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REVIEW ARTICLE

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Insights into Novel Drugs Targeting Bcl-2 Protein as Potential Anti-cancer Agents

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Abstract

Cancer remains one of the most difficult life-threatening diseases to treat. Breast cancer was one of the deadliest diseases which occupies the second place in the list of cancers with the highest mortality rates. Despite many successes in cancer therapy, many tumors are not efficiently killed by chemotherapy, leading some to suggest that cancer cells are generally blocked the apoptotic signaling. Consequently, there are a plethora of studies that are trying to decipher the apoptotic processes deregulated in specific diseases. The Bcl-2 family proteins comprise the sentinel network that regulates the intrinsic apoptotic response. Clinical trials of several investigational drugs, targeting the Bcl-2 family, are ongoing which up to date confirmed the efficiency of these agents in killing cancer cells and overcoming chemotherapy resistance. Here, we review the role of the Bcl-2 family in apoptotic pathways and those agents that are known and/or designed to inhibit the anti-apoptotic Bcl-2 family of proteins.

Keywords: Cancer; Bcl-2 family; Inhibitors of anti-apoptotic signaling.

1. Introduction

Although there are numerous achievements in cancer treatment, numerous cancers are not professionally destroyed by chemotherapy, which make some to think that cell of cancer are commonly blocked the signaling of apoptosis (Mcvie, Schipper, & Sikora, 2010) (Hata et al., 2014). Several early reports raised the hope that research on apoptosis would help to elucidate the pathogenesis of cancer it was also hoped that proteins involved in apoptosis regulation would be useful as predictive markers of tumor response to treatment. The proteins of Bcl-2 family were initially identified to be involved in the first stages of the development of a hematological malignancy. However, such observation is currently broadened into two important directions from a clinical viewpoint. First, Bcl-2 was shown to be transcriptionally upregulated by other mechanisms

that did not involve chromosomal translocation extending its role has been extended far beyond hematological malignancies to include many different types of cancers. Secondly, it was shown that inhibition of apoptosis by Bcl-2 was involved not only in the development of cancer but also in the mechanism whereby cancers develop resistance to cancer therapeutics, including chemotherapy and radiotherapy. Therefore, because most cancer therapies funnel through the induction of apoptosis, being able to 'open this funnel wider' with drugs that interfere with Bcl-2 was recognized early as an important general way of improving conventional cancer therapy. These suggestive findings have therefore motivated a widespread attempt to find novel drugs that would inhibit the mechanism, whereby Bcl-2 prevents apoptosis. Here we discuss the mechanistic role of Bcl-2 family in blocking the system that controls apoptosis and chemical agents targeting such anti-apoptotic family, within the current clinical trials.

2. Bcl-2 family in orchestrating the anti-apoptotic signaling

One of the two major pathways leading to apoptosis is the mitochondrial or intrinsic biochemical pathway. The signature biochemical change during activation of this pathway (Figure 1) is the leakage of cytochrome c (Cyt c) into the cytoplasm where it facilitates caspase 9 activation to initiate a caspase cascade (Danial & Korsmeyer, 2004). This release of cytochrome c from mitochondria is regulated by members of the Bcl-2 protein family, which include three functionally and structurally distinct subfamilies: i) pro-apoptotic effector proteins Bax and Bak, which mediate mitochondrial outer membrane permeabilization (MOMP); ii) anti-apoptotic family members, including Bcl-2, Bcl-xL, Mcl-1, Bcl-w and A1, which antagonize MOMP; and iii) pro-apoptotic BH3-only proteins, which promote apoptosis either directly by binding and oligomerizing Bax and Bak or indirectly by neutralizing anti-apoptotic family members. When the balance between these Bcl-2 family members tips in favor of cell death, Bax and Bak form oligomers that permeabilize the mitochondrial outer membrane (MOM), resulting in release of Cyt c and many other mitochondrial intermembrane space proteins.

