Diminished Sensitivity of Chronic Lymphocytic Leukemia Cells to ABT-737 and ABT-263 Due to Albumin Binding in Blood

Meike Vogler1, Silviya D. Furdas2, Manfred Jung2, Tomomi Kuwana3, Martin J.S. Dyer1, and Gerald M. Cohen1

Abstract

Purpose: Inhibition of the antiapoptotic BCL2 family is one of the most promising areas of anticancer drug development. However, ABT-737, a specific BCL2 inhibitor, is neither orally bioavailable nor metabolically stable. To overcome these problems, the structurally related molecule ABT-263 was synthesized and recently entered clinical trials in hematologic malignancies, including chronic lymphocytic leukemia (CLL). Almost all laboratory studies have been carried out with ABT-737 rather than ABT-263, the drug being used in clinical trials. Currently there are no published data on the comparative effects of these inhibitors. To gain insight into the potential value or limitations of ABT-263 in the clinic, we assessed its ability to induce apoptosis in clinically relevant cellular models of CLL.

Experimental Design: The susceptibility of freshly isolated primary CLL cells to these inhibitors was compared in standard culture conditions and in conditions that more closely mimic in vivo conditions in a whole blood assay system.

Results: ABT-737 was more potent than ABT-263 at inducing apoptosis in CLL cells. In whole blood, ∼100-fold higher concentrations of both drugs were required to induce apoptosis. We found that ABT-263 was highly bound by albumin and that an increased albumin binding of ABT-263 as compared with ABT-737 accounted for the differential sensitivity of CLL cells.

Conclusions: Our data indicate that the exquisite in vitro sensitivity of CLL cells to BCL2 inhibitors may be lost in vivo due to high cell densities and the albumin binding of ABT-263. Modification of ABT-263 may yield a BCL2 inhibitor with greater bioavailability and more favorable pharmacokinetics.

The induction of apoptosis by targeting BCL2 proteins is one of the most promising therapeutic approaches in various malignancies, including chronic lymphocytic leukemia (CLL). CLL is generally considered incurable, although chemotherapy, radiotherapy, and antibody therapy are all applied to slow down the progression of the disease in aggressive cases of CLL. Therefore, less toxic and more efficient therapies are urgently required for this very common leukemia. CLL cells display very high levels of BCL2 and are dependent on BCL2 expression for their survival. Antiapoptotic BCL2 family proteins, including BCL2, BCL-XL, MCL1, and BCL2A1, inhibit apoptosis by sequestering proapoptotic BCL2-homology 3 (BH3) domain-containing proteins, such as BIM, PUMA, or BAX/BAK. The interaction of antiapoptotic BCL2 family members with these proteins occurs via a hydrophobic groove on the protein surface, into which BH3 domain-containing proteins can bind (1, 2). Dependent on the structure of the hydrophobic groove and of the BH3 domain, this binding can be very tight and very specific. Upon inhibition of BCL2 proteins, the proapoptotic binding partners are released and induce the release of cytochrome c from mitochondria into cytosol, resulting in caspase-dependent apoptosis.

Several small molecule BCL2 inhibitors that mimic BH3 peptides and target the hydrophobic groove on BCL2 proteins have been developed (3–5). Among these obatoclax, gossypol, and ABT-263 are currently in early clinical trials, e.g., for CLL and non-Hodgkin’s lymphoma. However, more detailed mechanistic studies have highlighted that of all these potential BCL2 antagonists probably only ABT-737 and ABT-263 are specific BCL2 family antagonists (6, 7). Many other putative BCL2 antagonists seem to exert other major effects, which could lead to unwanted nonmechanism-based toxicities (6, 7). Thus, at the present time we propose that only ABT-737 or ABT-263 can be
Translational Relevance

Targeting the antiapoptotic BCL2 family is an exciting area for novel anticancer drug development. One such inhibitor, ABT-263, has recently entered clinical trials. Almost all mechanistic and animal studies have been carried out with the structurally related ABT-737. Although such inhibitors will undoubtedly have greatest value in combination chemotherapy, ABT-737 has shown promising potent single-agent activity against certain primary tumor cells, including chronic lymphocytic leukemia (CLL) cells. We now show that although somewhat less active than ABT-737, ABT-263 is also a potent inducer of apoptosis in CLL cells by a similar mechanism. However, when tested in whole blood to mimic the in vivo situation, the activity of both inhibitors decreased ~100-fold largely due to binding to albumin, resulting in a loss of the potency and thus the selectivity of these inhibitors. The high binding of ABT-263 to albumin highlights the necessity to monitor carefully patients for potential drug interactions.

