Breast Cancer RESEARCH

VIEWPOINT

Priming BCL-2 to kill: the combination therapy of tamoxifen and ABT-199 in ER$^+$ breast cancer

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Abstract

The B-cell lymphoma/leukemia 2 protein (BCL-2) may help many types of cancers to evade cell death. However, identifying exactly where this is the case is a challenge. ABT-199 is a small molecule that selectively inhibits BCL-2, which is currently in clinical trials in lymphoid malignancies. While inhibiting BCL-2 by itself can cause cell death in hematopoietic tumors, single-agent activity is harder to observe in solid tumors. Combining ABT-199 with tamoxifen, the standard endocrine therapy for estrogen receptor-positive breast cancers, 85% of which have BCL-2 expression, represents a new strategy to prime cancer cells for apoptosis and elicit better cancer cell death responses.

Breast cancer is a heterogeneous disease with at least four categories according to its molecular markers and gene expression profiles [1]. Estrogen receptor (ER), progesterone receptor, and human epidermal growth factor receptor 2 (HER2) are the hallmarks for the classification and they determine chemotherapy choices and clinical outcome. Anti-estrogen therapy with tamoxifen or aromatase inhibitors is a standard endocrine therapy in many clinical situations for ER$^+$ tumors. Unfortunately, a significant fraction of patients with ER$^+$ do not respond to such therapies or they relapse after the initial remission [2,3]. Looking for more effective treatments is an urgent need in breast cancer research. In *Cancer Cell* (the July 8 issue of 2013 [4]), Vaillant and colleagues addressed this issue with the newest member of the AbbVie (North Chicago, IL, USA) BCL-2 (B-cell lymphoma/leukemia 2 protein) inhibitor drug family, ABT-199.

ABT-199 belongs to the anti-BCL-2 inhibitor family originally developed by Abbott, whose research-based pharmaceuticals operation is now AbbVie. ABT-737 and the orally bioavailable ABT-263 (navitoclax) are the other two closely related inhibitors. ABT-737 and ABT-263 inhibit BCL-xL and BCL-w as well as BCL-2. They have been extensively studied in *in vitro* cell-based or animal models and in primary patient samples [5,6]. Clinical application of ABT-263 has been limited, however, at least partially due to the thrombocytopenia caused by inhibition of BCL-xL in circulating platelets [7,8]. ABT-199 more selectively inhibits BCL-2 and has demonstrated little or no effect on platelets *in vitro* and *in vivo* [9-11].

BCL-2 is one of the most important anti-apoptotic proteins in the BCL-2 family with regard to cancer. This family comprises both anti- and pro-apoptotic proteins to govern commitment to cell death via the mitochondrial-dependent apoptotic pathway. The most dominant BCL-2 dependence has been demonstrated in hematopoietic cancers such as lymphoma or leukemia [9]. However, recent analysis for 11,212 early-stage breast cancer cases has concluded that BCL-2 is a favorable prognostic marker for breast cancer across molecular subtypes and independent of adjuvant therapy [12]. The addition of BCL-2 into the model for a subset of cases improved survival prediction. Luminal breast cancer (mostly ER$^+$ breast cancer as studied by Vaillant and colleagues) has the highest BCL-2 expression (83% compared with 50% for HER2$^+$, 18.5% for basal-like, and 41.4% for marker-null subtypes). The high BCL-2 protein levels (by immunohistochemistry) suggest an opportunity to target these cancers with BCL-2 inhibitors.