Currently, there are three identified models of the mechanism of apoptosis regulation by Bcl-2 family members. The 'direct activation' model proposes that there are two suBclasses of BH3-only proteins (Kim, Rafiuddin-Shah et al. 2006). The 'activator' suBclass of proteins [including truncated Bid (tBid) and Bim)] directly bind to and activate Bax or Bak. In this case, the sole function of antiapoptotic proteins such as Bcl-2 is to sequester these Bax/Bak activators. On the other hand, the 'sensitizer' BH3-only proteins (such as Bad or Noxa) do not directly activate Bax/Bak, but instead act as a 'decoy' and displace tBid or Bim from binding to antiapoptotic members (Letai, Bassik et al. 2002). The second model is known as the The competing 'derepression' model postulates that Bax/Bak is always active and that the antiapoptotic Bcl-2 proteins must constitutively bind to them to prevent apoptosis (Chen, Willis et al. 2005). The model states that the only role of the BH3-only proteins is to displace activated Bax/Bak from antiapoptotic Bcl-2 proteins. According to this model, the different BH3-only proteins are distinguished by which antiapoptotic Bcl-2 family members they bind

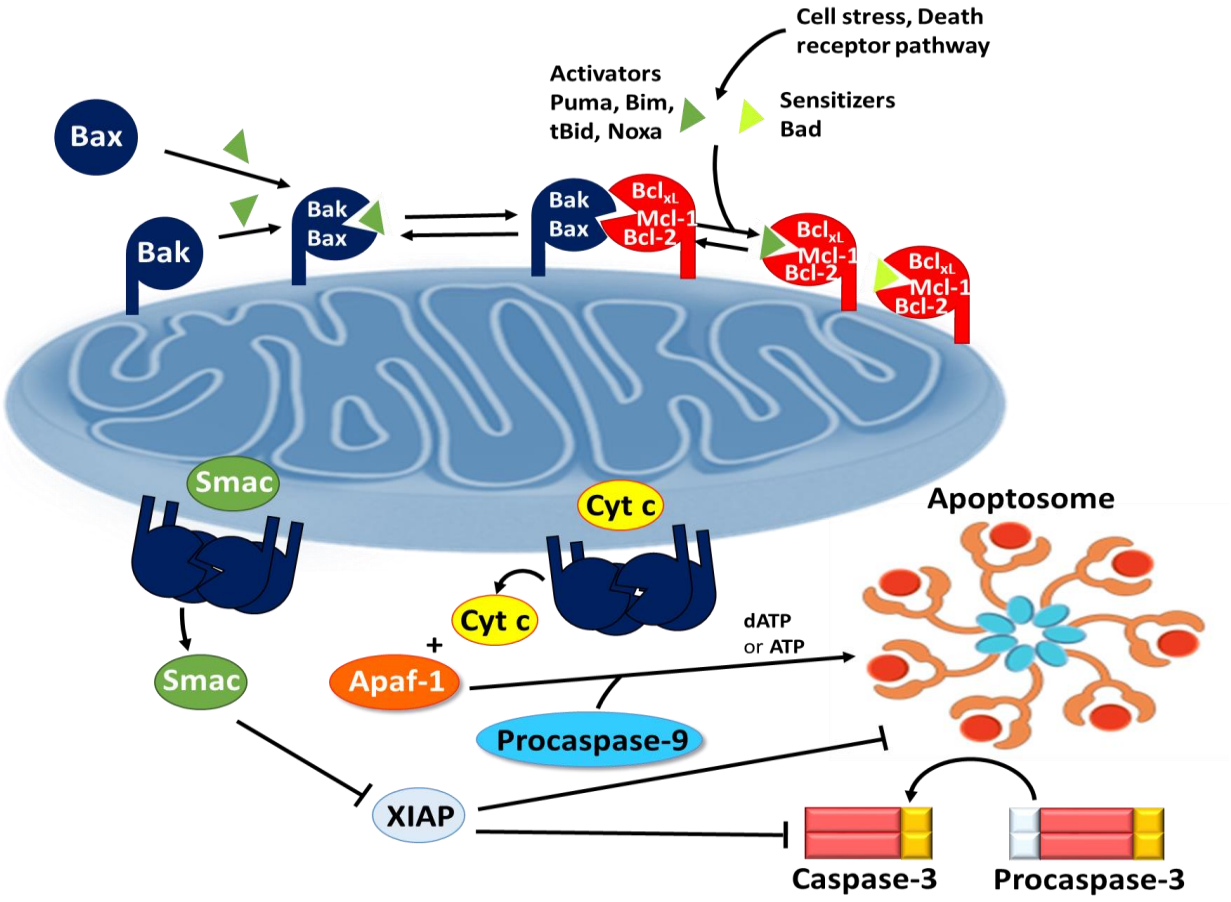

Figure 1. Overview of the mitochondrial pathway

to: all of them (such as tBid, Bim or PUMA) or just a subset (e.g. Bad binds only to Bcl-2 and Bcl-XL and not to Mcl-1, whereas for Noxa it is the reverse) (Willis, Fletcher et al. 2007). The last and third model is the 'embedded together' model combining features of both models. Here, the antiapoptotic Bcl-2 family member Bcl-XL binds to and sequesters both BH3-only activators and activated Bax/Bak (Billen, Kokoski et al. 2008). Furthermore, a major factor that regulates these binding interactions is the membrane because interaction with the membrane alters the binding surfaces between proteins for all three classes of Bcl-2 family members. In this way the interactions with membranes change the relative affinities of specific interacting pairs (Leber, Lin et al. 2007)

3. Molecular structure of Bcl-2 and its Ligand binding pocket

