

# BH3 mimetics: Their action and efficacy in cancer chemotherapy

Wataru Nakajima and Nobuyuki Tanaka\*

Department of Molecular Oncology, Institute for Advanced Medical Sciences, Nippon Medical School, Japan

## Abstract

Evading apoptosis is a hallmark of cancer, and anti-apoptotic BCL-2 family proteins are frequently highly expressed in cancers. In cancer cells, aberrant DNA replication invokes replication-associated DNA damage signaling in cancer cells; however, DNA damage-induced apoptotic signals are masked by such apoptosis evasion systems. Therefore, it is considered that targeting of apoptosis is efficient for cancer cell-selective therapeutic methods. BCL-2 family proteins are critical regulators of mitochondrion-mediated apoptosis, and 'BH3-only' subfamily proteins induce apoptosis by binding to anti-apoptotic BCL-2 family proteins via their BH3 domain. BH3 mimetics are small molecules that mimic BH3-proteins by binding to anti-apoptotic BCL-2 family proteins. To date, more than 20 compounds have been identified, and their effects in cancer therapy have been analyzed. In this review, their efficacy in cancer chemotherapy will be discussed.

## Introduction

Mechanistic-based molecular-targeted therapies to treat human cancers have undergone rapid development [1]. For example, small molecules specifically blocking certain aspects of signaling pathways associated with tumor growth are widely utilized for cancer chemotherapy, such as cancer-associated tyrosine kinase inhibitors [2-4]. Furthermore, drugs targeting chromatin modifiers, cancer-specific metabolic regulators, telomerase regulators and immune checkpoint regulators have also been investigated [5-8]. In addition to these approaches, targeting apoptosis regulators has been considered as an attractive option in cancer therapy.

BH3 mimetics are small compounds that antagonize anti-apoptotic BCL-2 family proteins, resulting in apoptosis induction in cancer cells [9,10]. Recently, several BH3 mimetics were identified, and accumulating evidence has shown their efficacy in cancer therapy. However, at present, their effects are limited by their target specificity and adverse drug reactions. We present here the recent advances in BH3 mimetics research, and discuss their efficacy and limitations.

## Regulation of apoptosis by BCL-2 family proteins

Apoptosis is a major barrier to cancer that must be circumvented, and evasion of apoptosis is a hallmark of cancer, causing resistance to cancer chemotherapy [1,11,12]. Therefore, therapeutic agents that can overcome the effect of evading apoptosis may be utilized for cancer therapy. BCL-2 family proteins are critical regulators of apoptosis and function immediately upstream of mitochondria. BCL-2 family proteins possess conserved BCL-2 homology (BH) domains and are classified into anti- and pro-apoptotic members that are further subdivided into 'multidomain' proteins, which contain four BH domains (BH1 to BH4), and 'BH3-only' proteins [10,13,14]. Among these proteins, the pro-apoptotic multidomain members BAX and BAK function as mitochondrial executioners and directly open pores in the mitochondrial outer membrane, resulting in the release of the apoptogenic factors such as cytochrome c and Smac/Diablo. Studies in mice lacking both *Bax* and *Bak* showed that *Bax* and *Bak* are

essential inducers of mitochondrion-mediated apoptosis in response to various stimuli, including DNA damage. In contrast, anti-apoptotic multidomain members, Bcl-2, Bcl-XL and Mcl-1, inhibit the pore formation of Bax and Bak through direct binding [10,13,14]. BH3-only proteins are critical for initiating apoptosis, functioning immediately upstream of multidomain members, and activate Bax and Bak through direct and/or indirect activation [13,15]. Quadruple deficiency of *Bim*, *Bid*, *Puma* and *Noxa* abrogates apoptosis induced by various stimuli, suggesting the importance of these direct activator type BH3-only proteins in triggering Bax/Bak-mediated apoptosis induction [16]. In addition to their direct effect, BH3-only proteins also inactivate anti-apoptotic multidomain proteins, resulting in indirect activation of Bax and Bak [15,16]. Among BH3-only proteins, BIM and PUMA appear to bind to all anti-apoptotic multidomain proteins with equal affinity, whereas the other members display differential affinity. Particularly, NOXA, an inducer of tumor suppressor p53-mediated apoptosis [17], shows a unique feature in that it does not bind to BCL-2, BCL-XL or BCL-W but does bind to MCL-1 and A1 with high affinity [15]. Therefore, it is possible that differences in BH3 domain structure control altered apoptosis-induction pathways.

