Targeted Therapy in Chronic Lymphocytic Leukemia: Past, Present, and Future

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ABSTRACT

Background: Chronic lymphocytic leukemia (CLL) is the most prevalent leukemia in the western world. Recent advances in understanding the biology of B-cell malignancies have resulted in the development of novel agents targeting key prosurvival pathways in the neoplastic B cell.

Objective: The goal of this article was to summarize current literature on the emerging therapeutic approaches in CLL and B-cell malignancies.

Methods: A literature review was performed, identifying pathways and key clinical trials involving novel therapies in CLL, with special emphasis on B-cell receptor (BCR)-targeting agents.

Results: Understanding the biology of the BCR-signaling pathway has led to identification of novel molecular targets. Most notably, inhibitors of Bruton tyrosine kinase and phosphatidylinositide 3-kinase-δ have entered clinical trials and demonstrated high response rates in CLL, including high-risk disease. Cyclin-dependent kinase inhibitors may evolve into an alternative therapeutic approach in CLL. New drugs that target molecules within and outside of the BCR-signaling pathway have shown promise in preclinical studies.

Conclusions: Both preclinical and early clinical trial results involving novel targeted therapies suggest that the standard treatment paradigm in CLL and B-cell malignancies will soon change. Particular attention should be paid to the BCR-targeting agents, whose favorable adverse effect profile may improve the lives of elderly patients with CLL. (*Clin Ther*. 2013;35:1258–1270)

Key words: B-cell receptor, chronic lymphocytic leukemia, ibrutinib, NF-κB.

INTRODUCTION

Chronic lymphocytic leukemia (CLL) is the most prevalent leukemia in the western world, with ~100,000 patients living with the disease in the United States. It is estimated that 15,680 men and women will be diagnosed with CLL and 4580 patients will die of CLL and its complications in 2013.[1] The median age of a patient with CLL at diagnosis is 72 years, and two thirds of cases are diagnosed among those aged ≥65 years. Age-adjusted incidence of CLL is estimated at 3.9 per 100,000 people, increasing to 22.3 per 100,000 among those aged ≥65 years and an estimated underreporting of 10% to 30% of cases.[2,3]

The goal of the present article was to summarize the current literature on the emerging therapeutic approaches in CLL and B-cell malignancies.

METHODS

In the process of manuscript preparation, review of the English language articles listed in PubMed over the past 10 years was performed using the following key words: CLL, B-cell receptor, ibrutinib, CAL-101 and NF-kappaB. Additionally, abstracts presented at the Annual Meeting of the American Society of Hematology between 2010 and 2012 were searched with the same key words (http://bloodjournal.hematologylibrary.org/site/misc/ASH_Meeting_Abstracts_Info.xhtml). Abstracts presented at the International Workshop on CLL in 2011 (Houston, Texas) were also reviewed. Finally, select clinical trials in CLL registered at clinicaltrials.gov were listed in this manuscript.

RESULTS

Background

Therapy of CLL has significantly evolved over the past 2 decades, resulting in an improved survival of patients with this disease.[4] Alkylating agents and glucocorticoids were first used in the treatment of CLL in the 1950s.[5,6] Purine analogues (cladribine, fludarabine, and pentostatin) were introduced in the

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1980s. Development of rituximab by IDEC Pharmaceuticals and its subsequent approval by the US Food and Drug Administration (FDA) for the treatment of non-Hodgkin lymphoma in 1997 introduced highly efficacious chemoimmunotherapy regimens, which to this day remain the standard approach to initial therapy of younger, fit patients with CLL.[7] FCR (fludarabine, cyclophosphamide, rituximab) leads to an overall response rate (ORR) of ~90% and a complete response rate (CR) of 30% to 72% when administered to previously untreated patients with CLL.[7,8]

