Selecting efficacious Bcl-2 family inhibitors for optimal clinical outcome

Irfana Muqbil¹, Ramzi M. Mohammad¹²

¹Department of Oncology, Karmanos Cancer Institute, Wayne State University, Detroit, MI, USA; ²Interim translational Research Institute, Hamad Medical Corporation, Doha, Qatar

Correspondence to: Prof. Ramzi M. Mohammad, PhD. Department of Oncology, Karmanos Cancer Institute, Wayne State University, 4100 John R, HWCRC 732, Detroit, MI 48201, USA. Email: mohammar@karmanos.org.

Submitted Aug 28, 2015. Accepted for publication Sep 06, 2015.
doi: 10.3978/j.issn.2305-5839.2015.09.15
View this article at: http://dx.doi.org/10.3978/j.issn.2305-5839.2015.09.15

Despite several decades of extensive research focus in the development of small molecule inhibitors that target the pro-survival BH-3 family members especially Bcl-2, a clinically successful agent is yet to emerge. The majority of agents either show poor target engagement in humans or their use is limited by acute toxicity, especially thrombocytopenia. In the recent paper in Science Translational Medicine, Leverson and colleagues investigate a novel combination of Bcl-2 family inhibitors that is predicted to present a less toxic yet highly selective way of targeting the Bcl-2 pathway (1).

The concept of selective shutting of the cell survival pathways in cancer cells has persisted in academia and drug industry (2). The idea received attention from the time when Korsmeyer first proposed a very simplistic rheostat model that a balance between pro-survival and pro-death family proteins can predict the life and death of cell (3). Advancements in the X-ray crystallography sciences not only identified the structures of pro-survival family members particularly Bcl-2, Bcl₆, and BclₓL, it also provided detailed insight into the binding pockets that could be harnessed for specific attachment of very specific type of small molecule compounds. Whether these pro-survival proteins could be exploited to artificially induce cell death came from proof of concept studies where highly selective agents for example the first in class Bcl-2 inhibitor ABT-737 (4) (from Abbott) or Gossypol (5) (and related analogs), a natural product from cotton seed were shown to induce cancer cell death in somewhat selective manner through down-regulation of Bcl-2 protein.

Since these initial proof of concept studies a number of different Bcl-2 inhibitors have emerged and were investigated for their anti-cancer potential in pre-clinical laboratories across the globe and some of them have advanced to early stage Phase I and II clinical studies (6). Notable among them is the gossypol racemic mixture AT-101 developed at Ascenta Therapeutics. Around 24 clinical studies have so far been conducted or are ongoing with AT-101 for different tumor indications. While these studies do show the translational potential of targeting Bcl-2, we are still far from seeing any cure in humans. The majority of the clinical studies with AT-101 have shown lack of objective response or cytotoxicity especially manifested as thrombocytopenia (7,8). These consistent findings across a broad spectrum of tumors in various clinical trials indicate that there is indeed a need for better patient selection prior to initiating such clinical trials.

While designing a clinical study with Bcl-2 targeted drugs, the role of additional family members especially BclₓL cannot be ignored. In cases where a fairly robust inhibition of Bcl-2 was achieved, the cell dependency on BclₓL or newer players such as Mcl-1 caused evasion of cell death leading to tumor recurrence at least in pre-clinical models (9). This led to the increasingly attractive concept of pan Bcl-2 inhibition using “dirty” drugs. In this regard agents such as navitoclax (ABT-263) have been shown to collectively hit Bcl-2/BclₓL/BclₓW resulting in promising clinical activity in lymphoid malignancies such as chronic lymphocytic leukemia (CLL) (10). Another two agents TW-37 and Apogossypolone (a derivative from gossypol and developed by Ascenta Therapeutics) show similar pan Bcl-2 inhibition and can hit Mcl-1 as well (11-13). Nevertheless, these agents (TW-37 and Apogossypolone in preclinical studies and ABT-263 in clinical studies) were proven to be toxic and cause thrombocytopenia. This highlights that Pan
Bcl-2 inhibition may not be the optimal strategy. Building on these initial failures newer generation Bcl-2 inhibitors such as venetoclax have been developed that spares platelets. However, these too are recognized to induce neutropenia in combination with docetaxel. Collectively, the above investigations do prove that there needs to be a very careful selection of Bcl-2 targeted drugs or their combinations. The choice of agent (mono-targeted or dirty/promiscuous) and the BH-3 family member to be shut requires much more evaluation prior to designing a clinical study for the treatment of cancer patients.