## BH3 mimetics and their action

The pro-apoptotic BH3 domain consists of an amphipathic  $\alpha$ -helix and binds to the hydrophobic groove, which contains BH1, -3 and -4, of anti-apoptotic multidomain proteins, resulting in the release of sequestered pro-apoptotic proteins BAX, BAK, and the activator type BH3-only proteins [10,18]. Released BAX and BAK activate themselves

**Correspondence to:** Nobuyuki Tanaka, Department of Molecular Oncology, Institute for Advanced Medical Sciences, Nippon Medical School, 1-396 Kosugicho, Nakahara-ku, Kawasaki 211-8533, Japan, Tel: +81-44-733-1860, Fax: +81-44-733-1821, **E-mail:** nobuta@nms.ac.jp

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**Table 1.** BH3 mimetics and their action.

BH3 mimetics	Target	Targeting apoptosis in cancer chemotherapy	Limitation in cancer therapy and other characteristics
ABT-737 [21]	BCL-2, BCL-XL, BCL-W	ABT-737 is mainly active in hematological malignancies, but less active in solid tumors. Particularly, some small cell lung cancer (SCLC) cell lines are highly sensitive [40-43].	ABT-737 is not orally bioavailable, which can limit drug administration methods particularly in long-term therapy [44].
ABT-263 (Navitoclax) [44]	BCL-2, BCL-XL, BCL-W	ABT-263 is mainly active in hematological malignancies but less active in solid tumors. ABT-263 shows limited activity against advanced and recurrent SCLC [45].	ABT-263 was highly bound with albumin and an increased albumin binding accounted for the differential sensitivity of CLL cells [46]. Inactivation of BCL-XL reduces platelet half-life and causes thrombocytopenia in a dose-dependent manner [47].
ABT-199 [37]	BCL-2	ABT-199 efficiently induces apoptosis in BCL2-dependent hematological malignancies, without causing thrombocytopenia [37].	ABT-199 is less sensitivity in solid tumors compared with ABT-263 or ABT-737 [32-35].
WEHI-539 [48]	BCL-XL	WEHI-539 sensitizes colon cancer stem cells to chemotherapy [49].	Pharmacological inactivation of BCL-XL causes thrombocytopenia [47].
BXI-61, BXI-72 [50]	BCL-XL	Effects were investigated in lung cancer cell lines, and inhibition of tumor cell proliferation was demonstrated <i>in vitro</i> and <i>in vivo</i> in xenograft animal models [50].	
GX15-070 (Obatoclax) [51]	All of the anti-apoptotic BCL-2 family proteins	Because of its ability to bind MCL-1, obatoclax may be particularly promising for the treatment of solid tumors. Therefore, its efficacy was investigated in clinical trials for SCLC [52].	Early clinical trials with obatoclax have indicated neuronal toxicity [52]. Obatoclax added to topotecan did not exceed the response rate seen with topotecan alone in patients with relapsed SCLC following the platinum-based therapy. Currently, there are no open clinical trials with obatoclax in solid tumors.
S1 [53]	BCL-2, MCL-1	Anti-tumor activity of S1 was shown in a mouse liver carcinoma xenograft model [54].	Resistance to S1 has been reported in SCLC by the activation of the MAPK/ERK pathway and the subsequent phosphorylation of BCL-2 [55]. S1 increases reactive oxygen species, resulting in initiation of endoplasmic reticulum (ER) stress [56]. S1-mediated death is in part because of autophagy through ER stress and disruption of Beclin 1/BCL-2 interaction [57].
