Review Article
Drugs and Clinical Approaches Targeting the Antiapoptotic Protein: A Review

Zeping Han,1 Jiening Liang,2 Yuguang Li,1 and Jinhua He1

1Department of Laboratory Medicine, Central Hospital of Panyu District, Guangzhou, Guangdong 511400, China
2School of Chemistry and Molecular Biosciences, The University of Queensland, St. Lucia, QLD, Australia

Correspondence should be addressed to Jinhua He; 332518579@qq.com

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B-celllymphoma2(Bcl-2)isaregulatorproteininvolvedinapoptosis.Inthepastfewdecades,thisproteinhasbeendemonstrated
tohavehighefficacyincarentherapy,andseveralapproachestargetingBcl-2havetestedclinically(e.g.,oblimersen,ABT-
737, ABT-263, obatoclax mesylate, and AT-101). This review reports potential Bcl-2 inhibitors according to current information
ontheirunderlyingmechanismandtheresultsofclinicaltrials.Inaddition,thefunctionandmechanismsofotherpotentially
valuableBcl-2inhibitorsthatdidnotshowefficacyinclinicalstudiesarealsodiscussed.ThissummaryofthedevelopmentofBcl-2
inhibitorsprovidesworthwhileviewpointsonthelossofbiomedicalapproachesinfuturecancertherapy.

1. Introduction

In current gene and cell immunotherapy techniques, cellular
pathways are popular and effective targets for curing cancer.
It is important to discover a switch or inhibitor of a cellular
pathway that is expressed not only in leukemia but also in
solid tumors because solid tumors remain a critical barrier to
cell therapy due to their size and the protective effects of the
microenvironment [1]. Therefore, the identification of cel-
lular pathway inhibitors is a valuable research topic for
destroying the tumor microenvironment from the inside.

In the last few decades, researchers have tried to induce
tumor regression by blocking cellular pathways to enhance
the efficiency of therapeutic treatments. One such candidate
is B-cell lymphoma 2 (Bcl-2) protein, a potential inhibitor of
apoptosis that belongs to the Bcl-2 family, members of which
are involved in several cellular pathways such as DNA
damage/p53 pathway, survival/NF-xB pathway, estrogen
pathway, STAT pathway, and PI-3 kinase/AKT pathway [2].
Bcl-2 was the first identified mammalian regulator of apo-
ptosis [3] and consists of four conserved domains (BH4, BH3, BH1, and BH2), which differentiate it from other Bcl-2
family members, (e.g., Bim, Bid, Puma, Noxa, Bad, Hrk,
Bmf, and Bik) [4]. Among these homology motifs, BH3,
BH1, and BH2 are the most commonly targeted in clinical
approaches.

2. Clinical Approaches

In the past 30 years, efforts have been made to identify
methods to cure Bcl-2 protein-related diseases, including
molecular antibodies, small molecule drugs, and antisense
oligonucleotides. In currently reported cases, the efficiency
andsafetyofsomeclinicaldrugstargetingBcl-2proteinhave
been demonstrated in hematologic carcinoma.

The mechanism of action of Bcl-2 inhibitors has been
widely studied. Most Bcl-2 inhibitors block the binding of
BH3-only proteins (mostly Bim) to Bcl-2 via a small mol-
ecule that mimics the BH3 domain. This process allows free
Bim to activate Bak/Bax on the surface of mitochondria and
induces mitochondrial outer membrane permeabilization
(MOMP) to release cytochrome C, which leads to the death
of cancer cells. The proliferation of specific cancer cells is
also inhibited in the presence of cytochrome C [5] (Figure 1).

Oblimersen (G3139, Genasense) was the first developed
drug that utilized Bcl-2 inhibitors and was produced by
Genta Inc. It utilizes an 18-mer short sequence RNA to
inactivate mRNA via hybridization to inhibit the production
of Bcl-2 protein and the proliferation of lymphoma cells. Unfortunately, no difference was found in the 5-year survival rate of patients in phase III clinical trials of oblimersen between the test and reference groups, so oblimersen has been rejected twice for approval by the US Food and Drug Administration (FDA) [6]. Most clinical studies using only oblimersen ended before 2010, and it is unknown whether it decreased cancer cells by an antisense drug mechanism or the induction of interferon release via its own CpG motif. After the failure of single-use oblimersen, the antitumor efficacy of oblimersen combined with other drugs has been examined. Clinical trials of Bcl-2 inhibitors conducted from 2010 to 2019 are shown in Table 1. In 2010, Raab et al. reported a phase I trial of oblimersen combined with cisplatin and 5-fluorouracil in 15 patients with advanced esophageal, gastroesophageal junction, or gastric carcinoma, which resulted in 1 case with complete remission and 2 with a partial response [7]. In 2011, Galatin et al. indicated that 5 of 16 patients with refractory and advanced malignancies had stable disease after combined treatment with oblimersen and gemcitabine [8]. In 2013, Ott et al. reported that treatment of patients with advanced melanoma with oblimersen combined with temozolomide and albumin-bound paclitaxel resulted in 2 cases with complete remission, 11 with a partial response, and 11 with stable disease [9].

