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New Therapeutic Advances in Chronic Lymphocytic Leukemia

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Abstract

Treatment of Chronic Lymphocytic Leukemia (CLL) is entering a new era. In the last 5 years, several new exciting drugs have entered the realm in hopes for a success in curing the disease. The drugs fall into different classes such as BTK inhibitors, BCL-2 inhibitors, CD 20 Antibody, PI3 Kinase inhibitors, and Syk inhibitors. Numerous studies have shown that these agents have clinical activity both as initial therapy and as treatment of recurrent disease. Novel strategies combining or sequencing new agents with established chemotherapy and chemoimmunotherapies combinations are likely to change the treatment of CLL in the near future.

Keywords: Lymphocytic; Leukemia; Car T cells; Obinutuzumab; Lenalidomide

BTK inhibitor-Ibrutinib

Ibrutinib is a BTK inhibitor recently approved, February 2014, for the treatment of recurrent CLL. BTK plays an important role downstream the B cell receptor signaling (BCR) and is part of the Tec family of kinases. Signaling through BCR is essential to the AKT pathway and the NF-KB pathway (nuclear factor kappa light-chain enhancer of activated B cells). BCR signaling is also involved in B cells cell adhesion, migration and differentiation [1]. Ibrutinib has been evaluated as frontline in elderly patients. It was found that the toxicities associated to this agent were mild. For example 68% of patients had grade 1 diarrhea and 45% grade 2 diarrhea. Responses were 71% had objective response, 13% had complete response (CR), 3% had nodular response (nPR) and 55% had partial response (PR). Ibrutinib was found safe and effective for untreated elderly with symptomatic CLL [2]. The activity of ibrutinib was studied in 40 high risk CLL patients (20 patients with 17p del) showed that 87% achieved PR and 8% CR. Responses were seen early, most patients had a more than 50% reduction in lymph nodes at their first radiographic response assessment after 12 months on therapy. Median progression free survival at 18 months was 78% of all patients and deletion 17p had 72%. Future studies are being conducted to evaluate the whether the addition of Rituximab to ibrutinib will create a longer PFS and OS in relapsed and refractory CLL [3]. There have been reports of resistance to ibrutinib. Recent reports have shown that a mutation that changed the cysteine at BTK position 481 to serine (C481S) is one of the mechanisms responsible for resistance blocking the ability of ibrutinib to bind covalently to BTK. Another mechanism involved in acquiring resistant to this agent is a gain-of-function mutations found in PLCγ2, a downstream target of the BTK phosphorylation pathway [4]. Current and future clinical strategies will evaluate the activity of ibrutinib in combination with agents with different mechanisms of action and targeting separate pathways. The current dosing of ibrutinib is 420 mg oral daily (3 capsules daily).

BCL-2 inhibitor-ABT 199

ABT 199, a BH3 mimetic, is a targeted agent which promotes apoptosis by inhibiting BCL-2. Preliminary results on the activity of this agent report overall response rate of 84% in 56 patients with CLL. Treatment with ABT 199 was accompanied by a significant decrease in bone marrow infiltrate and lymphocyte count reduction. High response rates (89%) were observed in 27 patients with fludarabine refractory disease. Furthermore, clinical activity has been shown irrespective of the status of the TP53 pathway with observed responses in 82% of patients with deletion 17, known poor prognostic factors in CLL. Side effects included neutropenia (20%), tumor lysis syndrome, anemia and thrombocytopenia (9%) were the most common adverse events [5]. Administration of ABT 199 has been associated with rare, but severe cases of tumor lysis syndrome and needs close monitoring during the initial days of drug administration and at times of dosage increase. Resistance to ABT 199 have been created in vitro lymph node models of CLL by using a combination of CD40 and cytokine stimulation (IL 4 or IL 21) with a kinase inhibitor that are known to change micro environmental signals (Mcl-1, Bcl-XL, Bfl-1 and Noxa) and increase resistance to ABT 199. Interestingly, in this model, dasatinib inhibited CD 40 therefore preventing resistance to ABT 199 [6].

CD 20 Antibody–Obinutuzumab

Obinutuzumab is a type II CD 20 antibody with a glycoengineered Fc region. With respect to rituximab, the modified structure of obinutuzumab translated in preclinical studies, in superior efficacy in inducing direct CLL cell death and enhanced antibody-dependent cellular cytotoxicity. In phase III CLL 11 trial, which evaluated obinutuzumab-chlorambucil versus rituximab-chlorambucil versus chlorambucil alone, Goede and coll. showed that the combination of obinutuzumab-chlorambucil showed a prolong progression free survival compared to chlorambucil alone (26.7 months vs 11.1 months respectively). There was a significant prolongation in progression free survival when obinutuzumab-chlorambucil compared to rituximab-chlorambucil (26.7 months vs 15.2 months respectively; hazard ratio 0.39 with P<0.001). The same study showed that treatment with the

combination of obinutuzumab-chlorambucil was associated with a trend toward a survival advantage when compared to the combination of rituximab- chlorambucil [7]. The most common adverse events associated with obinutuzumab are infusion reaction in 20% and thrombocytopenia in 10% of the patients.