Building on this clinical need for less toxic Bcl-2 targeted regimen, Leverson and colleagues evaluated the combination of venetoclax and BclXL inhibitors A1155463 and A1331852 to assess the relative contributions of inhibiting Bcl-2 or BclXL in the response and adverse toxicity (1). Aptly summarized in the first image of the paper, they utilized venetoclax that targets only Bcl-2 and compared its activity to navitoclax in presence or absence of highly selective Bcl-3xl inhibitor A115463. This could allow the functional dissection of the effects of navitoclax for its role in neutropenia. These studies gave some striking outcomes including: (I) combination studies involving venetoclax and A-115463 identified Bcl-2 family dependence profile of cancer cell lines; (II) marked synergy was observed in the docetaxel-A-115463 combination; (III) superior anti-tumor activity with lesser toxicity [as single agent (Bcl-2 selective inhibitor) or its combination with docetaxel]; (IV) the selective inhibition of Bcl-2 was shown to suppress granulopoiesis ex vivo and also was shown to reduce circulating neutrophil counts.

From these comprehensive studies, it is quite safe to conclude that successful therapeutic combination involving Bcl-2 inhibitors should stay away from pan Bcl-2 approach. Rather the design of a regimen should be based on selective inhibition of individual family members. Such an approach may result in better management of the toxicity related issues that have plagued the design of pro-survival signaling targeted drugs for the treatment of cancer.

In parallel to these studies, other newer approaches are emerging in the area of Bcl-2 selective targeted therapeutics. Silencing Bcl-2 at the transcriptional level has emerged as an interesting concept (14). Developed by ProNi therapeutics, the DNAi Bcl-2 anti-sense agent PNT100 is a 24-base, chemically unmodified DNA oligonucleotide sequence that is complementary to a region upstream of the Bcl-2 gene. PNT100 exposure causes suppression of proliferation and cell death by a process called DNA interference. A new formulation PNT2258 that is nothing but PNT100 encapsulated in protective amphoteric liposomes developed to efficiently encapsulate the PNT100 oligonucleotide, provides enhanced serum stability, optimized pharmacokinetic properties and antitumor activity of the nanoparticle both in vivo and in vitro. PNT2258 has been shown to demonstrate broad antitumor activity against Bcl-2-driven WSU-DLCL2 lymphoma, highly resistant A375 melanoma, PC-3 prostate, and Daudi-Burkitt’s lymphoma xenografts. In clinical studies, PNT2258 was found to be safe and well tolerated at the doses tested (15). Most importantly, exposure to PNT2258 resulted in clinically manageable decreases in lymphocytes. Nevertheless, this novel technology needs to be evaluated in a larger patient population before coming to the final conclusion as an effective alternate to small molecule approach.

Contrary to the concept of pan Bcl-2 inhibition strategy, Leverson’s study showed that the successful design of Bcl-2 targeted therapeutics requires careful selection of very specific drugs that single out Bcl-2 and not any of the additional family members. This selection may prevent some of the common side effects observed by older generation pan Bcl-2 inhibitors resulting in greater therapeutic effects and better treatment outcomes in cancer patients.

Acknowledgements

NIH R21 1R21CA16984801 and 1R21CA17597401 to Ramzi M. Mohammad is acknowledged.

Footnote

Provenance: This is a Guest Editorial commissioned by Executive Editor Bing Gu, MD (Department of Laboratory Medicine, the Affiliated Hospital of Xuzhou Medical University, China).

Conflicts of Interest: Dr. Ramzi M. Mohammad owns equity in ProNAi. I Muqbil has no conflicts of interest to declare.

References


© Annals of Translational Medicine. All rights reserved. www.atmjournal.org Ann Transl Med 2015;3(20):312