The Bcl-2 protein is made up of four homology domains: BH1, BH2 BH3 and BH4. The hydrophobic cleft is made up from BH1, BH2, and BH3 that it is crucial to capture the BH3 domain of pro-apoptotic proteins via hetero-dimerization (Czabotar et al., 2007). BH4 is somewhat needed for the activity of anti-apoptosis (Kazi et al., 2011). The BH3 and BH4 domains have In between, a flexible loop domain (FLD) that exist between the putative α1 and α2 helices. It is considered to be one of the most significant domains in Bcl-2 (Petros, Olejniczak, & Fesik, 2004). Bcl-2 protein consists of eight α helices connected by various

omega loops α5 is primarily hydrophobic and forms the center of the protein, while the remaining helices cluster around α5, α2 & α3 are connected by a single residue, a tyrosine at residue 105 which results in a perpendicular orientation of α2 & α3. Both α3 & α4 are separated by fourteen residues, α4 & α5 is separated by four residues, and α5 & α6 is separated by three residues, which allow for nearly 180 degree chain reversal between α 2 & α 3, α 3 & α 4, and α 5 & α 6 (Petros et al., 2004). Meanwhile the borders of α3 helix one sideways of the hydrophobic binding groove, this leads to a markedly Bcl-2 broader groove. Inside the groove itself, there exist 108Met which have flexible side chain in the middle of the Bcl-2 α3 helix that enable a deep hydrophobic pocket penetration. we assumed that gaining access to this deep hydrophobic pocket groove may considerably improve the affinity of the Bcl-2 for more and more inhibitors (Willis et al., 2005).

For representing the Bcl-2 hydrophobic pocket groove, we represent a 3D-visualization of the X-ray co-crystallized structure of Bcl-2 using the pymol software (**Figure 2**). Here, the co-crystallized tetrahydroisoquinoline-phenyl pyrazole ligand binds the exact hydrophobic groove like the pro-apototic BH3-only peptides and resemble the interactions of the side chains with a number of key binding pockets (Czabotar et al., 2007). Specifically, the n-butyl side chain of the pyrazole amide occupies the site normally filled by Leu92 of BIM. Founded on this X-ray structure, the polar substituents at tetrahydro-isoquinoline 3-position would be solvent exposed and so expected to improve aqueous solubility while preserving potent binding affinity. Remarkably, the acyl sulfonamide does not interact with the two arginines that are in close vicinity (Arg66 , Arg105), but somewhat engages in a hydrogen bond with Glutamine Gln58 from asymmetry-related molecule (not shown) as well as a couple of hydrogen bonds with Tyrosine Tyr67. Finally, the iodo-naphthalene fills the BIM