Despite this success, both fludarabine- and pentostatin-based regimens are associated with a high frequency of grade 3 to 4 neutropenia, which occurs in up to 71% of younger patients, as well as prolonged suppression of T cell–mediated immunity.[7,9] In an attempt to ameliorate toxicity in the elderly, recent studies with dose-reduced (50%−60%) oral or intravenous FCR (fludarabine, cyclophosphamide, rituximab) were undertaken but unfortunately still reported a similar occurrence of severe neutropenia, high frequency of lethal infections, and suboptimal treatment completion rates.[10,11] These outcomes are a significant problem because most patients with CLL are older and present with a median of 2 comorbidities at diagnosis.[12] The majority (89%) have a concurrent medical condition, and 46% have ≥1 major comorbidity (eg, cerebrovascular disease, coronary artery disease, diabetes mellitus, another malignancy). Key clinical trials in CLL, including trials investigating newer chemotherapy agents (eg, bendamustine), have generally accrued nonrepresentative populations: either younger or "fit" CLL patients selected to have zero or minor medical comorbidities.[13–16] Therefore, there is an acute need for new treatment approaches in CLL because: (1) current chemoimmunotherapy regimens are commonly associated with unfavorable adverse events, particularly in the elderly and patients with comorbidities, who represent the majority of patients with CLL; (2) clonal evolution in response to chemotherapy in CLL[17] and eventual emergence of fludarabine-resistant disease are both now well recognized; and (3) there is a lack of a curative strategy, as well as high risks associated with stem cell therapy.

Arguably, prednisone is historically the first agent that could serve as an example of targeted therapy in CLL. Although steroid hormones modulate many intracellular pathways, at least 2 examples of their "targeted" action are of relevance to lymphoid malignancies. First, glucocorticoid receptors interfere with nuclear factor–κB (NF-κB) pathway activity; by inducing the inhibitory proteins inhibitor of κB (IκB), they promote sequestration of the NF-κB in the cytoplasm.[18] This results in diminished transcription of NF-κB target genes and reduced cell proliferation and survival. Second, glucocorticoids bind to and inhibit activity of AP-1 transcription factor, which is necessary for cell proliferation.[19] Shaw et al[6] demonstrated that patients with CLL receiving prednisone at an initial dose of 1 mg/kg followed by a slow taper exhibited reductions in lymphadenopathy and organomegaly and improvement in bone marrow function. However, responses were short-lived. Interestingly, the authors noted marked responses in a patient with hemolytic anemia and 2 patients with "severe" (probably immune) thrombocytopenia, and they recommended further use of steroids under those circumstances, a practice which continues to this day.

Targeted antibody therapy represents a major success in the treatment of CLL and associated autoimmune conditions. Rituximab is a first-generation chimeric murine/human monoclonal IgG1 antibody directed against CD20, a glycosylated phosphoprotein expressed on the surface of all B cells beginning at the pro–B phase. Rituximab induces direct apoptosis as well as complement-dependent cytotoxicity and antibody-dependent cell-mediated cytotoxicity in neoplastic B cells. Although the efficacy of rituximab as a single agent in CLL/small lymphocytic lymphoma (SLL) was underwhelming in the initial studies (partial response [PR] rate, 12%),[20] use of higher doses of the drug (eg, 3 times weekly) achieved improved activity in CLL.[21] In 1997, rituximab received FDA approval for the treatment of non-Hodgkin lymphomas. A second-generation (humanized) antibody, ofatumumab, targets an alternative CD20 epitope and was FDA approved in 2009 for the treatment of CLL refractory to fludarabine and alemtuzumab. Third-generation anti-CD20 monoclonal antibodies, in addition to being completely humanized, carry an engineered Fc region to increase their avidity to the FcγRIIIa receptor. Obinutuzumab (GA101, Genentech Inc) entered early-phase clinical trials in CLL. For detailed information regarding the anti-CD20 monoclonal antibodies, the reader is referred to recently published review articles on this subject.[22,23]

Recently, encouraging results were seen among agents that target the B-cell receptor (BCR) pathway, and hence a brief introduction of this pathway, along with more detailed discussion of some of its components, is presented next.