



A Review on Venetoclax – An Antineoplastic Agent

Authors

Vendra S R¹, Ragav S R^{2*}

¹III MBBS, Raja Muthiah Medical College and Hospital, Annamalai University
Annamalainagar Chidambaram

²I MBBS, Madha Medical College and Research Institute, Madha Nagar, Kovur, Chennai

*Corresponding Author

Ragav S R

Email: srragavsr@gmail.com, Mobile No: +91 9941691694

Abstract

This review will focus on the drug information of Venetoclax, a small molecule oral drug that treats chronic lymphocytic leukemia (CLL) in those with a specific chromosomal abnormality, in adults with 17p deletion. Venclexta is the first FDA-approved treatment that targets the B-cell lymphoma 2 (BCL-2) proteins, which supports cancer cell growth and is over expressed in many patients with CLL.

Venetoclax is used a second line treatment for chronic lymphocytic leukemia, only if there is a 17p deletion. Venclexta (venetoclax) inhibits a certain protein in cancer cells (abnormal lymphocytes produced in chronic lymphocytic leukemia) that helps keep those cells alive and makes them resistant to chemotherapy. Venetoclax binds to this protein, which helps kill the cancerous lymphocytes in blood and bone marrow. Venclexta is usually given after at least one other cancer medicine has been tried without success.

Keywords: Venetoclax, chronic lymphocytic leukemia.

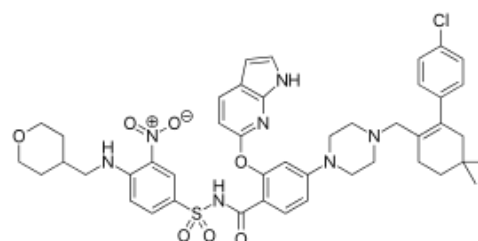
1 Introduction

Venetoclax (INN,^[1] tradename Venclexta *ven-KLEKS-tuh* in the US^[2] and Venclyxto in Europe, is a small molecule oral drug that treats chronic lymphocytic leukemia (CLL) in those with a specific chromosomal abnormality,^[3] in adults with 17p deletion. Venclexta is the first FDA-approved treatment that targets the B-cell lymphoma 2 (BCL-2) proteins, which supports cancer cell growth and is over expressed in many patients with CLL.

Venetoclax is used a second line treatment for chronic lymphocytic leukemia, only if there is a 17p deletion as determined by an approved test.^[2] Venclexta (venetoclax) inhibits a certain

protein in cancer cells (abnormal lymphocytes produced in chronic lymphocytic leukemia) that helps keep those cells alive and also makes them resistant to chemotherapy. Venetoclax binds to this protein, which helps kill the cancerous lymphocytes in blood and bone marrow. Venclexta is usually given after at least one other cancer medicine has been tried without success.

1.1 Chemical structure



1.2 IUPAC Name

4-(4-{[2-(4-Chlorophenyl)-4,4-dimethyl-1-cyclohexen-1-yl]methyl}-1-piperazinyl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

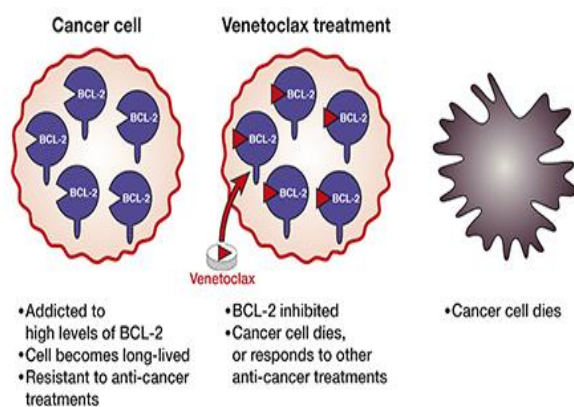
1.3 Chemical Formula:

C₄₅H₅₀ClN₇O₇S

Molar Mass: 868.44 g/mol

2 Mechanism of action

Venetoclax is a BH3-mimetic and acts as a Bcl-2 inhibitor. It blocks this anti-apoptotic B-cell lymphoma-2 (Bcl-2) protein, which in turn leads to the programmed cell death of CLL cells. Over expression of Bcl-2 in some lymphoid malignancies has sometimes shown to be linked with increased resistance to chemotherapy.^[4]



