Review

Novel Agents in the Treatment of Chronic Lymphocytic Leukemia: A Review About the Future

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Abstract

Half of a century ago, physicians managing chronic lymphocytic leukemia (CLL) recognized some of its presenting features such as lymphocytosis, lymphadenopathy, and splenomegaly. Subsequently, an enhanced understanding of the disease mechanisms involved in CLL led to new, more targeted treatments. There is now a plethora of treatments available for CLL. In this review article we discuss in detail several of the novel agents that are being studied or approved for the treatment of CLL including: phosphatidylinositol 3-kinase inhibitors (idelalisib and IPI-145), Bruton tyrosine kinase inhibitors (ibrutinib), B cell lymphoma 2 inhibitors (ABT-263 and ABT-199), new anti-CD20 monoclonal antibodies (obinutuzumab), cyclin-dependent kinase inhibitors (flavopiridol and dinaciclib), immunomodulators (lenalidomide) and chimeric antigen receptor T-cell therapy.

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Introduction

Chronic lymphocytic leukemia (CLL) is a subtype of leukemia arising from immunologically less mature lymphocytes that spread to the blood, bone marrow, and lymphatic tissues. The disease manifests as lymphocytosis usually with characteristic phenotype on B cells (CD5 and CD23 positive markers). Recently, the age-adjusted incidence of CLL in the United States from 1975 to 2011 has been 4.8/100,000 population with a male to female ratio of 2:1. The median age at diagnosis of CLL is 72 with 56.5% of cases between the ages of 65 and 84 years with a median age at death of 79 years.[1] The National Cancer Institute estimates that 15,680 Americans were diagnosed with CLL and 4580 died of the disease in 2013. CLL is an extremely heterogenous disease that can range from asymptomatic for decades to rapidly progressive disease. Two staging systems were created to establish prognostic implications for survival: Rai and Binet staging systems.[2,3] However, with the advent of molecular profiling, several new prognostic features have been identified. The simplified Rai system relies mainly on the fact that there is progressive accumulation of lymphocytes in the lymph node, splenomegaly, and hepatomegaly, followed by bone marrow involvement manifested peripherally as anemia and thrombocytopenia. Binet staging takes into consideration the number of involved sites plus the presence of anemia (hemoglobin < 10 g/dL) or thrombocytopenia (platelets $< 100 \times 9$ g/dL). Afterward, clinicians identified high-risk genetic and molecular features in CLL that helped to predict disease outcomes; examples of such features include unmutated immunoglobulin heavy chain variable genes (*IGHV*), *17P* deletion, CD38, and zeta chain associated protein kinase 70 (ZAP-70) expression.[4]

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Disease Mechanisms

Anatomically, the CLL tumor cell microenvironment consists of peripheral blood and tissue compartments (bone marrow and secondary lymphatic organs).[5] In this microenvironment, the malignant B cells are the main players that interact with bone marrow stromal cells (BMSCs), monocyte-derived nurse-like cells (NLCs), and T cells to proliferate and survive by defeating the host's immune system. First, the interaction between the C-X-C Chemokine Receptor 4 receptor on CLL cells with BMSC/NLC allows tissue homing and transendothelial migration.[6] This interaction, in turn, correlates with the degree of lymphoid infiltration.[7] The other molecules on CLL cells are ZAP-70,[8] CD38, and very large antigen-4 (VLA-4) integrins, all of which play a role in the interaction with chemokine (C-X-C

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motif) ligand 12 to achieve a greater state of disease aggressiveness.[9,10] Moreover, B-cell receptors interact with NLC to secrete CCL3 and CCL4[11] that attract CD4-positive ($CD4^+$) T cells and monocytes to the tumor cell microenvironment.[12] This is what helps to maintain the selective survival advantage of CLL cells. CLL cells are also able to induce changes in cytoskeletal gene transcription,[13] causing defective actin polymerization and T-cell dysmotility[14]; these changes can be reversed by the immunomodulators, such as lenalidomide,[15] one of the novel drugs that is being studied in CLL treatment.

Established Treatments

One of the first chemotherapeutic agents used in the treatment of patients with CLL was chlorambucil, which is an alkylating agent. However, because of the drug's low response rate as a single agent, it is currently reserved mainly for elderly frail patients who are unable to tolerate combination treatment because it is given orally and has few side effects with efficacy similar to other chemotherapeutic agents.[16] Fludarabine, a purine analogue, has been compared with chlorambucil[17] and was shown to have a better response rate. Subsequently, immunotherapy agents that work through complement-mediated cytotoxicity and antibody-dependent cellular toxicity were introduced in the treatment of CLL, leading to the emergence of combination regimens. We list in the following sections a few of the available chemoimmunotherapy treatments for CLL using rituximab, a monoclonal antibody against CD20, which was used initially as a single agent in the treatment of CLL[18] before being incorporated into newer combination regimens.