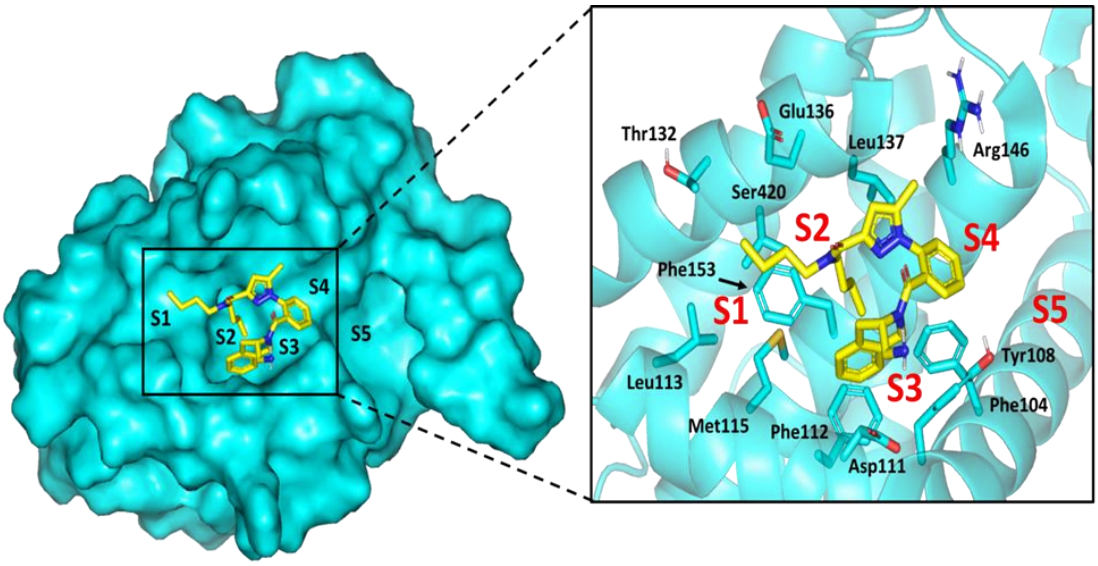

Figure 2. The X-ray crystallized Bcl-2 (PDB ID: 6qgk) bounded to tetrahydroisoquinoline-phenyl pyrazole derivative. The zoomed image is the stereoview of crystallized tetrahydroisoquinoline-phenyl pyrazole derivative (yellow sticks) occupying the active binding site. Only significant residues (cyan sticks), located within 4 Å radius of the bound ligand, are displayed and labeled with sequence number.

Phenylalanine Phe99 hydrophobic pocket (Boersma, Sadowsky, Tomita, & Gellman, 2008).

3. Promising Bcl-2 inhibitors through clinical studies

Bcl-2 rises the cell survival kinetics precisely by blocking the pro-apoptotic factors. Consequently it inhibits the cell from going to some suicidal activity which usually necessitate new RNA, ATP, protein synthesis, and stimulating a variability of changes of cellular ultra-structure like nuclear fragmentation, DNA degradation, and cell shrinkage. Bcl-2 proteins are the main arbiter macromolecule of apoptosis functioning as potent anti-death molecule (Chen-Levy, Nourse, & Cleary, 1989).The anti-apoptotic proteins are overexpressed in many sorts of human cancer and such overexpression protects cancer cells from a variety of apoptotic stimuli, including those associated with cancer chemotherapeutic agents, and confers on cancer cells resistance to current therapeutic agents. That is why, Bcl-2 proteins are a promising molecular target for the several pharmaceutical companies and academia to develop promising anti-cancer agents (Thomadaki & Scorilas, 2006). Within the following context, a descriptive review of the small molecules within clinical development targeting Bcl-2 family proteins (**Figure 3**).

