Venetoclax: A Primer

Manuscript Type: Blood Advances Talk

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Conflicts of Interest: A.W.R. received research funding from AbbVie and Genentech, the co-developers of venetoclax; and is an employee of the Walter and Eliza Hall Institute of Medical Research which receives royalty income related to venetoclax. Dr Roberts has no
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personal financial interest in venetoclax. He has also received research funding from Janssen and Servier.

**Acknowledgements:** Andrew Roberts wrote the entire audio script. AWR’s research is supported by the Australian National Health and Medical Research Council (Practitioner Fellowship 1079560 and Program grant 1113577); the Leukemia and Lymphoma Society (SCOR grant 7001-13); the Cancer Council of Victoria; the Australian Cancer Research Foundation and a Victorian State Government Operational Infrastructure Support (OIS) grant.
Summary
Venetoclax is a BH3-mimetic small molecule drug that directly and selectively inhibits BCL2. BCL2 is highly expressed in many hematological malignancies, and is the predominant pro-survival protein in diseases such as chronic lymphocytic leukemia (CLL), follicular lymphoma and mantle cell lymphoma. In pre-clinical animal models and in vitro assays of primary cells from patients, venetoclax induces apoptosis rapidly in the majority of CLL cells and BCL2-overexpressing lymphoma cell lines, and in subsets of cell lines and primary samples of myeloma and AML. Venetoclax kills cells independently of TP53.

Venetoclax is an oral medication, taken daily with food. As a single agent, it is most effective in patients with relapsed CLL and mantle cell lymphoma, where response rates are approximately 80% and complete remission (CR) rates of 20% are observed. Responses are typically achieved rapidly, but the depth of response often continues to deepen with ongoing therapy for > 1 year. The drug is generally well tolerated, but mild gastro-intestinal side effects are common, as is neutropenia in CLL patients. Venetoclax 400mg/day is approved for previously treated patients with deletion 17p CLL in USA, Canada and Europe.

Single agent response rates are more modest in follicular lymphoma, diffuse large B cell lymphoma, multiple myeloma (predominantly t(11;14)-bearing disease) and acute myeloid leukemia (AML). Preliminary clinical data combining venetoclax with monoclonal antibodies, tyrosine kinase inhibitors, hypomethylating agents and DNA-damaging chemotherapy suggest incremental efficacy across a spectrum of blood cancers. Randomized trials of combination therapy are underway in all these diseases.
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Introduction
Venetoclax is the first FDA-approved drug to directly inhibit BCL2. This primer will briefly review its mechanism-of-action, the rationale for targeting BCL2, the hematological malignancies where venetoclax has shown activity as a single agent and discuss preliminary data highlighting the potential for combination therapy.

So what is venetoclax, and how does it work?
Originally called ABT-199, venetoclax was developed specifically to inhibit the function of BCL2, an intracellular protein known to be important in the survival of many hematopoietic cancer cells.\(^1\) High level expression of BCL2 in blood cancers is associated with resistance to apoptosis, enabling these cells to more effectively survive and adapt to challenges such as the proliferative and metabolic stresses associated with strong oncogenic drivers, DNA damage from chemotherapy, and loss of microenvironmental survival signals.\(^2-4\) Theoretically, inhibition of BCL2 should induce malignant cells that are dependent on BCL2 for survival to undergo apoptosis.

The key to the development of venetoclax was creation of a drug that mimicked the action of the naturally occurring antagonists of BCL2 – the BH3-only proteins.\(^5\) In healthy cells, BCL2 prevents cells undergoing apoptosis by inhibiting the activation of two related proteins, BAX and BAK.\(^4,6\) Apoptosis only occurs when BAX and BAK are activated, and for this to happen BCL2 has to be inhibited. Normally, apoptosis is triggered when so-called BH3-only proteins are produced or activated due to cellular stress. These BH3-only proteins bind and antagonise BCL2, allowing BAX and BAK to initiate the disruption of the mitochondrial membrane which is the first critical step towards apoptosis.\(^7\) In nature, there are multiple BH3-only proteins that bind both BCL2 and related proteins that have similar pro-survival functions, such as MCL1 and BCLxL.\(^8\) By modelling how these BH3-only proteins bind and inhibit BCL2, chemists were able to design a drug that acted like a BH3-only protein, but was specific for its inhibition of BCL2.\(^1\) So venetoclax is what is referred to as a “BH3-mimetic”, and it acts more selectively against BCL2 than any naturally occurring BH3-only protein.
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*Why target BCL2?*
Firstly, BCL2 is overexpressed in many hematological cancers through mechanisms such as chromosomal translocation (as for follicular lymphoma), gene amplification, and genetic loss of negative regulatory elements, such as *mir15* and *mir16* in CLL.\(^9-11\) High level expression of BCL2 is observed in the great majority of samples from patients with follicular lymphoma, CLL, mantle cell lymphoma, Waldenstrom’s macroglobulinemia, and multiple myeloma. BCL2 is more variably expressed in other cancers such as DLBCL, acute lymphoblastic leukemia, T cell lymphomas, and acute myeloid leukemia. Secondly, in animal models, enforced overexpression of BCL2 is associated with resistance to standard cytotoxic chemotherapy\(^{12,13}\), but susceptibility to venetoclax, either alone or in combination with other therapies\(^1\). Thirdly, preclinical testing using primary patient samples indicates that inhibition of BCL2 by venetoclax is highly active against nearly all CLL\(^{1,14,15}\) and mantle cell lymphoma\(^16\), and against some subsets of lymphoma\(^1,17\), myeloma\(^18\) and AML\(^19,20\).

