reduced by 50% when used concomitantly with these agents.

Table 1a: Escalating dose schedule in first 5 weeks in chronic lymphocytic leukemia

Week	Recommended daily dose level (mg)
1	20
2	50
3	100
4	200
5	400

Table 1b: Escalating dose schedule in first 4 days in acute myeloid leukemia

Day	Recommended daily dose (mg)
1	100
2	200
3	400
4 and beyond	400 (with azacitidine or decitabine)
4 and beyond	600 (with low-dose cytarabine)

Table 2: Dose de-escalation strategy for toxicity during venetoclax therapy

Dose at interruption (mg)	Restart dose (mg)*
400	300
300	200
200	100
100	50
50	20
20	10

*During the ramp-up phase, continue the reduced dose for 1 week before increasing the dose

Common Side Effects

Hematologic side effects

1. Neutropenia – In patients with AML with Grade 4 neutropenia occurring upfront, the drug is not withheld. However, in patients who have post remission, then the next dose is delayed till the recovery of counts
2. Febrile neutropenia – For the first occurrence with Grade ≥3 neutropenia with fever and or infection, interrupt venetoclax till the recovery of counts and then it may be restarted at the same dose level. For second and subsequent episodes, dose reduction should be done [Table 2]. Consider discontinuing venetoclax for patients who require dose reductions to <100 mg for more than 2 weeks
3. Anemia
4. Thrombocytopenia.

Nonhematologic side effects

1. TLS – In patients with laboratory TLS or clinical TLS post initiation of venetoclax, the drug for the next day is withheld. If the TLS requires more than 48 h to resolve, then the drug is restarted at a reduced dose [Table 2]. Blood biochemistry (uric acid, creatinine, potassium, phosphorus, and calcium) should be done periodically during therapy to monitor TLS parameters
2. Diarrhea
3. Edema
4. Upper respiratory tract infection.

Landmark Trials

Phase I and II trial

A Phase I trial was conducted to optimize the dose of venetoclax in relapsed CLL. Among the two different subgroups, the dose-escalation group was treated with dose schedules from 20 mg weekly to 1200 mg daily, whereas the expansion cohort group was treated with 20 mg daily followed by a stepwise increase up to 400 mg weekly. The overall response of the entire cohort was 79%, with TLS reported as a dose-limiting toxicity.[9] Its role in relapsed multiple myeloma and B-cell non-Hodgkin lymphoma (NHL) is ongoing.

A Phase II study by Jain *et al*. among treatment naïve high risk elderly CLL populations treated with ibrutinib monotherapy (420 mg daily) for three cycles followed by adding venetoclax (weekly dose escalation to a target dose of 400 mg daily) from cycle four onwards. This combination therapy was given for two years' duration (total 24 cycles). At 1 year, 88% of patients were in

complete remission and 61% achieved undetectable minimal residual disease (MRD) in the bone marrow.[10]

MURANO trial

The Phase III randomized trial (MURANO) established the role of venetoclax with rituximab in comparison to bendamustine with rituximab with a superior overall survival and progression-free survival (PFS) benefit in patients with relapsed CLL irrespective of p53 status.[11] The 2-year PFS rate was significantly higher (84% vs. 36%) in the venetoclax arm. Although the rate of Grade 3 and Grade 4 neutropenia was higher in the venetoclax and rituximab group, the rate of febrile neutropenia and infection was less in comparison with the bendamustine arm.[11]

VIALE trial

Venetoclax received accelerated approval for the treatment of elderly AML who are unfit for intensive chemotherapy based on the Phase 1 and 2 VIALE trials which compared venetoclax with low-dose azacytidine (LDAC) versus LDAC alone.[12] This showed to have improved PFS in the venetoclax arm with superior complete remission rates.

Cost-effectiveness

The cost-effectiveness of venetoclax was measured in a cost-effective model which showed to have a lower cost than bendamustine plus rituximab- and ibrutinib-based combinations in the treatment of CLL over a 12-month duration.[13]

Newer Uses in the Pipeline

There have been recent evidences on the use of venetoclax in certain aggressive NHL such as refractory mantle cell lymphoma,[14] relapsed diffuse large B-cell lymphoma,[15] and relapsed follicular lymphoma.[16] Recent clinical trials have also suggested the use of venetoclax in refractory ALL, especially T-ALL and relapsed multiple myeloma with (11:14) translocation.[17]

Take-Home Points

1. Venetoclax is the first selective BCL-2 inhibitor
2. It is approved by FDA in CLL and AML
3. Its role in other B-cell NHLs, multiple myeloma, and ALL is now being tested either in monotherapy or in combination in several clinical trials
4. It is used in escalating doses in CLL and AML.
5. TLS and neutropenia are the most common adverse reactions.