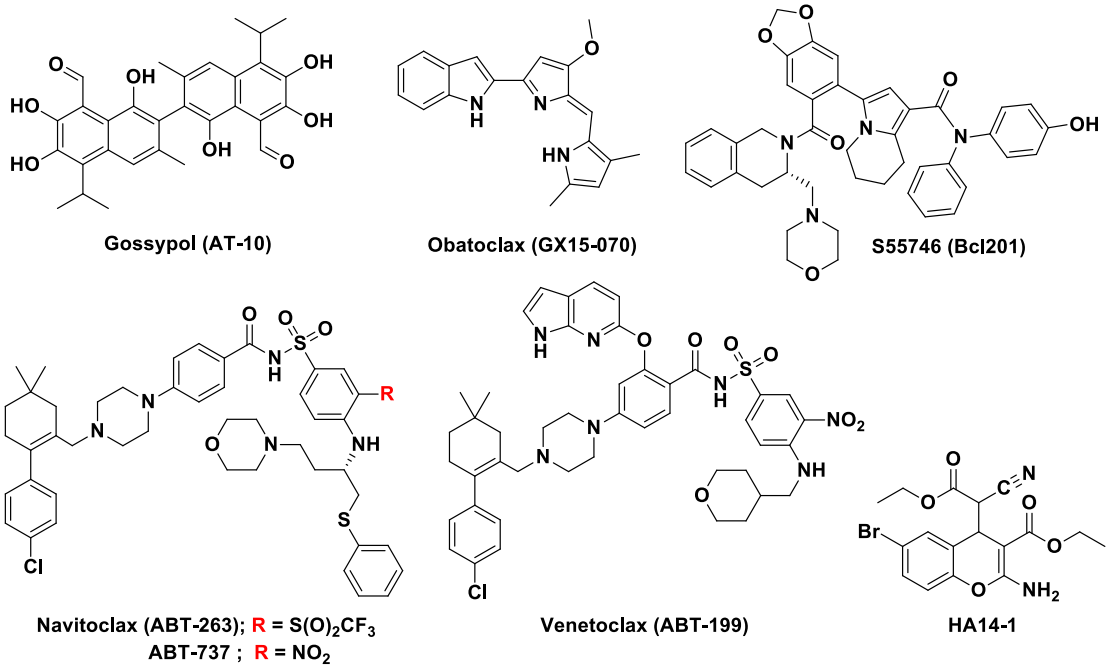

Figure 3. Disclosed structures for clinical BH3-mimitics as potential anti-cancer agents.

3.1. Gossypol (AT-101)

Gossypol (Phase-I ClinicalTrial in multiple myeloma; NCT02697344) is considered to be one of the initial BH3-mimetic compounds, that characterized by its anti-proliferative effect *in-vitro* to numerous types of cancer cell and its antitumor effects *in-vivo* in bare mice IC_{50} of 0.5 μM. Nonetheless, despite it is considered to be a favorable drug in the therapy of cancer and reaching clinical human trials, downside with

gossypol was found, because of its structure which contain two aldehydic groups that linked with toxicity and as potential targets for another proteins (Baggstrom et al., 2011). Therefore, derivatives of gossypol arisen such as apo gossypol, produced by eliminating the two aldehydic groups ,for which better activity in leukemias, liver cancer ,nasopharyngeal carcinoma cells, breast cancer, prostate cancer and pancreatic cancer has been stated; furthermost significantly, it has lesser toxicity than that of gossypol (Zheng et al., 2017).

3.2. Obatoclax (GX15-070)

GX15-070 is an experimental drug for the management of numerous types of cancer (Phase-II ClinicalTrial in myelodysplastic syndromes; NCT00413114). Obatoclax was discovered using a high throughput screen of natural compounds that disrupt protein–protein interactions in the Bcl-2 family. The mechanism of action of obatoclax as BH3-peptide mimetics against purified proteins has been confirmed in cell lines, as both drugs displace Bax and BH3-only proteins such as Bim from antiapoptotic proteins, as assessed by immune precipitation and western blotting, and cause the classical hallmarks of apoptosis in cells such as cytochrome c release from mitochondria and caspase activation. Some Phase two clinical trials considered the usage of Obatoclax in the management of lymphoma leukemia, myelofibrosis, and mastocytosis (Parikh et al., 2010). It is the Bcl-2 proteins inhibitor that has the capability to bind to Bcl-XL, Bcl-w, and Mcl-1 at concentrations of 1–7 μM. Furthermore, obatoclax has been shown to overcome Mcl-1-mediated resistance to ABT-737 in cell lines (Konopleva et al., 2008). This inhibition stimulate apoptosis in cells of cancer, inhibiting tumor growth. Solubility has been a matter in the improvement of the drug (Nguyen et al., 2015).

