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Review/Praca poglądowa

New horizons in the treatment of chronic lymphocytic leukemia

Nowe horyzonty w leczeniu przewlekłej białaczki limfocytowej

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ABSTRACT

Chronic lymphocytic leukemia (CLL) is the most common adult leukemia in the western world, accounting for approximately 30% of all leukemias in Europe and North America. Recently, significant progress in the characterization and understanding of the biology and prognosis of CLL has provided new opportunities for the development of innovative, more effective therapies. Several new anti-CD20 monoclonal antibodies directed against lymphoid cells have been developed and are under investigation in preclinical studies and clinical trials. Currently, the most promising is obinutuzumab, a novel third generation anti-CD20 monoclonal antibody that exhibits superior caspase-independent apoptosis and antibody-dependent cellular cytotoxicity than rituximab. The antibody has shown a safety profile similar to that of rituximab and promising efficacy in patients with CLL. The CD37 antigen may be advantageous over CD20 in diseases in which the level of CD37 expression is higher than that of CD20. The results of recent preclinical and early clinical studies suggest that anti-CD37 antibodies and related agents can be useful in the treatment of CLL, and many small molecule inhibitors targeting B-cell antigen receptor (BCR) signaling pathways have recently been under investigation in patients. Promising clinical results have been observed with a Btk inhibitor, ibrutinib, and a selective inhibitor of PI3Kδ, idelalisib. Several other agents including immunomodulating agents and those targeting the antiapoptotic bcl-2 family of proteins also show promise in treating CLL. Moreover, immune-based treatment strategies intended to augment the cytotoxic potential of T cells offer exciting new treatment options for patients with CLL.

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Introduction

Chronic lymphocytic leukemia (CLL) is a B-cell malignant disease with a progressive accumulation of B cells in the blood, bone marrow and lymphatic tissue, and follows an extended disease course. It is the most prevalent leukemia in the Western World with an estimated 15, 720 new cases in 2014 and almost 4600 attributable deaths per year in the United States [1]. The median age at diagnosis is 72 years and 90% of patients are older than 50 years. The diagnosis of CLL requires the presence of at least 5000 leukemic B lymphocytes per microliter in the peripheral blood [2]. The management of CLL is determined by the stage and activity of the disease, as well as age and comorbidities. Randomized studies and a meta-analysis indicate that early initiation of chemotherapy does not show benefit in CLL and may increase mortality. There is no evidence that cytotoxic therapy based on alkylating agents has beneficial effects in patients with the indolent form of the disease [3]. The strategy of watchful waiting or observation, *i.e.* closely monitoring patient status without giving any treatment until progression, may be adopted [4]. However, patients with symptomatic and/or progressive disease should be immediately treated.

CLL is typically sensitive to a variety of cytotoxic drugs, but the disease is considered incurable. There has been an important increase in the range of available therapeutic options in recent years, and many drugs are now in the process of making the transition to the clinic [5]. The approval of rituximab-based immunochemotherapy can be viewed as a substantial therapeutic advance in CLL. A large phase III randomized trial demonstrated that rituximab combined with fludarabine and cyclophosphamide (RFC) increased the overall response (OR) and complete response (CR) rates, and prolonged progression free survival (PFS) and overall survival (OS) compared with fludarabine and cyclophosphamide (FC) in previously untreated and relapsed/refractory patients [6, 7]. For the last twenty years, significant progress in molecular and cellular biology has resulted in a better characterization and understanding of the biology and prognosis of CLL. These achievements have provided new opportunities for the development of innovative, more effective therapies in this disease.

Monoclonal antibodies and related agents

Several new anti-CD20 monoclonal antibodies directed against lymphoid cells have been developed and investigated in preclinical studies and clinical trials [8]. The results of preclinical and clinical studies suggest that therapy which uses monoclonal antibodies (mAbs) directed at a target other than CD20 can be useful in treating CLL [9]. Such treatments include lumiliximab (anti-CD23), epratuzumab (anti-CD22), apolizumab (anti-MHC-II), galiximab (anti-CD80), anti-CD40 monoclonal antibodies and TRU-016, a small modular immunopharmaceutical (SMIP) derived from the fusion of key domains of an anti-CD37 antibody with a human protein.

Novel anti-CD20 antibodies

Several new anti-CD20 monoclonal antibodies directed against lymphoid cells have been developed and investigated in preclinical studies and clinical trials [8]. Obinutuzumab (Gazyva™, GA-101, RO5072759, Roche) is a novel third generation monoclonal antibody which is distinct from rituximab [10]. The antibody is based on proprietary GlycoMAb® technology, which incorporates glycoengineered antibodies that specifically increase antibody-dependent cellular cytotoxicity (ADCC) and thereby increase immune-mediated target cell death, and is obtained by humanization of the parental B-Ly1 mouse antibody followed by a glycoengineering process developed by GlycArt Biotechnology (later Roche Glycart AG). Compared to rituximab, obinutuzumab treatment leads to 5–100 times greater induction of ADCC, as it binds with high affinity to the CD20 epitope, and also exhibits superior caspase-independent apoptosis induction [11, 12]. However, reduction in complement-dependent cytotoxicity (CDC) upon binding to CD20 was observed. Based on this data, obinutuzumab mAb is a promising therapeutic agent for CD20 positive B-cell lymphoid malignancies, including CLL.

In a phase I/IIa study, obinutuzumab was administered as a single agent to 24 patients, at doses from 50 to 2000 mg [13]. The antibody has shown a safety profile similar to that of rituximab and promising efficacy in patients with CLL and other $CD20^+$ malignant disease, for whom no therapy of higher priority was available [14]. The results of a large randomized phase III trial testing three first-line chemoimmunotherapy regimes, *i.e.* combined obinutuzumab and chlorambucil, combined rituximab and chlorambucil and chlorambucil monotherapy, in patients with comorbidities have been recently reported (CLL11) [15, 16]. In this trial 781 patients with previously untreated CLL and a score higher than 6 on the Cumulative Illness Rating Scale (CIRS) or an estimated creatinine clearance of 30–69 ml per minute were included. Treatment with obinutuzumab–chlorambucil, as compared with rituximab–chlorambucil, resulted in higher rates of complete response (20.7% *vs.* 7.0%) and molecular response. The primary end point was investigator-assessed PFS. Treatment with obinutuzumab–chlorambucil or rituximab–chlorambucil increased response rates and prolonged PFS as compared with chlorambucil monotherapy. Median PFS was 26.7 months with obinutuzumab–chlorambucil, 15.2 months for rituximab–chlorambucil, and 11.1 months for chlorambucil alone ($P < 0.001$). In addition, patients treated with obinutuzumab–chlorambucil had longer OS than those treated with chlorambucil alone ($P = 0.002$). However, infusion-related reactions and neutropenia were more common in patients treated with obinutuzumab–chlorambucil than with rituximab–chlorambucil. Obinutuzmab–chlorambucil treatment was associated with more grade 3–4 adverse events, mainly infusion-related reactions that occurred during the first infusion. Infusion-related reactions were noted in 20% of patients treated with obinutuzumab–chlorambucil and 4% of patients treated with rituximab–chlorambucil. In contrast, the risk of infection was similar in both arms. The U.S. Food and Drug Administration (FDA) approved obinutuzumab for use with chlorambucil in patients with previously untreated chronic lymphocytic leukemia [17].