Materials and Methods

Reagents

ABT-737 was provided by S. Rosenberg (Abbott Laboratories, Abbott Park, IL), and ABT-263 was provided by G. Shore (GeminX, Montreal, Canada). ABT-263 was synthesized by published methods (8, 15), and its purity was 95.1% as assessed by high-performance liquid chromatography and a correct mass of m/z = 975. After the start of this study a commercial source of ABT-263 also became available (Selleck Chemicals Co.). Essentially identical results were obtained with both sources of ABT-263 (data not shown). Bovine serum albumin (BSA) was from Sigma, CD5-phycoerythrin and CD19-FITC antibodies were from Dako Cytomation, rabbit anti-BAK antibody was from Upstate, and Annexin-APC and tetramethylrhodamine ethyl ester were from Invitrogen.

Cell culture

Peripheral blood samples from CLL patients were obtained with patient consent and local ethics committee approval. Unless otherwise indicated, lymphocytes were purified and cultured in RPMI 1640 medium supplemented with 10% FCS and 2 mmol/L L-glutamine (all from Life Technologies, Inc.) at 1 × 10⁶ cells mL⁻¹. CLL cells were incubated with ABT-737 or ABT-263 at 37°C and apoptosis assessed as previously described (14). Alternatively, blood from patients was incubated with ABT-737 or ABT-263 at 37°C in 48-well plates as described previously (16). Murine embryonic fibroblasts were cultured in DMEM (Life Technologies, Inc.) supplemented with 10% FCS and 2 mmol/L L-glutamine.

Release of cytochrome c

CLL cells (10 × 10⁶) were washed and permeabilized with 0.05% digitonin in mitochondrial isolation buffer [250 mmol/L sucrose, 20 mmol/L HEPES (pH 7.4), 5 mmol/L MgCl₂, 10 mmol/L KCl] for 10 minutes on ice. The cytosol was removed by centrifugation at 13,000 rpm for 3 minutes. The permeabilized cells were washed three times in mitochondrial isolation buffer without digitonin and incubated with different concentrations of ABT-737 or ABT-263 for 1 hour at 37°C. Upon incubation, the supernatant containing the released cytochrome c was isolated by centrifugation at 13,000 rpm for 3 minutes, and the supernatant and pellet were analyzed by Western blotting.

Fluorescein-dextran release assay

The release of fluorescein-dextrans (F-dextrans) from liposomes was measured as described previously (17). Briefly, liposomes containing 7% cardiolipin were generated by the extrusion method and internally loaded with F-dextran (10 kD; Invitrogen). They were incubated with recombinant proteins (human origin): BAX, N/C-BID

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(cleaved form of BID), BCL-XL with and without ABT-737 or ABT-263 (0.04-5 μmol/L). After incubation, the assay mix was filtered to collect released dextrans in the filtrate, and the fluorescence was measured against a detergent solubilized sample, which gave 100% release.

**Immunoprecipitation**

For immunoprecipitation, 5 × 10⁸ CLL cells were treated with ABT-737 or ABT-263 for 2 hours before lysis in buffer containing 1% CHAPS, 20 mmol/L TrisHCl (pH 8), 150 mmol/L NaCl, and Protease Inhibitor Cocktail (Roche Diagnostics). Hamster anti-BCL2 antibody (BD Bioscience) was cross-linked with ProtA-dynabeads using 20 mmol/L dimethylpimelinediimidate (Fluka Biochemika). Cross-linked antibody or ProtA-dynabeads were incubated with 500 μg protein for 2 hours at 4°C. Beads were washed with lysis buffer before elution in SDS-loading dye and Western blotting.

**Fluorescence polarization assay**

The binding affinity of ABT-737 and ABT-263 to human serum albumin (HSA) was measured using fluorescence polarization assay as described previously (18). Briefly, 500 nmol/L dansyl sarcosine or 1 μmol/L dansyl L-glutamate (both from Sigma Aldrich) were mixed with 5 or 10 μmol/L HSA (CSL Behring), respectively, and different concentrations of ABT-737 or ABT-263. Polarized light (Exc: 340 nm, Em: 535 nm) was measured using EnVision 2102 Multilabel Reader (Perkin Elmer).