3.3. ABT-737

The quest to develop new compounds binds with great affinity less than 1 nmol/L to anti-apoptotic proteins comprising Bcl-2, ABT-737 was introduced (Suvarna, Singh, & Murahari, 2019). The sulphonamide-based compound was developed as a rational Bcl-2 inhibitor that binds to and inhibits Bcl-2, Bcl-XL and Bcl-w with nanomolar affinities when truncated versions of these proteins are used as binding targets. The mechanism of action of ABT-737 as BH3-peptide mimetics against purified proteins has been confirmed in cell lines, as both drugs displace Bax and BH3-only proteins such as Bim from antiapoptotic proteins, as assessed by immune precipitation and Western blotting, and cause the classical hallmarks of apoptosis in cells such as Cyt c release from mitochondria and caspase activation. The proapoptotic agent is also extremely effective at enhancing the cytotoxicity of a variety of chemotherapy agents in many different cancer cell lines *in-vitro*, it has been verified as single drug owing

activity against lymphoid malignancies, lung cancer and small cell. Nonetheless, views for it as a therapeutic agent have been troubled by its weak pharmacological and physicochemical possessions.

3.4. Navitoclax (ABT-263)

Navitoclax (Phase-I ClinicalTrial in relapsed/refractory acute lymphoblastic leukemia or lymphoma; NCT03181126 and Phase-II ClinicalTrial in myelofibrosis; NCT03222609). Unlike ABT-737, it has enhanced oral bioavailability of 20-50% with t1/2 of 8.9 hour making it appropriate for once dosing per day with preferred pharmacokinetics. ABT-263 has activity against Bcl-2, BCL-XL, and BCL-w with a Ki of ≤1 nM, and a Ki of 550 nM against MCL-1(Lampson & Davids, 2017) and develop its antitumor activity (Gandhi et al., 2011). The mechanism of action of ABT-263 as BH3-peptide mimetics against purified proteins has been confirmed in cell lines, as both drugs displace Bax and BH3-only proteins such as Bim from antiapoptotic proteins, as assessed by immunoprecipitation and western blotting, and cause the classical hallmarks of apoptosis in cells such as Cyt c release from mitochondria and caspase activation.

3.4. Venetoclax (ABT-199)

Venetoclax is the modified form of navitoclax for the aim of increasing its Bcl-2 selectivity. This drug has been market launched as Venclexta® for managing of chronic lymphocytic leukemia on 11 April 2016 following the US-FDA approval. Venetoclax binds to Bcl-2 with affinity K_i < 0.010 nM, with acceptable oral bioavailability and an expected half-life of 26 hr inducing apoptosis in primary chronic lymphocytic leukemia with significant IC_{50} (3nM). The drug has been tried in different combinations with other antitumor monoclonal antibodies or small molecule drugs; however, these attempts have mostly focused on hematologic carcinoma (Fischer et al., 2019). Currently, venetoclax is in successive clinical trials for managing non-Hodgkin lymphoma, myeloblastic syndrome, B-cell lymphoma, Waldenstrom macroglobulinemia, follicular lymphoma, diffuse large B-cell lymphoma, multiple myeloma, acute myeloid leukemia, and Mantel cell lymphoma (Phase-I ClinicalTrial; NCT02055820, Phase-II ClinicalTrial; NCT03223610, and Phase-II ClinicalTrial; NCT04161885 and NCT03946878). Most of these studies investigated ABT-199 in combination with other therapies, as RNA/DNA inhibitors, including the anti-CD20 antibody rituximab, glycoengineered anti-CD20 antibody obinutuzumab, and bendamustine/rituximab suggesting that such combination will be more effective than their single usage.

3.5. S55746 (Bcl201)

S55746/Bcl201 (Phase-I ClinicalTrial in myeloblastic syndrome; NCT02920541) is an orally active well-tolerated BH3-mimetic compound targeting selectively and potently the Bcl-2 protein (Ki = 1.3 nM) which has recently entered the clinical development. S55746 occupies the hydrophobic groove of Bcl-2. Its selectivity profile demonstrates no significant binding to MCL-1, BFL-1 (BCL2A1/A1) and poor affinity for Bcl-XL.