**Clinical data with venetoclax monotherapy**
Venetoclax commenced clinically trials in mid 2011, and was FDA-approved for its first indication, previously treated deletion 17p CLL, in April 2016. I would now like to summarize what have we learned to date from clinical experience with venetoclax.

*Firstly, pharmacology:* This drug is taken once daily as an oral medication and is principally metabolised in the liver.\(^21\) It is significantly better absorbed when taken with food. Peak concentrations are reached approximately 6 hours after ingestion, and with daily dosing there is minimal drug accumulation.\(^21\) Exposure is approximately dose-proportional between 300 and 900 mg/day.\(^21\)

There is no clinically applicable assay to measure whether full inhibition of BCL2 has been achieved *in vivo*, and so the determination of recommended Phase 2 doses has been based on modelling and the balance of efficacy and safety observed in early phase clinical trials.\(^22-24\) For patients with relapsed CLL, the approved daily dose is 400mg/day. The recommended Phase 2 doses are higher for patients with B cell lymphomas\(^23\), multiple myeloma\(^25\) and AML\(^26\).
Secondly, the clinical experience in CLL: The most extensive clinical experience to date has been in patients with relapsed or refractory CLL. The Phase 1 trial revealed potent anti-CLL activity with doses ranging from 20-1200mg. Circulating CLL cells undergo apoptosis and are rapidly cleared, and the median time to objective response is 6 weeks. Across a range of doses, the overall response rate was 79%, with 20% of patients achieving a complete remission (CR). The chance of responding was not affected by the presence of negative prognostic factors. The Phase 2 study was conducted in patients with previously treated deletion 17p CLL. That trial confirmed the 79% response rate and projected a 12 month progression-free survival estimate of 72%. Venetoclax has recently been reported to induce similar response rates in patients whose CLL has failed treatment with ibrutinib or idelalisib.

Some patients have now received over 4 years of continuous therapy with venetoclax. Maximum cytoreduction may take >1 year to be achieved, and a minority of patients actually achieve a CR with no evidence of minimal residual disease (MRD) by multi-color flow cytometry. Longer term follow up suggests that the most durable responses are seen in those patients who achieve a CR.

With respect safety of treatment with venetoclax, the drug is generally well tolerated, with only 9% discontinuing because of toxicity. The most common side effects are gastrointestinal. Mild nausea and sometimes vomiting are common early after commencing therapy, and mild diarrhea can be problematic in some patients. Reductions in neutrophil counts are also common, with approximately 50% of heavily pre-treated CLL patients experiencing absolute neutrophil counts < 1000/µL at some time on therapy. Despite the neutropenia, serious infections and febrile neutropenia were relatively infrequent. The neutropenia reflects an on-target toxicity on granulocytic progenitor cells in the bone marrow, and responds promptly to intermittent doses of G-CSF. Neutropenia is also observed in patients with lymphoma and myeloma, but is less frequent (11% & 20%).

Early in clinical development, tumor lysis syndrome was the most serious complication of venetoclax therapy in patients with CLL, particularly in patients with very high tumor
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However, with the introduction of a five week ramp up in dosing from 20mg/day, through 50, 100 and 200 mg/day to 400mg/day in week 5, and careful monitoring, tumor lysis is now avoided, and most patients can be managed safely in the ambulatory setting.27,30

As of January 2017, venetoclax has been approved in USA, Canada, Australia and Europe for therapy of previously treated patients with deletion 17p CLL. In Canada and Australia, the approval also extends to patients with CLL without deletion 17p and for whom there are no other available treatment options. In Europe, patients with either deletion 17p or TP53 mutated CLL are approved if they are unsuitable for, or have failed, treatment with a B cell receptor pathway inhibitor. Approval in Europe also extends to CLL without these genetic changes if previously failed both chemo-immunotherapy and B cell receptor pathway inhibitor.