JY-1-106 [58]	BCL-XL, MCL-1	JY-1-106 was able to suppress tumor growth in a lung cancer xenograft model [58].	Data on the specificity and toxicity of JY-1-106 have not yet been published [58].
Apogossypolone (ApoG2) [59]	BCL-2, MCL-1	ApoG2 inhibited the proliferation of nasopharyngeal carcinoma (NPC) cells in a dose-dependent manner [59,60].	ApoG2 inhibits the binding of BCL-2 to Beclin 1, inducing autophagy and radio-sensitizing NPC cells both <i>in vitro</i> and <i>in vivo</i> [61]. However, several studies have reported that autophagy attenuates apoptosis and promotes cell survival.
BI97C1 (sabutoclax) [62]	BCL-2, BCL-XL, BCL-2A1, MCL-1	BI97C1 induce apoptosis in culture cells in a BAX/BAK- and caspase-9-dependent manner [63].	BI97C1 had little apoptotic effect on benign prostate tissue in transforming growth factor $\beta$ receptor type II in stromal fibroblastic cells and wild-type mice. BI97C1 was able to block c-Met activation, a critical axis in PCa metastatic progression [64].
TW-37 [65]	MCL-1, weekly BCL-2 and BCL-XL	Effect has been demonstrated in prostate and pancreatic cancer cells [65].	TW-37 were more effective than ABT-263 and also resulted in BAX/BAK- and caspase-9-dependent apoptosis [63]. However, such specificity was generally lost when TW-37 was used at high concentrations (>10 $\mu$ M), possibly because of off-target effects [63].
MIM1 [66]	MCL-1	MIM1 induced apoptosis in a MCL-1-dependent leukemia cell line.	MIM1 induced BAK-dependent apoptosis only at high concentrations (>10 $\mu$ M) and failed to induce apoptosis in MCL-1-, BCL-2- and BCL-XL-dependent cell lines. Its potency may be limited and cell-type-dependent [63].
MS1 (MCL-1-specific peptide) [67]	MCL-1	MS1 induced apoptosis in MCL-1-dependent triple-negative breast cancer cells [33]	Data on the specificity of MS1 have been published only at high concentrations (100 $\mu$ M) in triple-negative breast cancer cells [33].
BH3I-1 and its structural derivatives [68,69]	MCL-1	N.D.	Neither compound killed Jurkat cells, even at high concentrations (<30nM), as a single agent or in combination with ABT-737 [63].
UMI-77 [70]	MCL-1	UMI-77 inhibits proliferation of pancreatic cancer cells and induces intrinsic apoptotic pathways [70].	
Compounds from Takeda Pharmaceutical Company [71]	MCL-1, BCL-XL (MCL-1/BCL-XL dual inhibitor)	N.D.	
University of Michigan Compounds [72]	MCL-1	This compound inhibited cell proliferation and activated caspase-3 in a dose-dependent manner [72].	
Marinopyrrole A (Maritoclax) [73,74]	MCL-1	Marinopyrrole A induces apoptosis in MCL-1-dependent but not BCL-2- and BCL-XL-dependent manners in leukemia and melanoma cells [73,74].	Marinopyrrole A fails to induce apoptosis of MCL-1-dependent cell lines. Its potency may be limited and cell type-dependent [75].
Compounds from Eutropics Pharmaceuticals [76]	MCL-1 and weekly BCL-XL	These compounds were found to induce dose-dependent cytochrome c release and antiproliferative activity against several MCL-1-dependent cell lines [76].	
AbbVie Compounds [77]	MCL-1	N.D.	
Vanderbilt University Compounds [78]	MCL-1	N.D.	

and/or are activated by released BH3-only proteins to induce apoptosis, suggesting that BH3 peptides or small compounds structurally similar to the BH3 domain could be utilized as therapeutic agents against cancer.