**Results**

**ABT-263 is less potent than ABT-737 in inducing apoptosis in CLL cells**

In this study we compared the in vitro efficacy of two very closely related BCL2 antagonists, ABT-737 and ABT-263. A direct comparison of the susceptibility of freshly isolated CLL cells to ABT-737 and ABT-263 in RPMI supplemented with 10% FCS revealed that both compounds induced efficient apoptosis but ABT-737 was ∼4-fold more potent (Fig. 1A). This higher susceptibility of CLL cells to ABT-737 was observed in all 21 samples examined (Fig. 1B). These initial findings indicate that despite their apparent structural similarity (Fig. 1C) the two compounds possess different properties.

One possible explanation for the reduced potency of ABT-263 compared with ABT-737 could be due to the former being inherently less potent. To investigate this possibility we compared their activities in a model biochemical system, using liposomes loaded with fluorescein-conjugated

![Fig. 1. Apoptosis induced by ABT-737 and ABT-263 in purified CLL cells. A, CLL cells freshly isolated from peripheral blood of CLL patients were incubated in RPMI plus 10% FCS with different concentrations of ABT-737 or ABT-263 for 4 hours before apoptosis was assessed by externalization of phosphatidylserine (PS) and staining with AnnexinV-FITC (n = 21; *, P < 0.05). B, the half-maximal effective concentration (EC₅₀) values for ABT-737 and ABT-263 were calculated with GraphPad Prism and compared for each patient. C, the chemical structures of ABT-737 and ABT-263 are shown. Positions 1, 2, and 3 indicate the 4-chlorobiphenyl, arynitro, and dimethylamino groups of ABT-737, respectively.](attachment://Fig1.png)
10 kD dextran (F-dextran; ref. 17). The addition of a combination of BAX and N/C-BID resulted in permeabilization of the liposomes, as assessed by the release of F-dextrans, and this permeabilization was inhibited by BCL-XL, in agreement with previous findings (17). The BCL-XL-mediated inhibition of liposome permeabilization was reversed in an almost identical concentration-dependent manner by both ABT-263 and ABT-737 (Fig. 2A). These results showed that both ABT-263 and ABT-737 target antiapoptotic BCL-XL with similar efficiency in this model liposome system containing only BCL2 family members but devoid of extraneous proteins. Another explanation for the lower potency of ABT-263 could be a lower plasma membrane permeability, which would result in less drug reaching its intracellular target(s), the antiapoptotic BCL2 family members. To address this possibility, we investigated the potential of ABT-737 and ABT-263 to induce cytochrome c release from permeabilized CLL cells (containing nuclei, mitochondria, and endoplasmic reticulum; Fig. 2B). ABT-737 was clearly more potent in inducing cytochrome c release from permeabilized cells. Taken together these results indicate that the reduced potential of ABT-263 to induce apoptosis cannot be explained solely by either differential plasma membrane permeability or by a lower potency of ABT-263 compared with ABT-737 to inhibit antiapoptotic BCL2 family members.

To gain insight into the mechanism of ABT-263-induced cell death, we asked whether ABT-263 induced activation of apoptotic signaling pathways. ABT-263 induced a rapid cleavage of caspase-3 and loss of mitochondrial membrane potential, but was again less potent than ABT-737 (Fig. 3A and Supplementary Fig. S1A). Because unstimulated CLL cells express very little or no BCL-XL, the main target of ABT-263 and ABT-737 in CLL cells is BCL2, where they act by displacing proapoptotic BH3 domain-containing proteins. To investigate the activity of both compounds at the level of BCL2 inhibition, we immunoprecipitated BCL2 upon drug treatment and measured the levels of BAK displaced by ABT-737 and ABT-263. Previously, we had shown that small amounts of BAK but not BAX were sequestered by BCL2 (12). In agreement with our earlier study, BAK was again shown to be associated with BCL2 (Fig. 3B). ABT-737 (10 or 100 nmol/L) efficiently displaced BAK from BCL2, whereas higher concentrations of ABT-263 (100 nmol/L) were required to induce release of BAK (Fig. 3B). These data show that although both compounds have the ability to displace BAK from BCL2, ABT-263 is less efficient than ABT-737. In addition, we recently described that ABT-737 induces a novel paradigm of apoptosis in CLL cells involving all the normal characteristics of apoptosis accompanied by a rupture of the outer mitochondrial membrane (14). Here we show that ABT-263 (100 nmol/L) induced similar ultrastructural changes to ABT-737 (10 nmol/L), including condensed chromatin, rupture of the outer mitochondrial membrane, and loss of mitochondrial matrix density (Fig. 3C and Supplementary Fig. S1B). Finally, ABT-263-induced apoptosis was completely inhibited in murine embryonic fibroblasts deficient for Bax and Bak (Fig. 3D), suggesting that ABT-263, like ABT-737 (6, 7), is a specific inhibitor of BCL2 proteins. Taken together, our data indicate that both compounds induce cell death by a similar mechanism involving displacement of BAK from BCL2 and activation of the intrinsic apoptotic pathway accompanied by rupture of the outer mitochondrial membrane.