What about experience in other BCL2-expressing hematological malignancies? Mantle cell lymphoma also appears to be highly susceptible to single agent treatment with venetoclax. In the Phase 1 study, 75% of patients with relapsed or refractory MCL achieved responses, including 21% with complete responses.23 Somewhat surprisingly, follicular lymphoma does not appear as sensitive to venetoclax as a single agent.23 Responses were observed in 38%, with 14% CRs. In keeping with the observations in CLL, patients with CRs had durable responses. However, the drug is less active against relapsed DLBCL. Responses were infrequent and short-lived.23

Preclinical data predicted that among patients with myeloma, those with translocation t(11;14) disease would be most responsive.18,32 Phase 1 data confirmed this, with a response rate of 40% seen in t(11;14) myeloma, while few objective responses were observed with other genetic subtypes.25

Outside the B cell malignancies, venetoclax has also shown activity against AML. In the phase 2 monotherapy trial of 800mg/day, CR or CR with incomplete count recovery was observed in 6 of 32 (or 19%) patients.26 A further 19% of patients showed evidence of antileukemic activity that did not meet standard criteria for response. Consistent with preclinical predictions that AML with IDH mutations would be most sensitive to
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venetoclax\textsuperscript{20}, the CR rate in patients with IDH mutant AML was 33%. However, responses were generally not durable, and the median leukemia-free survival was only 2.3 months.\textsuperscript{26}

The clinical trial data to date in follicular lymphoma, DLBCL, myeloma and AML indicate that as a single agent venetoclax is only highly active in subsets of these diseases. In both myeloma\textsuperscript{18,32} and AML\textsuperscript{26}, dependence on BCLxL or MCL1 for survival in functional assays \textit{in vitro} appears to predict lack of response. Collectively, the preclinical and clinical data indicate that the future clinical application of venetoclax will be in combination in these diseases.

\textbf{Clinical data for venetoclax in combination}

During 2017 we will see the first peer-reviewed publications of trials combining venetoclax with monoclonal antibodies, tyrosine kinase inhibitors, hypomethylating agents and DNA-damaging cytotoxics. In pre-clinical model systems of B cell malignancies and AML, synergy has been demonstrated for such combinations.\textsuperscript{1,16,18,33} Key questions include: 1) how substantial an increment in efficacy can be achieved over single agents or current combinations; and 2) whether there is significant additional toxicity, especially when venetoclax is added to chemotherapy.

In CLL, the early indications are that combinations with anti-CD20 antibodies are both highly tolerable and increase the proportion of patients achieving CR and also MRD negativity. In a very recent publication, a venetoclax / rituximab combination was reported to induce CRs in 51% of patients with relapsed CLL, with an MRD negativity rate of 80% in complete responders.\textsuperscript{34} Similarly, obinutuzumab and venetoclax were reported at the ASH 2016 meeting to achieve 100% response rates in treatment-naïve patients, with 80% being complete responders.\textsuperscript{35} Such results have prompted the design of trials comparing venetoclax/CD20 antibody combinations with standard chemo-immunotherapy.

Also reported at the EHA and ASH 2016 meetings were preliminary data for combinations of venetoclax and ibrutinib in either mantle cell lymphoma\textsuperscript{36} or CLL (plus obinutuzumab)\textsuperscript{37}, venetoclax with bortezomib and dexamethasone in myeloma\textsuperscript{38}, and venetoclax with either hypomethylating agents\textsuperscript{39} or low-dose cytosine arabinoside in AML\textsuperscript{40}. All suggested higher
response rates than historically expected and none reported major additional toxicities. Randomized trials are now accruing to assess these regimens against standard-of care, and other trials are assessing the efficacy of venetoclax in combination with standard chemo-immunotherapy.

Conclusion

In conclusion, the introduction into practise of venetoclax now provides an additional line of therapy for patients with del17p CLL. However, the true therapeutic potential of BCL2 inhibition is only just beginning to be explored. As trial data emerge over the next 2-3 years, we will learn whether the addition of venetoclax to existing treatments augments response rates and durable remissions in other B cell lymphoproliferative diseases, myeloma and AML.
References