3 Pharmacokinetics

The maximum plasma concentration achieved after oral administration occurred 5-8 hours after dose.^[2] Steady state maximum concentration with low-fat meal conditions at the 400 mg once daily dose was found to be 2.1 ± 1.1 ug/mL. It is recommended that Venetoclax be administered with a meal.^[2]

The apparent Volume of Distribution for Venetoclax is approximately 256-321 L. It is highly bound to human plasma protein. Within a concentration range of 1-30 μ M (0.87-26 μ g/mL), the fraction unbound in plasma was less than 0.01.^[2]

Venetoclax is metabolized by CYP3A4/5 as proven by in-vitro studies.^[2]

4 Drug Interactions

Venclexta should not be used if it produces any allergy. Those using the drug should not consume grapefruit products Seville oranges (often used in marmalades), or star fruit because they contain CYP3A inhibitors.^[2] These products may increase the amount of Venclexta in blood.

Additionally, while using venetoclax it is not recommended to use other drugs which are supposed to contain CYP3A inhibitors (i.e: erythromycin, ciprofloxacin, diltiazem, dronedrone, verapamil).^[2] It should not be used along with imatinib, isoniazid, nefazodone, an antibiotic such as clarithromycin, telithromycin, antifungal medicine - itraconazole, ketoconazole, posaconazole, voriconazole, heart medication such as nifedipine, quinidine or antiviral medicine to treat hepatitis C or HIV/AIDS such as atazanavir, boceprevir, cobicistat, delavirdine, fosamprenavir, indinavir, nelfinavir, ritonavir, saquinavir, telaprevir.

5 Side Effects

Many drugs can interact with venetoclax, and some drugs should not be used together. Common side effects of venetoclax are neutropenia (low white blood cell count), nausea, anemia, diarrhea, upper respiratory tract infection, fatigue, and thrombocytopenia (low platelet count). Major side effects include tumor lysis syndrome and severe neutropenia. Additionally, this drug may cause fertility problems in males.^[2]

Tumor lysis syndrome (TLS) TLS is caused by the fast breakdown of cancer cells. TLS can cause kidney failure, the need for dialysis treatment, and may lead to death. Plenty of water should be consumed when taking venetoclax to help reduce the risk of getting TLS. 6 to 8 glasses (about 56 ounces total) of water should be taken each day, starting 2 days before the first dose, on the day of the first dose of venetoclax, and each time the dose is increased.

The patient medical condition has to be observed before prescribing whether the patients have/are

- Kidney or liver problems.
- Problems with body salts or electrolytes, such as potassium, phosphorus, or calcium.
- a history of high uric acid levels in blood or gout.
- Any vaccination schedule. These vaccines may not be safe or may not work as well during treatment with venetoclax
- Pregnant or plan to become pregnant.
- Breastfeeding or plan to breastfeed.

6 Dosage and administration

The therapy may be initiated with Venetoclax at 20 mg once daily for 7 days, followed by a weekly ramp-up dosing schedule to the recommended daily dose of 400 mg. It should be taken orally once daily with a meal and water. They are not to be chewed, crushed, or broken. Prophylaxis should be performed for tumor lysis syndrome. [5]

6.1 Dosage forms and strengths: Tablets: 10 mg, 50 mg, 100 mg^[5]

7 History

The most common types of leukemia in adults are CLL, according to the National Cancer Institute. Approximately 15,000 new cases are diagnosed each year. It is characterized by the progressive accumulation of abnormal lymphocytes, a type of white blood cell. Patients with CLL who have a 17p deletion lack a portion of the chromosome which acts to suppress cancer growth. This chromosomal abnormality occurs in approximately 10 percent of patients with untreated CLL and also in approximately 20 percent of patients with relapsed CLL.

Richard Pazdur, director of the Office of Hematology and Oncology Products in the FDA's Center for Drug Evaluation and Research told that the patients now have a new, targeted therapy that inhibits a protein involved in keeping tumor cells alive. He also said that for certain patients with CLL who have not had favorable outcomes with

other therapies, Venclaxta may provide a new option for their specific condition

Single-arm clinical trial of 106 patients with CLL who have a 17p deletion and also who had received at least one prior therapy was carried out to test the efficacy of Venclaxta. 20 mg was given orally every day to the trial participants and the dose was increased over a five-week period to 400 mg. Results showed that 80 percent of trial participants experienced a complete or partial remission of their cancer.