As shown in the article by Vaillant and colleagues [4] and a relevant article published by the same group [13], however, BCL-2 inhibitors alone do not yield breast tumor xenograft regression. This contrasts to single-agent applications for ABT-263 or ABT-199 in chronic lymphocytic leukemia, which can elicit notable responses even in chemo-refractory disease [9]. Vaillant and colleagues, using breast primary tumor xenografts in a nonobese diabetic/severe combined immunodeficient (IL2Rγc$^{-/-}$)

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mouse model, demonstrate that the combination of tamoxifen and ABT-737 or ABT-199 produced the largest reduction of tumor volumes and much longer survival outcome than tamoxifen or ABT drug alone. This is consistent with the finding in BCL-2$^+$ basal-like breast cancer xenografts, in which the tumor burden was reduced only in the combination of ABT-737 and cytotoxic docetaxel [13]. A mechanism of the activity of ABT-199 is that the BCL-2 protein was primed with pro-apoptotic protein BIM, suggesting that ABT-199 was provoking release of BIM and initiation of apoptosis. In other studies, BCL-2 complexes with pro-apoptotic protein BIM have been shown to be important in determining cellular sensitivity to BCL-2 inhibition [14,15].

Many chemotherapies kill cancer cells via the mitochondrial apoptotic pathway. The interplay of BCL-2 family proteins largely determines the fate of cancer cells. ABT-199 offers a great clinical opportunity because of its specificity to BCL-2 which enhances its tolerability as well as its unique mechanism of action directly at mitochondria. In combination therapy, BCL-2 inhibition, even when it does not cause outright cell death, can prime cancer cells so that they move closer to the threshold of commitment to apoptosis. In this position, cancer cells are thus rendered more sensitive to subsequent therapies, as with tamoxifen in the article by Vaillant and colleagues [4]. Thus, in ER$^+$ breast cancer, the combination of ABT-199 with tamoxifen provides a new strategy to overcome the protective effects of BCL-2 and deliver efficacious therapies. In the coming years, it will be very interesting to see in which cancers analogous combinations of ABT-199 with standard therapies can be used to improve clinical outcome.

Abbreviations

BCL-2: B-cell lymphoma/leukemia 2 protein; ER: Estrogen receptor; HER2: Human epidermal growth factor receptor 2.

Competing interests

AL discloses that he is a paid advisor for AbbVie Pharmaceuticals. JD declares that she has no competing interests.