The efficiency of ABT-263 and ABT-737 decreases in whole blood

To more closely mimic the in vivo situation, we compared the efficacy of the two compounds to induce apoptosis using whole blood from CLL patients rather than the standard cell

![Fig. 2.](image-url)
culture medium. At 4 hours, ~100-fold higher concentrations of both BCL2 antagonists were required to induce apoptosis in CLL cells in blood compared with cell culture medium (compare Figs. 1A and 4A). The reduced potency of ABT-263 as compared with ABT-737 was even more pronounced in whole blood than in purified CLL cells. To investigate whether longer exposure times increased apoptosis, we incubated blood with different drug concentrations for up to 12 hours. Whereas lower concentrations of ABT-737 (0.1-1 μmol/L) induced apoptosis at longer exposure times, ABT-263 only induced apoptosis at concentrations >1 μmol/L even when incubated for up to 12 hours (Fig. 4B).

Binding to albumin confers resistance to ABT-737 and ABT-263
As these data clearly showed that CLL cells lose their striking sensitivity towards these inhibitors in the presence of whole blood, we next investigated which components of whole blood caused the loss of sensitivity to ABT-737 and ABT-263. In CLL, the WBC count in peripheral blood is regularly >1 × 10^8/mL, much higher than the concentration of cells typically used in vitro (1 × 10^6/mL). To examine the influence of cell density on the sensitivity to BCL2 antagonists, CLL cells were incubated at different densities in culture medium. Although a 10-fold higher cell density than used in our standard culture did not significantly affect sensitivity, higher cell densities similar to those found in the blood of CLL patients (1-5 × 10^8 cells/mL) required higher concentrations of ABT-737 and ABT-263 to induce cell death (Fig. 5A and B). Furthermore, we investigated whether the high serum content in blood compared with the 10% serum routinely used in cell culture medium affected susceptibility to BCL2 antagonists. Higher serum concentrations (50% FCS) induced resistance to ABT-737 and ABT-263, whereas lower serum concentrations (1% FCS) markedly sensitized CLL cells to apoptosis induced

Fig. 3. Mechanism of cell death induced by ABT-737 and ABT-263. A, CLL cells were incubated with 10 or 100 nmol/L ABT-737 or ABT-263 for 4 hours before staining with 50 nmol/L tetramethylrhodamine ethyl ester (TMRE) and analysis of the loss of mitochondrial membrane potential (n = 3; *, P < 0.05). B, CLL cells were incubated with 10 or 100 nmol/L ABT-737 or ABT-263 for 2 hours before immunoprecipitation (IP) of BCL2. Binding of BAK was detected by Western blotting. C, CLL cells were exposed to 100 nmol/L ABT-263 for 4 hours before electron microscopy. High power magnification shows swollen mitochondria and breaks in the outer mitochondrial membrane (bar, 100 nm). The morphology resembles that previously described for ABT-737. D, murine embryonic fibroblasts (wt or Bax/Bak double knockout, DKO) were exposed to different concentrations of ABT-263 for 48 hours and apoptosis was assessed by externalization of phosphatidylserine (PS) and staining with AnnexinV–FITC.
Discussion

