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Antibody therapy alone and in combination with targeted drugs in chronic lymphocytic leukemia

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ABSTRACT

The development of non-chemotherapeutic agents, including monoclonal antibodies (mAbs) and other targeted drugs, makes chemotherapy-free treatment an attractive option for chronic lymphocytic leukemia (CLL). The classical mAb, rituximab, has been authorized for use in both first-line and second-line therapy for CLL. New mAbs directed against CD20, ofatumumab, and obinutuzumab (GA-101) have also been approved for the treatment of this disease. Recently, several new mAbs with potential benefits over the approved anti-CD20 antibodies have been developed for use in CLL. Anti-CD37, anti-CD19, and anti-CD40 mAbs are in early clinical trials and show promise in treating CLL. In addition, the combination of mAbs with B-cell receptor signaling pathway inhibitors and immunomodulatory drugs makes the chemotherapy-free option a reality today. Combinations of antibodies with targeted drugs like ibrutinib, idelalisib, or lenalidomide are expected to replace chemotherapy-based combinations for treating CLL in the near future. However, phase III trials should confirm the benefit of these new treatment strategies and establish their exact place in the therapeutic armamentarium for CLL.

1. Introduction

Despite significant progress in chronic lymphocytic leukemia (CLL) with fludarabine or chlorambucil-based immunochemotherapy, novel drugs are needed. Particularly for patients with del 17p and patients refractory to initial treatment, current therapeutic options are limited.

In recent years, anti-CD20 monoclonal antibodies (mAbs), rituximab, ofatumumab, and obinutuzumab have been approved for use in CLL therapy (Fig. 1, Table 1) [1]. In addition, several new mAbs have been developed to provide potential benefits over currently approved anti-CD20 antibodies, and are now in the process of making the transition to the clinic (Fig. 1, Table 2) [1,2]. Chimeric, humanized, and fully-human mAbs increase the potency and improve the tolerance of this class of therapeutic agents. Their antileukemic activity can further be enhanced by posttranscriptional modifications of the constant region, as well as by selection of glycosylated or defucosylated isoforms. The most promising newer mAbs are directed against CD37, CD19, and CD22. In addition, new chemotherapy-free treatment options have been introduced within clinical trials with the hope of improving responses, impacting survival, and ultimately curing CLL. The most promising are B-cell receptor (BCR) signaling pathway inhibitors, such as ibrutinib and idelalisib [3]. Moreover, immunomodulatory drugs (IMiDs), particularly lenalidomide, and BCL-2 inhibitors (ABT-199) are being explored in this disease.

2. Single anti-CD20 monoclonal antibodies in CLL

Rituximab is the first mAb to be used both in monotherapy and in combination with chemotherapy for the treatment of CLL. New generations of anti-CD20 mAbs have augmented antitumor activity by increasing complement-dependent cytotoxicity (CDC) or antibody dependent cellular cytotoxicity (ADCC), and increasing Fc-binding affinity for the low-affinity variants of the FcγRIIIa receptor on immune effector cells (Table 1) [4].

2.1. Rituximab

Rituximab (Mabthera, Rituxan, F. Hoffmann–La Roche, Basel, Switzerland) is a chimeric, human-mouse, anti-CD20 monoclonal antibody containing murine light- and heavy-chain variable-region sequences and human constant-region sequences [1]. The drug induces CDC and ADCC in addition to exerting a direct antiproliferative effect. In 1997, rituximab was the first mAb approved specifically for the treatment of patients with relapsed or refractory $CD20^+$ low-grade noHodgkin's lymphoma (NHL). Subsequently, the US Food and Drug Administration (FDA) and

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