In this context, a number of natural or synthetic small molecule inhibitors of anti-apoptotic BCL-2 family proteins were determined, but initially these compounds did not bind to the anti-apoptotic proteins with a high enough affinity and/or activated BAX and BAK to kill target cells efficiently [19,20]. Among these compounds, ABT-737 mimics the BH3-only proteins by binding to BCL-2, BCL-X<sub>L</sub> and BCL-W, but not MCL-1, and effectively induces mitochondrion-mediated apoptosis in several cancer cells, particularly MCL-1-suppressed cells [21,22].

### Targeting apoptosis in cancer chemotherapy

In cancer cells, oncogenes induce aberrant DNA replication, which initiates replication-associated DNA-damage signaling, so-called replicative stress [23]. Although DNA-damage signals induce apoptosis in p53-dependent and -independent manners [24], apoptosis is suppressed in cancer cells by various mechanisms including high expression of anti-apoptotic multidomain proteins [1,11]. Therefore, anticancer drugs that damage DNA enhance replicative stress, resulting in induction of apoptosis in cancer cells [25]. In addition, inhibition of cell proliferation by oncogenic kinase inhibitors induces BH3-only proteins, especially BIM, in several cancer cells [9,26,27]. These results suggest the efficacy of agents that target apoptosis in cancer chemotherapy.

As shown in Table 1, a number of BH3 mimetics were identified and analyzed for their effect against cancer cells and tumors [28,29]. Among these compounds, ABT-263 (navitoclax), an orally available derivative of ABT-737, has been shown to be significantly effective in most CLL patients in clinical trials, and ABT-199 (venetoclax), also has shown to be effective in patients with relapsed or refractory CLL [13,30]. Other BH3 mimetics, GX15-070 (obatoclax), BI-97C1 (sabutoclax), AT-101 (gossypol) and derivatives of AT-101 have also been clinically tested, but their efficacy was only limited. Therefore, combination therapy with another anticancer drug(s) is now undergoing clinical studies [13,30].

### Limitation of BH3 mimetics in cancer therapy

Extensive analyses of somatic copy-number alterations in human cancers revealed that *MCL-1* and *BCL-X<sub>L</sub>* are enriched in many cancers [31]. Moreover, it has been demonstrated that the survival and proliferation of several cancer cell lines and experimental cancers depend on MCL-1 [32-35]. In contrast to the importance of MCL-1 expression in cancers, clinically-effective BH3 mimetics ABT-263 and ABT-199 cannot affect MCL-1 (Table 1). Therefore, the discovery of BH3 mimetics that effectively inhibit MCL-1 is still expected at present.

Another problem of BH3 mimetics in cancer chemotherapy is their side effects. Clinical trials with ABT-263 revealed that dose-dependent thrombocytopenia occurred in all patients [36]. Therefore, the effect of ABT-263 is limited because of its restricted safety dose [13,30]. In contrast, ABT-199 only inhibits BCL-2, but not BCL-X<sub>L</sub>, and does not reduce platelet number compared with ABT-263 [37]; however, it is possible that the efficacy of specific inhibitors of BCL-2 may be limited in lymphocyte and hematopoietic cell malignancies because of specific roles of BCL-2 in lymphoid homeostasis [38].

### Conclusion

In contrast to their exhibited efficacies in cultured cells and

experimental tumors, and their theoretically reasonable application for cancer therapy, BH3 mimetics have only showed limited clinical efficacy in human cancer, especially in hematological malignancies. This limited efficacy may be caused by restricted target specificity and cytotoxicity of currently-available BH3 mimetics. In this context, recent approaches and discovery of new MCL-1-selective BH3 mimetics may overcome such restricted target problems in combination with BCL-X<sub>L</sub> inhibitors, such as ABT-263 [39]. Moreover, it has been demonstrated that BH3 mimetics efficiently kill cancer cells in combination with various anti-cancer therapies, especially with oncogenic kinase inhibitors [9]. Analyses of these combination therapies are important for efficient utilization of BH3 mimetics at their safety dose. If future approaches can overcome these limited efficacies, BH3 mimetics will be a powerful tool for cancer chemotherapy.

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