Due to their ability to directly induce apoptosis, BCL2 inhibitors offer a great potential for cancer therapy, especially for malignancies with high BCL2 expression and a dependency on BCL2 expression for survival (22). CLL cells were previously reported to be highly sensitive to BCL2 inhibition and treatment with ABT-737 (4, 13, 14, 23). To our knowledge we now show for the first time that freshly isolated CLL cells display a similar, albeit somewhat lower, nanomolar sensitivity to ABT-263 (Fig. 1). ABT-263 induced a rapid activation of the intrinsic pathway of apoptosis that was absolutely dependent on Bax and Bak. Induction of apoptosis in CLL cells by ABT-263 was accompanied by chromatin condensation together with rupture of the outer mitochondrial membrane and a decreased mitochondrial matrix density (Fig. 3), ultrastructural features virtually identical to those we had previously observed with ABT-737 and described as a novel paradigm of apoptosis (14). These results further emphasize the similar activities of ABT-737 and ABT-263, in agreement with recent studies (15, 24), and strongly support the hypothesis that they both act to induce apoptosis in CLL cells by an identical mechanism. We emphasize the importance of studying these effects with ABT-263, as this is the compound, not ABT-737, currently being used in clinical trials.
Most importantly our data show that isolated CLL cells lose their striking nanomolar sensitivity to both ABT-737 and ABT-263 in the presence of whole blood. The half-maximal effective concentration of CLL cells to ABT-263 in whole blood is >10 μmol/L at 4 hours of treatment (Fig. 4A). Notably, the maximal plasma concentrations of ABT-263 achieved in clinical trials with a 250 mg daily dosing schedule are around 5 μmol/L (25), indicating that the concentrations in whole blood might not be optimal in the current phase I and phase II clinical trials for ABT-263. In our study we identify two factors that affect the efficacy of these BCL2 inhibitors: high cell density and plasma protein binding. In leukemic patients, the high circulating cell densities might contribute to the resistance of CLL cells to ABT-737 and ABT-263 that we observed in whole blood as compared with standard cell culture (Fig. 5A and B). The impact of cell density on drug sensitivity may be a particular problem in certain microenvironments, such as lymph nodes, where drugs encounter even higher cell densities than in the peripheral blood. We also describe that these BCL2 inhibitors are extensively bound to albumin and that in the presence of albumin higher drug concentrations are required for apoptosis induction (Fig. 5C and D). Albumin is the most abundant protein in human plasma and is well known to bind a wide range of drugs as well as endogenous molecules (18, 20, 21). ABT-263 bound to albumin much more strongly than did ABT-737 (Fig. 6), and it bound to site 2 on subdomain IIIA more strongly than naproxen (18), indicating a very tight interaction between albumin and ABT-263. Extensive binding to albumin may have profound effects on the absorption, distribution, metabolism, and excretion of molecules, often meaning that higher doses need to be administered in vivo (26, 27). The high albumin binding of ABT-263 may also act as a reservoir of the drug, resulting in a long half-life. However, the high albumin binding might also be a source of potential drug interactions as ABT-263 may be displaced by other drugs that bind extensively to albumin, thus increasing the potential efficacy and toxicity of ABT-263. Additionally, our data indicate that patients with a hypoalbuminemia might react differently to ABT-263, and conditions where

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**Fig. 5.** Cell density and albumin binding confer resistance to ABT-737 and ABT-263. A and B, purified CLL cells were incubated at different cell densities in RPMI plus 10% FCS with different concentrations of ABT-737 (A) or ABT-263 (B) for 4 hours. Apoptosis was assessed by phosphatidylserine (PS) externalization and staining with AnnexinV–FITC (n = 8). C and D, CLL cells were incubated at 1 × 10⁶ cells/mL in RPMI with different concentrations of FCS and ABT-737 (C) or ABT-263 (D) with or without BSA (3%) for 4 hours. Apoptosis was assessed by PS externalization and AnnexinV–FITC binding (n = 8).
μdansyl L-glutamate was used as a probe. The IC50 was >1,000 and ABT-263, respectively. B, to measure binding to site 1 on HSA-IIA, dansyl sarcosine was used as a probe. In this assay the IC50 was 711 and 37 μmol/L for ABT-737 and ABT-263, respectively. B, to measure binding to site 1 on HSA-IIA, dansyl L-glutamate was used as a probe. The IC50 was >1,000 and 145 μmol/L for ABT-737 and ABT-263, respectively.

ABT-263 has a higher albumin binding affinity than ABT-737. The binding capacity of ABT-737 (solid lines) and ABT-263 (dotted lines) to HSA was investigated using a fluorescence polarization assay. A, to measure binding to site 2 on HSA-IIA, dansyl sarcosine was used as a probe. In this assay the IC50 was 711 and 37 μmol/L for ABT-737 and ABT-263, respectively. B, to measure binding to site 1 on HSA-IIA, dansyl L-glutamate was used as a probe. The IC50 was >1,000 and 145 μmol/L for ABT-737 and ABT-263, respectively.