Fludarabine/Rituximab

Initially, a randomized phase II study showed promising results for the combination of fludarabine and rituximab (FR) in the treatment of patients with CLL as part of a Cancer and Leukemia Group B (CALGB) study.[19] In this study, 104 patients were enrolled and randomized to a sequential regimen or a concurrent regimen. The median age of the patients was 64 years and 61 (59%) of the patients had intermediate-risk (Rai stage I or II) and 43 (41%) had high-risk (Rai stage III or IV). In the concurrent regimen group, induction complete response (CR) was 17 patients (33%) and overall response rate (ORR) was 46 patients (90%), and in the sequential regimen group, the induction CR was 8 patients (15%) and ORR was 41 patients (77%). This study established the superiority of the concurrent regimen. Afterward, a retrospective study that investigated 2 clinical trials conducted by the CALGB group showed FR to be superior to fludarabine alone.[20] Patients who had received FR had a greater incidence of CR (38% vs. 20%; $P = .002$) and ORR (84% vs. 63%; $P = .0003$) compared with fludarabine alone.

Fludarabine/Cyclophosphamide/Rituximab

Fludarabine, cyclophosphamide, and rituximab (FCR) was initially studied in a phase II study that enrolled 224 patients with previously untreated CLL; this study showed a CR in 156 patients (70%) and ORR in 213 patients (95%).[21] Seventy-five patients (33%) had high-risk disease. FCR was found to be myelosuppressive and Grade 3 to 4 neutropenia occurred during 52% of the courses with major and minor infections seen in 2.6% and 10% of the courses, respectively. One-third of the patients had ≥ 1 episode of infection, and 10% had a fever of unknown origin. Subsequently, a phase III study by the German CLL group (CLL8 study) compared FCR versus fludarabine and cyclophosphamide (FC).[22] In this study, 408 patients were assigned to the FCR regimen versus 409 to the FC regimen. Sixty-five percent of patients in the FCR group were free of disease progression compared with 45% in the FC group. Eighty-seven percent survived in the FCR group versus 83% in the FC group. Grade 3 and 4 neutropenia occurred in 34% of the FCR group versus 21% in the FC group. However, severe infections were not increased in the compared groups. This study established the superiority of FCR compared with FC.

Bendamustine/Rituximab

The bendamustine and rituximab (BR) regimen was initially studied in relapsed and/or refractory CLL patients in a phase II study by the German CLL group.[23] Seventy-eight patients were enrolled in the study who showed ORR of 59% with a CR of 9%. ORR was 45.5% in the fludarabine-refractory group of patients and 60.5% in the fludarabine-sensitive group of patients. Most patients (92.3%) had the *11q* deletion, 7.1% the *17p* deletion, and 58.7% with unmutated *IGHV* status had response to treatment. Grade 3 or 4 neutropenia occurred in 23.1% of patients and severe infection occurred in 12.8% of patients. Grade 3 or 4 thrombocytopenia and anemia occurred in 28.2% and 16.6% of patients, respectively. Subsequently, the BR regimen was studied in previously untreated CLL patients as a first-line treatment in a multicenter phase II study also conducted by the German CLL group.[24] One hundred seventeen patients were enrolled in the study with 46.2% of the patients having Binet stage C and 25.6% of patients being 70 years of age or older. The study showed ORR of 88.0% with CR of 23.1% and partial response (PR) of 64.9%. Most patients (90%) enrolled with *11q* deletion, 37.5% with *17p* deletion, and 89.4% with unmutated *IGHV* status had response to BR. Median event-free survival was 33.9 months and 90.5% of patients survived. Grade 3 or 4 neutropenia was observed in 19.7% of patients; 7.7% had severe infection. Grade 3 or 4 thrombocytopenia and anemia occurred in 22.2% and 19.7% of patients, respectively. This study established the efficacy and relative safety of the BR chemotherapeutic regimen as a first-line treatment for previously untreated CLL patients.

The CLL10 trial was conducted to compare the efficacy and safety of BR versus FCR in patients with advanced CLL. Six hundred eighty-eight CLL patients were enrolled and randomized to receive 6 cycles of either FCR or BR. As per the interim analysis of the study, an identical ORR was observed in both arms with 97.8% response ($P = 1.0$).[25] CR was 47.4% in the FCR arm versus 38.1% in the BR arm ($P = .031$). Progression-free survival (PFS) was 85% at 2 years in the FCR arm versus 78.2% in the BR arm ($P = .041$). The BR arm had a significantly better safety profile than the FCR arm. The study noted more adverse events (AEs) in the FCR group: hematotoxicity (FCR: 90% vs. BR: 66.9%; $P < .001$); severe neutropenia (FCR: 81.7% vs. BR: 56.8%; $P < .001$); and severe infection (FCR: 47.4% vs. BR: 26.5%; $P = .002$). Overall, the CLL10 trial interim analysis showed similar efficacy between BR and FCR but with a better safety profile seen with BR.

Novel Treatments

The main objective of this article was to focus on the novel treatments that are being studied or already approved in the