Conclusion

Venetoclax might become an important therapeutic agent against several hematological malignancies in the near future considering the acceptable toxicity profile. It is effective after failure of ibrutinib in CLL, but reverse is not true. In relapse/refractory CLL, this drug attained higher rates of MRD negativity in peripheral blood and bone marrow. We can predict that in the future, venetoclax either in monotherapy or in combination will achieve landmark milestones in the treatment of different hematological malignancies.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Ferlay J, Colombet M, Soerjomataram I, Mathers C, Parkin DM, Piñeros M, *et al*. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. Int J Cancer 2019;144:1941-53.
2. Martens U. Small Molecules in Hematology. USA: Springer Nature; 2018.
3. Brody T. FDA's Drug Review Process and the Package Label: Strategies for Writing Successful FDA Submissions. United Kingdom: Academic Press, Elsevier Science Publishing Co.; 2017.
4. Scheffold A, Jebaraj BMC, Stilgenbauer S. Venetoclax: Targeting BCL2 in Hematological Cancers. Recent Results Cancer Res 2018;212:215-42.
5. Lenz G, Salles G. Aggressive Lymphomas. USA: Springer International Publishing; 2018.
6. Fairbrother WJ, Leverson JD, Sampath D, Souers AJ. Discovery and Development of Venetoclax, a Selective Antagonist of BCL -2. Successful Drug Discovery, edited by János Fischer *et al*., 1st ed., Wiley; 2019. p. 225-45. DOI.org (Crossref),
7. 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;127:3215-24.
8. Ackler S, Oleksijew A, Chen J, Chyla BJ, Clarin J, Foster K, *et al*. Clearance of systemic hematologic tumors by venetoclax (Abt-199) and navitoclax. Pharmacol Res Perspect 2015;3:e00178.
9. Roberts AW, Davids MS, Pagel JM, Kahl BS, Puvvada SD, Gerecitano JF, *et al*. Targeting BCL2 with Venetoclax in Relapsed Chronic Lymphocytic Leukemia. N Engl J Med 2016;374:311-22.
10. Jain N, Keating M, Thompson P, Ferrajoli A, Burger J, Borthakur G, *et al*. Ibrutinib and venetoclax for first-line treatment of CLL. N Engl J Med 2019;380:2095-103.
11. Seymour JF, Kipps TJ, Eichhorst B, Hillmen P, D'Rozario J, Assouline S, *et al*. Venetoclax-rituximab in relapsed or refractory chronic lymphocytic leukemia. N Engl J Med 2018;378:1107-20.
12. A Study of Venetoclax in Combination With Azacitidine Versus Azacitidine in Treatment Naïve Subjects With Acute Myeloid Leukemia Who Are Ineligible for Standard Induction Therapy - Full Text View - ClinicalTrials.Gov. Available from: https://clinicaltrials.gov/ct2/show/NCT02993523. [Last accessed 2020 Aug 20].
13. Davids MS, Chatterjee A, Ravelo A, Shapouri S, Manzoor BS, Sail K, *et al*. Cost-effectiveness of a 12-month fixed duration of venetoclax in combination with obinutuzumab in first-line chronic lymphocytic Leukemia in the United States. Blood 2019;134 Suppl 1:4741.

14. Eyre TA, Walter HS, Iyengar S, Follows G, Cross M, Fox CP, *et al*. Efficacy of venetoclax monotherapy in patients with relapsed, refractory mantle cell lymphoma after Bruton tyrosine kinase inhibitor therapy. Haematologica 2019;104:e68-e71.
15. Morschhauser F, Feugier P, Flinn IW, Gasiorowski RE, Greil R, Illés Á *et al*. Venetoclax plus rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP) improves outcomes in BCL2-positive first-line diffuse large B-cell lymphoma (DLBCL): First safety, efficacy and biomarker analyses from the phase II CAVALLI study. Blood. 2018;132(supplement 1): –782.
16. Zinzani PL, Flinn IW, Yuen S, Topp MS, Rusconi C, Fleury I, *et al*. Efficacy and safety of venetoclax (Ven) + rituximab ® or Ven + Bendamustine (B) + R randomized versus B + R in Patients (pts) with relapsed/refractory (R/R) follicular lymphoma (FL): Final analysis of phase II CONTRALTO study. Blood 2018;132 Suppl 1:1614.
17. Wong KY, Chim CS. Venetoclax, bortezomib and S63845, an MCL1 inhibitor, in multiple myeloma. J Pharm Pharmacol 2020;72:728-37.