After oblimersen, Petros et al., comprising the Abbott team (Abbott Laboratories, USA), devised a new method called fragment-based drug discovery that could be used in the development of Bcl-2 inhibitors [29]. Initially, Abbott focused on Bcl-xL protein, but the high structural homology between Bcl-xL and Bcl-2 proteins (with a difference of only four amino acids in the active site) meant that the new drug was suitable for Bcl-2 and Bcl-xL [30]. Abbott divided the Bcl-xL binding site into two fragments, based on the previous discovery of two small chemical compounds (I and II) from a library of molecules specifically binding to the Bcl-xL BH₃ domain. The study data indicated that modified compound I was able to enter the P2 binding pocket, while compound II could readily enter the P4 pocket [31, 32]. Further developing the findings of Petros et al., an antibody targeting Bcl-2 protein appeared in 2005, when Oltersdorf et al. reported their candidate antibody ABT-737 and provided preclinical evidence for targeting Bcl-2 in treating solid tumors [34]. Even though this discovery was established using a mouse model, it led to the development of the orally administered drug navitoclax (ABT-263) by Tse et al. 3 years after the first report of ABT-737. Navitoclax showed effective tumor regression in patients with small-cell lung cancer and acute lymphocytic leukemia, but there was a large decrease in the number of platelets that encouraged the development of a new application with higher safety [35]. However, Zhang et al. suggested that Bcl-xL is crucial for the survival of mature platelets in vivo, so the previous two applications are not suitable drugs for patients [36]. Reports from 2012 and 2015 also confirmed the low efficacy of navitoclax [10–16]. AbbVie pharmaceuticals then introduced venetoclax (ABT-199) targeting BH₃-binding sites only on Bcl-2 that maintains efficiency while protecting the survival of platelets, and improved treatment of chronic lymphocytic leukemia was reported [37]. In 2016, the FDA approved the use of venetoclax. In recent years, venetoclax has been tried in different combinations with other anti-tumor monoclonal antibodies or small molecule drugs; however, these attempts have mostly focused on hematologic carcinoma [17–23].

Obatoclax mesylate (GX15-070), another drug targeting the Bcl-2 family, has also shown efficacy in phase III clinical trials. This drug is a BH₃ mimetic, so it can potentially bind to most Bcl-2 family members (including Bcl-2 protein). However, the main mechanism of this inhibitor is binding to Mcl-1 as a supplemental therapy in Bcl-xLlow or Bcl-xL− cancer cells or cells with resistance to Bcl-2 inhibitors [38]. Bcl-2 protein is reportedly crucial for sustaining hematopoietic stem cells, but this antiapoptotic factor is also expressed at a high level in acute myeloid leukemia and acute lymphocytic leukemia [39]. Therefore, obatoclax mesylate