Accordingly, S55746 has no cytotoxic activity on Bcl-XL-dependent cells, such as platelets. In a panel of hematological cell lines, S55746 induces hallmarks of apoptosis including externalization of phosphatidylserine, caspase-3 activation and PARP cleavage. *Ex vivo*, S55746 induces apoptosis in the low nanomolar range in primary Chronic Lymphocytic Leukemia and Mantle Cell Lymphoma patient samples. Finally, S55746 administered by oral route daily in mice demonstrated robust anti-tumor efficacy in two hematological xenograft models with no weight lost and no change in behavior (Casara, Davidson et al. 2018).

3.7. Palcitoclax (APG-1252)

APG-1252 (Phase-I ClinicalTrial in small cell lung cancer (SCLC) and other advanced solid tumors; NCT03387332; Structure not-yet disclosed) is a Bcl-2 homology (BH)-3 mimetic that specifically binds to Bcl-2 and Bcl-xl, which has shown efficacy in some Bcl-2 dependent hematological cancers. The recent phase-I study has showed APG-1252 to be well-tolerated across all dose levels tested with no reported hematologic toxicity so far. APG-1252 potently inhibits tumor growth in human cancer xenograft models including SCLC models while trigged significantly less platelet killing APG-1252 demonstrated a higher therapeutic index than ABT-263 in preclinical studies (Lakhani, Rasco et al. 2018). Recently, a study by Wang et al have investigated the ability of APG-1252-12A to inhibit the growth of leukemia cell lines showed that this new compound inhibited cell proliferation in five leukemia cell lines and induced apoptotic death while illustrating a link between the level of Bcl-2 protein and IC50 of the drug (Wang, Yang et al. 2017). In this study APG-1252 targeted mitochondria and induced caspase-dependent apoptosis by inducing the HL-60 cell Cyt c released, PARP cleavage and caspase activation. These data suggested that APG-1252-12A is a candidate drug for the in vivo analysis and clinical evaluation in AML.

3.8. HA14-1

HA14-1 is a small-molecule non-peptide inhibitor of the anti-apoptotic Bcl-2 family of proteins that was identified by structure-based screening (Wang et al., 2000). Interestingly, the binding affinity of HA14-1 to Bcl-2 (IC_{50} ~9 μmol/L) is relatively high compared with other inhibitors of anti-apoptotic Bcl-2 proteins depicted through the structure-based screening protocol. This compound showed promising preclinical studies where it induced apoptosis in various cancer cells, including leukemia, lymphoma, glioblastoma, neuroblastoma, and colon cancer (Manero, Gautier et al. 2006). Within tested human follicular lymphoma cell lines t(14;18), all cells were sensitive to HA14-1-induced cytotoxicity and apoptosis, as depicted by morphological changes, SYTO16/PI staining, oligonucleosomal DNA fragmentation and loss of Deltapsi(m). Moreover, HA14-1 enhanced doxorubicin- and dexamethasone -mediated (Within dependent and independent manner, respectively), but not vincristine-mediated cytotoxicity and apoptosis (Skommer, Wlodkowic et al. 2006).

4. Conclusion

Bcl-2 family of proteins are largely identified in normal cell and plays a crucial role in cell death and survival. Its anti-apoptotic role and overexpression in cancer cells have been widely studied and identified as a valid and potential target for cancer therapy. Most of the compounds summarized in this article have shown superior activity and efficacy in sensitive cancer cells at appropriate pharmacological concentrations. Overall Bcl-2 is progressive target with clinical efficacy in leukemic cancers and is further validated by FDA approval of venetoclax for chronic lymphocytic leukemia. Selectivity vs specificity of Bcl-2 inhibitors needs to be authenticated to avoid unrelated toxicity or side effects with an involvement of other antiapoptotic pathways. Additionally, results from the clinical trials conducted in the last few decades suggest that the combination of Bcl-2 inhibitors with other antitumor drugs or RNA/DNA inhibitors will be more effective than their single use. In brief, thirty years of wonderful journey with Bcl-2 in cancer has retrieved lot of information for moving towards to visualize clinical success in coming years. Personalized medicine and Bcl-2 inhibitors for cancer chemotherapy is definitely an unanswered question. Unravelling the recent challenges will turn Bcl-2 inhibitors into therapeutically beneficial drugs.

Conflict of interest

The authors declare a no conflict of interest nor receive any specific grant from any funding agencies in the public, commercial, or even not-for-profit sectors.

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