

BCL-2 inhibitors for Chronic Lymphocytic Leukemia

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Editorial

B-cell chronic lymphocytic leukemia (CLL) is the most common adult leukemia in Europe and North America, with an annual incidence of three to five cases per 100,000 [1]. The approval of rituximab-based immunochemotherapy represented a substantial therapeutic advance in CLL [2]. However, currently available therapies are only partially efficient, and there is an obvious need to develop better strategies and new, more specific and active drugs. BCL-2 proteins play a crucial role in the regulation of apoptosis [3]. High levels of the BCL-2 family anti-apoptotic proteins are considered primarily responsible for inhibiting apoptosis in CLL cells, and BCL-2 dysregulation results in the inhibition of apoptosis and uncontrolled proliferation of B-cells, leading to the development of many hematological malignancies and resistance to chemotherapy. The overexpression of BCL-2 is associated with chemotherapy-resistant disease, aggressive clinical course and poor survival in patients with B-cell lymphoid malignancies [4].

Therapeutic modulation of the BCL-2 pathway represents a promising new therapeutic strategy in CLL [5]. Currently, a number of small molecules binding to anti-apoptotic BCL-2 inhibitors are undergoing preclinical and clinical investigation [6]. Among the various small molecules that have entered preclinical studies, only navitoclax (ABT-263), venetoclax (ABT-199) and obatoclax (GX15-070) are under clinical trials for CLL [7-9].

Navitoclax (ABT-263, Abbott Laboratories) is a first-in-class Bcl-2 family protein inhibitor that restores the ability of cancer cells to undergo apoptosis [10]. This drug binds with high affinity to multiple anti-apoptotic BCL-2 family proteins, including Bcl-xL, BCL-2, and Bcl-w, while showing lower affinity for Mcl-1. CLL cells have demonstrated substantial susceptibility to navitoclax through BCL-2 inhibition. In a phase I/IIa trial performed in 17 patients with refractory or relapsed lymphoid malignancies, navitoclax was administered QD orally at doses of 10, 20, 40, 80 and 160 mg for 14 consecutive days followed by 7 days off drug [11]. Two patients with bulky CLL/small lymphocytic lymphoma (SLL) in the 40 and 160 mg cohorts demonstrated 95% and 64% tumour reductions after cycles 4 and 2, respectively. Another CLL-specific phase 1 study included 26 patients with relapsed or refractory disease [12]. Partial response (PR) was achieved in 35% of patients, with an additional 7 patients having stable disease for more than 6 months, and the median progression free survival (PFS) was 25 months. Importantly, drug activity was observed in patients with fludarabine-refractory disease, bulky lymphadenopathy, and in patients with del(17p) CLL. However, thrombocytopenia due to BCL-x (l) inhibition was a frequent toxic event. In an interim analysis of another phase II study of navitoclax including 31 patients with relapsed/refractory CLL, PR was observed in 38% (10/26) of patients, including two patients with del(17p) [13]. Trials testing the combination of navitoclax with fludarabine,

cyclophosphamide and rituximab (FCR) or bendamustin-rituximab (BR) regimens in refractory CLL are ongoing (NCT00868413).