Lenalidomide

Lenalidomide is a derivative of thalidomide. It belongs to a group of agents called immune modulators. Lenalidomide is an immunomodulatory agent with activity in the treatment of various lymphoproliferative disorders [**8**]. In CLL, lenalidomide alters the tumor microenvironment by modulating cytokine production by dendritic cells as well as modifying expression of co-stimulatory molecules by T-cells, potentially repairing defective humoral immunity and defective T-cell to B-cell synapse formation characteristic of CLL [**9**]. Lenalidomide has been investigated both as salvage therapy and as frontline therapy of patients with CLL. In patient with recurrent disease, different doses and schedules were evaluate and responses were seen in 12% to 47% of the patients treated [**10**-12].

Efficacy and toxicity of lenalidomide as initial therapy was evaluated in 60 patients. In this study, CR was reported in 48% and PR in 22% of the patients. In this elderly population, the overall survival with median follows up of 4 years was 82%. The most common toxicities associated with lenalidomide are myelosuppression, neuropathy, and persistent fatigue. Monitoring for tumor lysis syndrome and awareness of the development of tumor flare reactions are needed when patients with CLL are treated with lenalidomide respectively [**13**,14]. The activity of lenalidomide has also been studied in combination with chemotherapy and CD 20 monoclonal antibodies. Clinical studies evaluating combinations of lenalidomide and BTK inhibitors are ongoing.

PI3 Kinase inhibitor-Idelalisib

Idelalisib is a PI3 kinase inhibitor that directly inhibits the δ subunit which decreases the proliferation of B cells. It has been investigated in clinical trial, both as monotherapy and in combination with chemotherapy and CD20 antibodies. Idelalisib was combined with rituximab and compared with rituximab monotherapy in patients with recurrent disease. In this large study that enrolled 220 patients, overall response rate was higher in the patients randomized to receive idelalisib (81% vs. 13%). A superior survival at 12 months (92% vs 80%) was also observed in the patient treated with idelalisib and rituximab compared to rituximab as monotherapy [15].

Other inhibitors

GS-9973 is a Syk inhibitor is a non-receptor cytoplasmic tyrosine kinase that inhibits the signaling in B cells, macrophages, mast cells and neutrophils. This type of inhibitor is being investigated in CLL and other types of Non-Hodgkin Lymphomas both as single agent and in combination [16]. CC-292 is a selective irreversible BTK inhibitor with potential antineoplastic activity thru inhibiting the BCR signalling. It was found to induce responses in relapsed refractory CLL patients, even those with high risk features [17].

ONO 4059 is an oral agent for relapsed and refractory CLL that is very selective to BTK that works through phosphorylation. Preliminary results have shown that all patients had a reduction in lymphadenopathy during the first cycle. The best overall response rate was 70% [18].

CAR T-cells

CAR T-cells combine an antigen domain with intracellular signaling domain into single chimeric protein. Gene transfer to express CAR on T-cells confers novel antigen specificity. A lentivector was used to express the chimeric antigen receptor of the B cell CD 19 matched with CD 137 and CD 3 of the T-cell. These were infused in a small number of refractory CLL patients resulted in a complete remission. The grade 3 and 4 side effects associated with CARs was lymphopenia and tumor lysis syndrome. Remission was noted 10 months after treatment [19]. Several active programs are on-going evaluating different types of CAR T-cells directed toward various antigens (CD19, ROR1, etc.) in patients with CLL.

Conclusion

With these new drugs in progress and being approved by FDA, the hopes of curing and prolonging survival in relapsed and refractory CLL patients are possible. Future targeted therapy can be enhanced by combing different targeted pathway drugs for example BTK inhibitor with a PI3 Kinase inhibitor or lenalidomide with BTK inhibitor. It is likely that in the years to come, additional agents will be developed targeting newly identified gene mutations, such as NOTCH 1 mutation which is found in 5% to 20% of trisomy 12 and SF3B1 found with association to deletion. The treatment options for patients with CLL have expanded immensely over the last five years. With the expanded number of strategies, we are observing a steady improvement in the rate and duration of responses in patients with aggressive disease.

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