Targeted Therapy in Chronic Lymphocytic Leukemia

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Abstract

Chronic lymphocytic leukemia (CLL) is characterized by a monoclonal population of mature, activated B lymphocytes. It is a heterogeneous disorder with a variable clinical course. Although in recent years the introduction of chemoimmunotherapeutic combinations such as fludarabine, cyclophosphamide, and rituximab (FCR) has induced response rates of 95% in previously untreated patients and increased the rates of failure-free survival, CLL remains incurable for many patients. However, a better understanding of the molecular basis of CLL has led to the development of several novel therapeutic strategies that target molecular pathways. These targeted therapies inhibit signaling pathways involved in growth and proliferation in CLL cells. Among the targeted therapies being investigated in CLL are the following: monoclonal antibodies against CD52 (alemtuzumab), CD20 (rituximab, ofatumumab), CD23 (lumiliximab), and CD40 (HCD122); agents that target molecular pathways, such as cyclin-dependent kinase inhibitors (flavopiridol); peptidase inhibitors (talabostat); Bcl-2-targeting agents (antisense oligonucleotide, oblimersen; small molecule inducing apoptosis, gossypol); heat shock protein 90 inhibitors that target 70-kDa zeta-associated protein (17-AAG, CNF2024); immunomodulating agents (lenalidomide; immunostimulatory oligonucleotides CpG); hypomethylating agents (decitabine; valproic acid); antiangiogenic agents (bevacizumab); and gene therapies. This chapter reviews the use of targeted therapies as single agents and in combination with chemotherapy for CLL.

Key Words: CLL, Prognosis, Therapy, Targeted, Phase I, Fludarabine, Alemtuzumab, Rituximab, Lenalidomide, Gene therapy

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1. INTRODUCTION

Chronic lymphocytic leukemia (CLL) is characterized by a progressive accumulation of monoclonal CD5+ B cells in bone marrow, lymphoid tissue, and peripheral blood. CLL lymphocytes express HLA-DR, pan-B antigens (CD19 and CD20), CD5, CD23, weak surface immunoglobulins (IgM or IgM and IgD), and either $\kappa$ or $\lambda$ light chain-bearing B cells (1).

B-cell CLL is the most common type of leukemia in the Western world. In 2001, the age-adjusted incidence of CLL in the United States was 4.6 per 100,000 persons (2). According to the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute, the age-adjusted incidence rate was 3.8 per 100,000 persons per year from 2000 to 2003 (3). The American Cancer Society estimated that 10,020 people (6280 men, 3740 women) would be diagnosed with CLL in 2006 and that 4660 men and women would die from the disease (3).

The clinical course of CLL varies widely and is associated with prolonged survival (Fig. 1) Treatment of CLL is usually deferred until indications for therapeutic intervention are present (4). Combination therapy with nucleoside analogues and rituximab has led to improved outcomes of CLL, but chemotherapy causes myelosuppression and other toxicities. Therefore, there is interest in eliminating the use of chemotherapy for CLL. Targeted therapies that inhibit signaling pathways for growth and proliferation of cancer cells, such as molecularly targeted drugs, monoclonal antibodies, and gene therapies, are being investigated as alternatives or adjuvants to chemotherapy for CLL.

In this chapter, we review the characteristics and molecular mechanisms of CLL and focus on targeted therapeutic strategies and future directions.

1.1. Current Therapies

In recent years, the development of new therapeutic strategies has led to stepwise improvements in clinical outcomes in CLL (Fig. 2). For several decades, the alkylating agent chlorambucil was the standard of care for CLL (5). In two randomized trials, chlorambucil was shown to slow disease progression but not to prolong survival (Table 1) (5).

![Fig. 1. Overall survival among 1976 patients with chronic lymphocytic leukemia (CLL) treated at M. D. Anderson Cancer Center from 1985 to 2005.](image-url)