Venetoclax (GDC-0199, ABT-199, RG7601; Genentech, South San Francisco, CA), is a first-in-class, orally bioavailable BCL-2 family protein inhibitor that binds with high affinity to BCL-2 and with lower affinity to the other BCL-2 family proteins Bcl-xL, Bcl-w and Mcl-1 [14]. It induces apoptosis in CLL cells at concentrations 10-fold lower than those required by navitoclax. In addition, platelet apoptosis required a 200-fold higher concentration of venetoclax for induction compared with navitoclax [15,16]. Venetoclax was evaluated in a phase I study in 56 patients with relapsed/refractory CLL [8,17]. A single oral dose was administered followed by 6 days off drug, before continuous once-daily dosing. The overall response rate was 85%, and included 7 (13%) patients with a CR. Efficacy was independent of high risk markers including del(17p) and fludarabine-refractory disease. Thirteen patients discontinued therapy: 7 patients due to progressive disease and 6 patients for other reasons. The most common grade 3/4 adverse events (AEs) were neutropenia (38%), thrombocytopenia (11%) and tumor lysis syndrome (TLS) (9%). The combination of venetoclax and rituximab has the potential to improve efficacy and was recently evaluated in a phase II study [18]. The treatment induced an OR rate of 86% including 31% CRs in patients with relapsed or refractory CLL. Although anemia was the most common AE observed in an ongoing phase Ib study of the safety and tolerability of venetoclax, given in combination with bendamustin and rituximab, in six patients with relapsed/refractory or previously untreated CLL, no DLTs were observed [9]. A phase III study comparing the combination of venetoclax and rituximab with a combination of bendamustine and rituximab in patients with previously treated CLL is ongoing. Another anti-CD20 monoclonal antibody, obinutuzumab, shows synergistic activity in CLL when combined with venetoclax [19]. In addition, preclinical studies suggest that venetoclax is an ideal partner to be combined with ibrutinib, and these drug combinations should be tested clinically against CLL [20].

Obatoclax (GX15-070; Abbvie, Inc., North Chicago, IL) has been described as pan-BCL-2 family inhibitor. With activity against BCL-2, BCL-XL, BCL-w and MCL-1 [21,22]. In addition, obatoclax has the ability to overcome resistance to apoptosis-mediated specifically by Mcl-1 overexpression [23]. In a phase I trial in heavily pre-treated, largely refractory CLL patients, obatoclax was given to 26 patients with advanced CLL both as a 1-hour infusion, at doses ranging from 3.5 to 14 mg/m², and as a 3-hour infusion at doses ranging from 20 to 40 mg/m² every 3 weeks. One PR was observed along with reductions in lymphocyte counts and improvements in cytopenias in 18 patients. The dose-limiting toxicity was neurologic, including euphoria and ataxia occurring during the infusion or shortly afterwards, leading to a maximum tolerated dose of 28 mg/m² given over 3 hours every 3 weeks. Obatoclax also shows promising clinical activity and was well

tolerated in combination with fludarabine and rituximab [24]. In a phase I study, 13 relapsed CLL patients received obatoclax as a 3-hour infusion on days 1 and 3 and escalated through three dose levels, with standard doses of fludarabine and rituximab on days 1–5. The OR rate was 85%, with 54% CRs, according to the IWCLL 2008 criteria, and median PFS was 20 months.

Finally, a BCL-2 antisense called oblimersen has been investigated as a therapeutic agent in patients with CLL. It is a synthetic, 18-base, single-strand phosphorothioate DNA oligonucleotide designed to down-regulate BCL-2 mRNA expression [25]. In a phase I/II study, 40 patients with relapsed or refractory CLL previously treated with fludarabine received oblimersen at doses ranging from 3 to 7 mg/kg/day as a 5-day continuous intravenous infusion every 3 weeks [26]. Two (8%) of the 26 evaluable patients achieved a PR. The addition of oblimersen to chemotherapy with fludarabine and cyclophosphamide produced a significant increase in the number of durable remissions in patients with relapsed or refractory CLL [27]. In a phase I/IIa trial performed in 21 patients with relapsed/refractory CLL, the overall response rate was 33%. The most common adverse events were diarrhea (52%), nausea (44%), vomiting (24%), fatigue (24%) and thrombocytopenia (20%).

In conclusion, the strategy of targeting BCL-2 through venetoclax and other agents is an important step in changing the therapeutic approach for CLL. BCL-2 inhibitors appear to be appropriate drugs for use in combination with monoclonal antibodies and BCR inhibitors, for example ibrutinib or idelalisib. The combination of new non-chemotherapeutic agents can alter the treatment of CLL and may lead to the creation of therapy that is both more effective and less toxic. Well-designed, carefully controlled, randomized clinical trials should confirm any advantages of newly developed strategies over current standard therapies.

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