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Review Article

Possibly the Venetoclax/Bcl-2 Complex Interacts with the Antibody/Antigen Complex to Increase the Phagocytosis in Combined Venetoclax-Antibody Therapy in B-cell Malignancies

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Abstract

The anti-Bcl-2 therapy by the drugs like ABT-263, ABT-737, and ABT-199 have been a hit in treating Leukemia. Similar success has also been reported for the treatment of Leukemia by monoclonal antibodies. Hence a certain study combined the anti-Bcl-2 therapy with antibody therapy in treating a particular Leukemia, the Double-hit Diffuse Large B-cell Lymphoma (DHL). The DHL cells overexpress Bcl-2 proteins. Hence the drug Venetoclax (ABT-199), which inhibits the anti-apoptotic activity of Bcl-2 proteins only, has been combined with either the Rituximab (anti-CD20 monoclonal antibody) or the Daratumumab (anti-CD38 monoclonal antibody) in treating the DHL cell lines CARNAVAL (CD20+) or WILL-2 (CD20-/CD38+). I analyze in depth the above work and draw fresh conclusions which the authors of the above work have not drawn themselves. Particularly I show in my work that it is the ABT-199/Bcl-2/Antibody/Antigen Complex which increases Antibody-dependent Cellular Phagocytosis in the combined ABT-199/Antibody therapy against DHL cells when compared with the Antibody-only therapy against DHL cells. This conclusion is currently of academic interest, but holds promise to improve treatments of B-cell malignancies with more fertile research in future.

Keywords: Apoptosis; Monoclonal Antibody; BH3 sub-structure; Bcl-2 protein; Rituximab; Daratumumab

Introduction

Two different therapies, anti-Bcl-2 therapy and monoclonal Antibody therapy, have been combined together to study their effects in and the mechanism of action in B cell malignancies; this study was mostly conducted both in-vitro and in-vivo in B-cell malignancy derived cell lines and the patient-derived Xenograft (PDX) murine models [6]. This short communication mostly centers around the results obtained from work [6], and draws fresh conclusions. I will discuss in this paper the results of experiments on Double-Hit Lymphoma (DHL) cell lines CARNAVAL (CD20+), WILL-2 (CD20-/CD38+), and Bcl-2 negative Oci-Ly7 (CD20+/CD38+); and I will not discuss the results of experiments on Burkitt Lymphoma-PDX (BL-PDX) mice and Acute Lymphoblastic Leukemia-PDX (ALL-PDX) mice primarily because the experiments involving the use of pan-Caspase inhibitor Z-VAD-FMK, and the Bax-deficient and Bak-deficient cells were not conducted on these disease models. CD20 is normally expressed on B cells when they have fully grown but not when they are just beginning to grow [8]. CD38 is normally expressed on a variety of immune cells including the cranked up B cells [2]. The anti-CD20 monoclonal antibody and the anti-CD38 monoclonal antibody used in the study [6] are Rituximab (RTX) and Daratumumab (DARA) respectively. The monoclonal antibodies directed against the cancer cells kill them by any one of the or any combination of the following four mechanisms: direct killing [8], Antibody-dependent Cellular Cytotoxicity (ADCC) [7], Complement-dependent Cy-

totoxicity (CDC) [4], and Antibody-dependent Cellular Phagocytosis (ADCP) [1]. The term "Phagocytosis" used in the title of this short communication mean ADCP, and does not mean the phagocytosis of the apoptotic fragments by macrophages.

Before I move ahead, let me discuss the modus-operandi of most of the anti-Bcl-2 drugs. The anti-apoptotic proteins Bcl-2, Bcl-X_L, Bcl-w, Mcl-1 and A1,and the pro-apoptotic proteins Bax, Bak and Bad comprise the Bcl-2 family of proteins. The BH3 sub-structure in the pro-apoptotic proteins of Bcl-2 family (PAPBcl2) has the affinity for the BH3 binding sub-structure in the anti-apoptotic proteins of Bcl-2 family (AAPBcl2); and hence when the number of the AAPBcl2 is more than the PAPBcl2, the PAPBcl2 are not free and apoptosis is inhibited. There may be slight variations in the BH3 sub-structure amongst the PAPBcl2, and there also may be slight variations in the BH3 binding sub-structure amongst the AAPBcl2. The anti-Bcl-2 drugs have the BH3 sub-structure similar to that of the PAPBcl2, and hence outcompetes the PAPBcl2 in binding to the AAPBcl2 thereby freeing the PAPBcl2 [5]. Venetoclax (ABT-199) in particular binds to the Bcl-2 protein only, and has been shown to cause apoptosis successfully in AML cell lines [3]. Bcl-2 has been found to be over expressed in Double-hit Diffuse Large B-cell Lymphoma, and hence ABT-199 is the only anti-Bcl-2 drug studied in the work [6].