In 2015, the United States Food and Drug Administration (FDA) granted Breakthrough Therapy Designation to venetoclax. This was exclusively for subjects with CLL who have relapsed or have been refractory to previous treatment and have the 17p deletion genetic mutation.

On April 11, 2016, the FDA approved venetoclax for use in those with CLL who have 17p deletion (deletion located on the chromosome 17 short arm) and who have been treated with at least one prior therapy.^{[2][3]} Based on overall response rate, the indication was approved under accelerated FDA approval.^[2]

In October 2016 a European Medicines Agency committee recommended provisional marketing approval for venetoclax for CLL; the drug had already been granted orphan status in 2012 for that use.^[6]

Abbvie Inc. of North Chicago Illinois manufactures Venclaxta.^[7] It is marketed by both Abbvie Inc. and Genentech USA Inc. of South San Francisco, California, which is a member of the Roche Group.^[6] Abb Vie and Genentech are both commercializing the drug within the United States, but only AbbVie has rights to do so outside of the U.S.

According to Reuters 2016 Drugs to Watch, forecast sales for Venetoclax are 1.48 billion in the year 2020.^[9] Competition is definitely expected from other drugs such as Imbruvica (ibrutinib) and Zydelig (idelalisib), because these drugs were also approved in the year 2014 to treat CLL (chronic lymphocytic leukemia).^[9,10]

Venclexta patented by Abbvie Inc. US Patent: 9,174,982.^[10] Venclexta was approved based on response rate. Studies are going on to find out how Venclexta works over a longer period of time. It is not known if Venclexta is safe and effective in children.

Venclexta also received orphan drug designation, So, this drug provides incentives such as tax credits, user fee waivers and eligibility for exclusivity to assist and encourage the development of drugs for rare diseases^[11].

Venclexta is manufactured by AbbVie Inc. of North Chicago, Illinois, and marketed by AbbVie and Genentech USA Inc. of South San Francisco, California. The FDA protects the public health by assuring the safety, effectiveness, and security of human and veterinary drugs, vaccines and other biological products for human use, and medical devices. The FDA is also responsible for the safety and security of our nation's food supply, cosmetics, dietary supplements, products that give off electronic radiation, and for regulating tobacco products.

8 Research

As of 2016 venetoclax had been tested to treat other hematological cancers, including non-Hodgkin's lymphoma, diffuse large B-cell lymphoma and follicular lymphoma.^[12] In January 2017, the drug was approved for use by the Australian Therapeutic goods administration and made available to Australian patients^[13]

References

1. "International Nonproprietary Names for Pharmaceutical Substances (INN). Proposed International Nonproprietary Names: List 111" (PDF). WHO Drug Information. 2014;28 (2):270.
2. <http://adisinsight.springer.com/drugs/800034622>, Drug Profile, Venetoclax, Accessed 11 March 2017.
3. <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm495253FDA> approves new drug for chronic lymphocytic leukemia in patients with a specific chromosomal abnormality, Accessed 11 Mar 2017
4. The medical letter on drug and therapeutics , August 1, 2016, Venetoclax (Venclexta) for Chronic Lymphocytic Leukemia
5. <http://www.ema.europa.eu/ema>"CHMP summary of positive opinion for Venclyxto". European Medicines Agency. Accessed 11 March 2017.
6. <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm495253.htm> "Press Announcements - FDA approves new drug for chronic lymphocytic leukemia in patients with a specific chromosomal abnormality". Accessed 11 March 2017.
7. <http://www.biopharmadive.com/news/> "Inside the development of Venclexta, AbbVie's new leukemia drug". BioPharma Dive. Accessed 11 March 2017.
8. <http://images.info.science.thomsonreuters.biz/Web/ThomsonReutersScience>, "Drugs to Watch 2016 - Market Insight Report" (PDF), Accessed 11 March 2017
9. <http://www.onclive.com/web-exclusives> "Ibrutinib and Idelalisib Continue to Impress in CLL, May Eventually Replace Chemotherapy for Some Patients". OncLive. Accessed 11 March 2017
10. "United States Patent: 9174982". <http://patft.uspto.gov>. Accessed 11 March 2017.
11. "Drugs to Watch 2016 - Market Insight Report" (PDF). Thomson Reuters. Accessed 11 March 2017
12. <https://www.venclexta.com>, Medicationguide , Venclexta Accessed 11 March 2017 .
13. <http://www.wehi.edu.au/research-research-fields/clinical-translation/venetoclax> Accessed 11 March 2017