It is interesting to consider the higher albumin binding of ABT-263 compared with ABT-737 in relation to their structures. During the development of ABT-263, the 4-chlorobiphenyl, arylnitro, and dimethylamino groups of ABT-737 (Fig. 1C, positions 1, 2 and 3, respectively) were modified primarily to decrease metabolism and increase oral bioavailability without losing cellular activity. However, the dimethylamino group in ABT-737, which had been specifically designed to reduce binding to albumin (19), is replaced by a morpholino group in ABT-263 (8). In this regard the introduction of a morpholino group at this position in the development of ABT-737 (compound 77R in ref. 19) was much less effective than a dimethylamino group in reducing the deactivating effects of serum on the binding affinity to BCL-X0, and it was concluded that a charged species in this position was particularly effective in reducing serum binding (19). In the absence of serum, the lead compounds in the ABT-737 series with the dimethylamino or morpholino group showed similar binding affinities to BCL2 proteins, whereas in the presence of serum, the morpholino group resulted in a complete loss of binding to BCL-X0. These results indicate the potential deleterious effects of a morpholino group at this position and indicate that although ABT-263 clearly shows important biological activity the possibility of substitution of another group in this position may yield a BCL2 family inhibitor with more favorable pharmacokinetics.

To exclude any effects of serum or albumin, we had wished to test the susceptibility of CLL cells to ABT-737 and ABT-263 in a serum-free system. However, culture of CLL cells in the complete absence of any serum is not feasible because it is too toxic and cells underwent spontaneous apoptosis (data not shown). Using a biochemical F-dextran release assay in liposomes, we found that both compounds have the same capacity to target BCL2 proteins, in line with previously published data reporting a similar affinity of both compounds for BCL2 and BCL-X0 (4, 28). However, the reduced activity of ABT-263 was also observed in permeabilized cells in the absence of any serum or albumin (Fig. 2B). These data indicate that besides the binding to albumin, other factors determine the different biological activities of ABT-737 and ABT-263. One explanation could be that besides binding to albumin, ABT-263 is also sequestered by other cellular proteins, and therefore less drug reaches BCL2 even in the absence of serum. Some support for this hypothesis is provided by our finding that in contrast to ABT-737, ABT-263 also binds to site 1 on HSA-IIA, indicating that it binds in a more promiscuous manner than ABT-737. Another explanation for the reduced activity of ABT-263, even in permeabilized cells in the absence of serum, might lie in yet undescribed differences in their affinity to antiapoptotic BCL2 family proteins or in their potential to displace BH3-domain-containing proteins. In CLL cells obtained from blood, the main target of ABT-737 and ABT-263 is BCL2, because BCL-X0 and BCL-W expression in circulating CLL cells is very low. However, the published data on the binding affinities of ABT-737 and ABT-263 to BCL2 (<1 nmol/L) or BCL-X0 (<0.5 nmol/L) display no difference (4, 28), possibly due to insufficient assay sensitivity.

Interestingly, published data indicate that there might be cell type–specific differences in the sensitivity to ABT-737 and ABT-263. In agreement with this suggestion, small cell lung cancer cell lines H889 and H1417 showed a higher sensitivity to ABT-737 compared with ABT-263, whereas others, including H146 and H182, showed a similar sensitivity (28, 29). Our finding of a differential nonspecific binding of ABT-737 and ABT-263 to proteins, such as albumin, provides the first mechanistic explanation for a differential efficacy of ABT-737 and ABT-263. Whether a differential expression profile of BCL2 proteins also contributes to their differential sensitivity is not known.

Taken together our data suggest that although structurally similar and exhibiting similar binding affinities to antiapoptotic BCL2 family proteins, ABT-263 is less potent than ABT-737 at inducing apoptosis in CLL cells. Furthermore, our data indicate that binding of ABT-263 to albumin
will markedly increase the concentration of drug required to induce apoptosis and clear CLL cells from the blood in vivo. We suggest that modification of the albumin binding of ABT-263 either by alteration of its structure or by other strategies may restore the inherent susceptibility of CLL cells to these targeted BCL2 inhibitors, thereby increasing their therapeutic potential.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

References


Acknowledgments

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