![Figure 1: Bcl-2 inhibitors inducing apoptosis of cancer cells.](image-url)
| Bcl-2 inhibitor                          | Combined therapy with other drugs                          | Targeted cancer type                                                                 | No. of patients | Complete remission | Partial response  | Stable disease | Phase | Researchers       |
|----------------------------------------|----------------------------------------------------------|--------------------------------------------------------------------------------------|-----------------|--------------------|-------------------|----------------|-------|-------------------|
| Oblimersen                             | Cisplatin and 5-fluorouracil                              | Advanced esophageal, gastroesophageal junction, and gastric carcinoma                  | 15              | 1                  | 2 (1 gastric carcinoma with pulmonary metastases) | I              | Raab et al. [7]   |
|                                       | Gemcitabine                                              | Refractory and advanced malignancies                                                 | 16              | 0                  | 0                 | 5              | I     | Galatin et al. [8]|
|                                       | Temozolomide and albumin-bound paclitaxel                | Advanced melanoma                                                                    | 32              | 2                  | 11                | 11             | I     | Ott et al. [9]    |
| Navitoclax (ABT-263)                   | None                                                     | SCLC or pulmonary carcinoid                                                           | 47              | 0                  | 1 (SCLC)          | I              | Gandhi et al. [10]|
|                                       | None                                                     | Relapsed SCLC                                                                        | 39              | 0                  | 1                 | 9              | II    | Rudin et al. [11] |
|                                       | None                                                     | Relapsed or refractory CLL                                                           | 29              | 0                  | 9                 | 7              | I     | Roberts et al. [12]|
| Irinotecan                             | None                                                     | Advanced solid tumors                                                                | 31              | 0                  | 2 (1 Merkel cell carcinoma, 1 colon carcinoma) | 6              | I     | Tolcher et al. [13]|
| Erlotinib                              | None                                                     | Advanced solid tumors                                                                | 11              | 0                  | 0                 | 3              | I     | Tolcher et al. [14]|
| Rituximab                              | None                                                     | Relapsed or refractory CD20+ lymphoid malignancies                                   | 29              | 6                  | 10 (5 CLL/SLL, 4 follicular lymphoma, 1 lymphoma/ Waldenström’s macroglobulinemia) | I              | Roberts et al. [15]|
| Rituximab                              | Rituximab                                                | Previously untreated B-cell CLL                                                       | 78              | 2                  | 47                | 25             | II    | Kipps et al. [16] |
| Obinutuzumab                           | Obinutuzumab                                             | CLL and coexisting conditions                                                         | 216             | 107                | 76                | III            | Fischer et al. [17]|
| Ibrutinib                              | Ibrutinib                                                | CLL                                                                                   | 80              | 25                 | 1                 | II             | Jain et al. [18] |
| Ibrutinib                              | Ibrutinib                                                | CLL                                                                                   | 91              | 8                  | 48                | 22            | II    | Jones et al. [19] |
| Venetoclax (ABT-199)                   | None                                                     | Relapsed or refractory non-Hodgkin lymphoma                                           | 106             | 14                 | 33                | 32            | I     | Davids et al. [20]|
|                                       | Decitabine or azacitidine Bendamustine and obinutuzumab  | Acute myelogenous leukemia                                                           | 32              | 6                  | 0                 | 6             | II    | Konopleva et al. [21]|
|                                       |                                                          | Acute myeloid leukemia                                                               | 57              | 35                 | 1                 | 0             | I     | DiNardo et al. [22]|
|                                       |                                                          | CLL                                                                                   | 66              | 5                  | 55                |                | II    | Cramer et al. [23] |
provides an additional option for patients who need a Bcl-2 inhibitor. Unfortunately, the developers of obatoclax mesylate suddenly terminated their clinical trials in 2012, and no further details have been released since 2014 [24, 25].

AT-101 is an orally active pan-Bcl-2 inhibitor that consists of gossypol, a natural compound derived from the cotton plant [40]. In preclinical trials, it induced a strong apoptotic response in leukemic cells [41]. However, phase II trial data of AT-101 posted in 2010 indicated that it did not generate the expected response (NCT00286780), so the company stopped the clinical development of this drug until the founders decided to continue research in China. Recently, clinical trials using AT-101 in combination with other drugs for the treatment of solid tumors have been reported, such as its combination with docetaxel to treat head and neck cancer [27], in combination with docetaxel and prednisone to treat castration-resistant prostate cancer [42], in combination with paclitaxel and carboplatin for different carcinoma types [43], and in combination with cisplatin and etoposide for extensive-stage small-cell lung cancer [28]. Given the reported findings, it is reasonable to believe that AT-101 could be a potent inhibitor of Bcl-2.

### 3. Other Valuable Candidates

In 2007, Mohammad et al. introduced another Bcl-2 inhibitor named TW-37, which is a small molecule inhibitor of Bcl-2/Bcl-XL/MUC-1 that could prevent Bcl-2 overexpression [44]. TW-37 has a higher affinity and selectivity for Bcl-2 compared with Bcl-xL protein. According to in vitro tests, TW-37 acts in lymphoma cells from patients, but not in normal peripheral blood cells [44]. In a mouse model, the combination of TW-37 with an MEK inhibitor was found to prevent the growth of melanoma cells [45]. Considering the features of TW-37, it should be a potent drug for inhibiting Bcl-2; however, due to unknown reasons, this inhibitor was not examined in clinical trials. Besides TW-37, several Bcl-2 inhibitors are in the preclinical development stage, such as HA14-1, sabutoclax, S55746 (S055746, BCL201), and gambogic acid. Among these compounds, S55746 shows similar high affinity to Bcl-2 as ABT-737 and ABT-199 [46].

### 4. Conclusion

With regard to Bcl-2 protein inhibitors, two main streams have been utilized in clinical approaches, namely, antibodies and small molecule drugs. Techniques have been developed to inhibit the expression and function of Bcl-2 and its family proteins at the gene and protein levels. According to current data, approximately 19 different Bcl-2 inhibitors are the subjects of preclinical or clinical studies and various combinations of therapeutic methods are being assessed for Bcl-2-positive cancer. 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.

### Conflicts of Interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and publication of this article.

### Authors’ Contributions

Zeping Han & Jiening Liang contributed equally to this work.
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