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References

1. Sørlie T, Perou CM, Tibshirani R, Aas T, Geisler S, Johnsen H, Hastie T, Eisen MB, van de Rijn M, Jeffrey SS, Thorsen T, Quist H, Matese JC, Brown PO, Botstein D, Lønning PE, Børresen-Dale AL: **Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications.** *Proc Natl Acad Sci U S A* 2001, **98:**10869–10874.
2. Ring A, Dowsett M: **Mechanisms of tamoxifen resistance.** *Endocr Relat Cancer* 2004, **11:**643–658.
3. Musgrove EA, Sutherland RL: **Biological determinants of endocrine resistance in breast cancer.** *Nat Rev Cancer* 2009, **9:**631–643.
4. Vaillant F, Merino D, Lee L, Breslin K, Pal B, Ritchie ME, Smyth GK, Christie M, Phillipson LJ, Burns CJ, Mann GB, Visvader JE, Lindeman GJ: **Targeting BCL-2 with the BH3 mimetic ABT-199 in estrogen receptor-positive breast cancer.** *Cancer Cell* 2013, **24:**120–129.
5. Oltersdorf T, Elmore SW, Shoemaker AR, Armstrong RC, Augeri DJ, Belli BA, Bruncko M, Deckwerth TL, Dinges J, Hajduk PJ, Joseph MK, Kitada S, Korsmeyer SJ, Kunzer AR, Letai A, Li C, Mitten MJ, Nettesheim DG, Ng S, Nimmer PM, O'Connor JM, Oleksijew A, Petros AM, Reed JC, Shen W, Tahir SK, Thompson CB, Tomaselli KJ, Wang B, Wendt MD, Zhang H, Fesik SW, Rosenberg SH: **An inhibitor of Bcl-2 family proteins induces regression of solid tumours.** *Nature* 2005, **435:**677–681.
6. Tse C, Shoemaker AR, Adickes J, Anderson MG, Chen J, Jin S, Johnson EF, Marsh KC, Mitten MJ, Nimmer P, Roberts L, Tahir SK, Xiao Y, Yang X, Zhang H, Fesik S, Rosenberg SH, Elmore SW: **ABT-263: a potent and orally bioavailable Bcl-2 family inhibitor.** *Cancer Res* 2008, **68:**3421–3428.
7. Roberts AW, Seymour JF, Brown JR, Wierda WG, Kipps TJ, Khaw SL, Carney DA, He SZ, Huang DC, Xiong H, Cui Y, Busman TA, McKeegan EM, Krivoshik AP, Enschede SH, Humerickhouse R: **Substantial susceptibility of chronic lymphocytic leukemia to BCL2 inhibition: results of a phase I study of navitoclax in patients with relapsed or refractory disease.** *J Clin Oncol* 2012, **30:**488–496.
8. Wilson WH, O'Connor OA, Czuczman MS, LaCasce AS, Gerecitano JF, Leonard JP, Tulpule A, Dunleavy K, Xiong H, Chiu YL, Cui Y, Busman T, Elmore SW, Rosenberg SH, Krivoshik AP, Enschede SH, Humerickhouse RA: **Navitoclax, a targeted high-affinity inhibitor of BCL-2, in lymphoid malignancies: a phase 1 dose-escalation study of safety, pharmacokinetics, pharmacodynamics, and antitumour activity.** *Lancet Oncol* 2010, **11:**1149–1159.
9. Davids MS, Letai A: **ABT-199: taking dead aim at BCL-2.** *Cancer Cell* 2013, **23:**139–141.
10. Souers AJ, Leverson JD, Boghaert ER, Ackler SL, Catron ND, Chen J, Dayton BD, Ding H, Enschede SH, Fairbrother WJ, Huang DC, Hymowitz SG, Jin S, Khaw SL, Kovar PJ, Lam LT, Lee J, Maecker HL, Marsh KC, Mason KD, Mitten MJ, Nimmer PM, Oleksijew A, Park CH, Park CM, Phillips DC, Roberts AW, Sampath D, Seymour JF, Smith ML, *et al*: **ABT-199, a potent and selective BCL-2 inhibitor, achieves antitumor activity while sparing platelets.** *Nat Med* 2013, **19:**202–208.
11. Vogler M, Dinsdale D, Dyer MJ, Cohen GM: **ABT-199 selectively inhibits BCL2 but not BCL2L1 and efficiently induces apoptosis of chronic lymphocytic leukaemic cells but not platelets.** *Br J Haematol* 2013, **163:**139–142.
12. Dawson SJ, Makretsov N, Blows FM, Driver KE, Provenzano E, Le Quesne J, Baglietto L, Severi G, Giles GG, McLean CA, Callagy G, Green AR, Ellis I, Gelmon K, Turashvili G, Leung S, Aparicio S, Huntsman D, Caldas C, Pharoah P: **BCL2 in breast cancer: a favourable prognostic marker across molecular subtypes and independent of adjuvant therapy received.** *Br J Cancer* 2010, **103:**668–675.
13. Oakes SR, Vaillant F, Lim E, Lee L, Breslin K, Feleppa F, Deb S, Ritchie ME, Takano E, Ward T, Fox SB, Generali D, Smyth GK, Strasser A, Huang DC, Visvader JE, Lindeman GJ: **Sensitization of BCL-2-expressing breast tumors to chemotherapy by the BH3 mimetic ABT-737.** *Proc Natl Acad Sci U S A* 2012, **109:**2766–2771.
14. Del Gaizo MV, Brown JR, Certo M, Love TM, Novina CD, Letai A: **Chronic lymphocytic leukemia requires BCL2 to sequester prodeath BIM, explaining sensitivity to BCL2 antagonist ABT-737.** *J Clin Invest* 2007, **117:**112–121.
15. Deng J, Carlson N, Takeyama K, Dal Cin P, Shipp M, Letai A: **BH3 profiling identifies three distinct classes of apoptotic blocks to predict response to ABT-737 and conventional chemotherapeutic agents.** *Cancer Cell* 2007, **12:**171–185.

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