Venetoclax/Bcl-2 Complex

As expected the administration of high doses of ABT-199 alone caused apoptosis in CARNAVAL and WILL-2 cells but not in Bcl-2 negative Oci-Ly7 cells. However, at low concentrations ABT-199 was able to deregulate proliferation in CARNAVAL and WILL-2 cells but not in Bcl-2 negative Oci-Ly7 cells. This result points to the role of possible interaction between ABT-199 and Bcl-2 protein in freeing the PAPBcl2. The expression levels of the CD20 molecule and the CD38 molecule on the surfaces of CARNAVAL and WILL-2 cells respectively did not change when these cells were treated with ABT-199 alone. The combined ABT-199/RTX therapy against CARNAVAL cells, when compared to the RTX therapy alone, did not increase ADCC and CDC but increased ADCP. Similarly the combined ABT-199/DARA therapy against WILL-2 cells, when compared to the DARA therapy alone, did not increase ADCC and CDC but increased ADCP. However, the combined ABT-199/RTX therapy against Bcl-2 negative Oci-Ly7 cells did not increase ADCP when compared to the RTX therapy alone. This result shows that the interaction/association between ABT-199 and Bcl-2 protein is essential to enhance ADCP in DHL cells when subjected to the combined ABT-199/Antibody therapy. The ABT-199/Bcl-2 interaction creates two different free entities within the cell: the ABT-199/Bcl-2 complex, and the PAPBcl2 Bax and Bak. So, either the Bax and Bak proteins or the ABT-199/Bcl-2 complex interacts with the Antibody/Antigen complex on the surface of DHL cells to increase phagocytosis when the DHL cells are treated with ABT-199/Antibody combination. However, experiments performed on the Bax deficient and the Bakdeficient CARNAVAL and WILL-2 cells showed that the same increase in ADCP occurred on treatment with ABT-199/Antibody combinationvis-a-vis the conventional CARNAVAL and WILL-2 cells. This shows that the ABT-199/Bcl-2 Complex, and not the Bax or the Bak protein, interacts with the Antibody/Antigen Complex to increase the ADCP in combined Venetoclax-Antibody therapy against DHL cells.

Discussion

The use of Z-VAD-FMK in CARNAVAL cells did not affect the level of ADCP of these cells on ABT-199/RTX treatment. Also the use of Z-VAD-FMK in WILL-2 cells did not affect the level of ADCP of these cells on ABT-199/DARA treatment. Though the paper [6] clearly shows that the enhanced ADCP in DHL cells on treatment with ABT-199/Antibody combination vis-à-vis the treatment with antibody alone is apoptosis independent, one is not sure whether the apoptosis is blocked or not in the DHL cells on treatment with ABT-199/Antibody combination. To answer this question the same experimental platform as that described in [6] can be used but the macrophages deficient in the Fc receptor must be taken to mix with the CARNAVAL and WILL-2 cells in phagocytosis assays; taking the macrophages deficient in the Fc receptor will suppress ADCP. If even after suppressing the ADCP the way described above, phagocytosis takes place it would mean that the combined ABT-199/Antibody therapy against the DHL cells cause cell death by apoptosis too. It would be interesting to find out that, in the combined ABT-199/Antibody therapy against the B-cell malignancies, what proportion of cancer cells are dying by apoptosis and what proportion of cancer cells are dying by ADCP. It would also be interesting to find out that, in the combined ABT-199/Antibody therapy against the B-cell malignancies, why some cancer cells are dying by apoptosis and the others by ADCP. As pointed out in previous section the ABT-199/Bcl-2 complex possibly migrates towards the Antibody/Antigen Complex

and interacts with it in the combined ABT-199/Antibody therapy, whereas on the other hand (in the same therapy) the pro-apoptotic proteins Bax and Bak are also free inside the cell; hence a key question is, "In the competition between a possible activation of ADCP by the ABT-199/Bcl-2/Antibody/Antigen Complex and a possible activation of the apoptotic cascade by the Bax and the Bak proteins, which one wins and under what biological circumstances ?" The exact mechanism by which the ABT-199 in combination with monoclonal antibody increases ADCP when compared to the treatment of cancer cells by monoclonal antibody alone needs to be found out. Much work needs to be done, the paper [6] is just a starting point of new fertile area of research in Oncology.

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