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Short Communication Open Access

Combination Therapy for Chronic Lymphoid Leukemia

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Short Communication

For decades, the treatment of chronic lymphocytic leukemia (CLL) has relied on cytotoxic drugs with incremental benefit from anti-CD20 monoclonal antibodies. However, in the past 5 years, targeted drugs have fundamentally changed the management and outcome of CLL [1-3]. These new drugs are the result of improvements in our understanding of the pathogenesis of CLL, culminating in the development of new targeted treatments. It has been well documented that B cell lymphoma 2 protein (BCL-2) plays a major role in cellular apoptosis [4-6] and is a druggable target. Several small molecule inhibitors of BCL-2 are in active clinical studies [7,8] (Table 1). A phase 1 study of navitoclax showed activity in 50% of patients with relapsed or refractory CLL, but the drug was associated with dose-limiting thrombocytopenia owing to the inhibition of BCL2-like protein 1 (BCL-xL), a regulator of platelet senescence [9]. However, venetoclax showed 100 times less activity against BCL-xL and consistent with its binding characteristics, it showed markedly less thrombocytopenia but more neutropenia (because of potent BCL2 inhibition) than navitoclax. ABT-199 (venetoclax) represents the first-in-class, selective, oral BCL-2 inhibitor sparing platelets. It showed sub-nanomolar affinity to BCL-2 (Ki 0.010 nM) with antitumor activity against CLL *in vitro* [10]. The second-generation agent appears to improve substantially on the specificity of their first-generation sibling navitoclax. Venetoclax has been granted breakthrough designation by FDA for relapsed or refractory CLL with 17p deletion. In the article that accompanies this commentary, a novel approach was reported by Roberts et al. for the treatment of CLL with the use of venetoclax, a specific inhibitor of BCL-2, a protein central to the survival of CLL cells. Selective targeting of BCL-2 with venetoclax had a manageable safety profile and induced substantial responses in patients with relapsed CLL [11]. Venetoclax showed robust activity, with response rates of 71%-79% across molecular prognostic groups and a 15 month rate of progression-free survival of 69% at the expansion dose.

Compound	Molecular Targets	Preclinical Use	Clinical Trials
ABT-737	Bcl-2 and Bcl-X_L (low nM affinity)	Multiple myeloma; Acute myeloid leukemia; Small cell lung cancer; Lymphoma	Phase I/II
Navitoclax (ABT-263)	Bcl-X_L, Bcl-2, Bcl-w, Bcl-B	Multiple myeloma; Small cell lung cancer; Non-Hodgkin Lymphoma; Chronic lymphocytic leukemia	Phase I/IIa
Venetoclax (ABT-199)	Bcl-X_L, Bcl-2, Bcl-w, Bcl-B	Multiple myeloma; Small cell lung cancer; Chronic lymphocytic leukemia	Phase I/II
Obatoclax (GX015-070)	Bcl-2, Bcl-X_L, Bcl-w, Mcl-1	Myeloma; Mantle cell lymphoma	Phase I/II
Gossypol (BL -193, AT-101)	Mcl-1, Bcl-2, Bcl-X_L	Head and neck tumors; Malignant gliomas	Phase II/III
Apogossypolone (ApoG2)	Bcl-2, Mcl-1, Bcl-X_L (highest to lowest affinity)	Non-Hodgkins Lymphoma, Lymphoma	Preclinical
TW-37	Bcl-w, Bcl-X_L, A1, Mcl-1, Bcl-2	Non-Hodgkins Lymphoma, Pancreatic, Lung	Preclinical
Tetrocarcin A	Bcl-2 and Bcl-X_L	Leukemia and others	Preclinical

Table 1: List of BCL-2 family inhibitors.

At the other end, several observations have fostered optimism that chimeric antigen receptors (CARs) modified autologous T cells might act as a more specific immunotherapeutic approach and proved to be more potent anti-leukemic immunity with less toxicity. CTL019 is a chimeric antigen receptor that includes a CD137 (4-1BB) signaling domain and lentiviral-vector technology is used for its gene transfer and permanent T-cell modification. A study reported that autologous T cells that genetically modified to target CD19 showed the delayed development of tumor lysis syndrome and after 3 weeks of treatment a complete response was obtained. Anti-CD19 linked to CD3-zeta and CD137 signaling domains expressed with a lentivirus vector and targeting CD 19 was occurred through the transduction with this vector [12]. Across the CTL019 program, chimeric antigen receptor-modified T-cell therapy against CD19 was effective in treating well over 70 patients with both CLL and acute lymphoblastic leukemia (ALL). In a recently reported cohort of 30 patients, 27 (90%) achieved complete response. Three of the patients had previously failed blinatumomab therapy, and two of these responded. Patients for whom stem-cell transplantation had failed, CTL019 therapy was associated with a high and durable remissions up to 24 months were observed [13].

During the last few years, the exciting developments in the treatment of CLL open up an exciting era in the treatment of CLL and related disorders. The maximum benefit can be obtained by combining the novel agents in a logical way. Apoptotic pathway (targeting BCL-2) is being targeted with the agents that work in a variety of ways. Proper understandings of these pathways educate us to combine agents in a logical way to target the pathophysiology of CLL and to reduce toxicity. Combining CTL019 with ibrutinib represents a rational way to incorporate two of the most recent therapies in mantle cell lymphoma (MCL). The findings pave the way to a two-pronged therapeutic strategy in patients with MCL and other types of B-cell lymphoma [14]. A study evaluated the effect of ibrutinib treatment on the T-cell compartment in CLL, the authors examined the function of T-cells in CLL patients during ibrutinib treatment as it relates to CAR T-cell generation. They found that CAR T-cell function is not impaired with the exposure of ibrutinib *in vitro* and in fact simultaneous administration improves tumor clearance, CAR T-cell engraftment and survival in human xenograft models of resistant ALL and CLL. This finding indicates that clinical trials with combination therapy are warranted as ibrutinib

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enhances CAR T-cell function [15]. Targeting BCL-2 through venetoclax is a significant first step approach can be acquired for the therapeutic strategy in CLL. BCL2 also plays an important role in CLL survival, as indicated by the activity of venetoclax, but complete remission is also infrequent, which is probably a result of the up-regulation of alternative BCL2 family members [16]. BCL-2 inhibitor (venetoclax) used in combination with CTL019 provide promises to radically alter the treatment of CLL and may ultimately lead to therapy that is more effective and less toxic. This approach appears likely to indicate the beginning of a revolution in the treatment of CLL with the development of a series of small molecules for different phases that target novel aspects of CLL biology.

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