Monoclonal Antibodies for Waldenström Macroglobulinemia

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KEYWORDS

• Mechanism of action • Treatment • Monoclonal antibodies
• Waldenström macroglobulinemia

KEY POINTS

- For the last 2 decades, anti-CD20 monoclonal antibodies have revolutionized the treatment of patients with B-cell lymphomas. These agents have shown efficacy when used as single agents and also have improved response and survival rates when added to chemotherapy.
- Monoclonal antibodies are safe and effective as well in patients with Waldenström macroglobulinemia (WM).
- The purpose of the present article is to briefly review the mechanism of action of monoclonal antibodies and to discuss current clinical data supporting their use in patients with WM.
- This review focuses on retrospective as well as clinical trials on the anti-CD20 antibodies rituximab, ofatumumab, and obinutuzumab, the anti-CD38 antibody daratumumab, and the anti-CXCR4 antibody ulocuplumab.

INTRODUCTION

The anti-CD20 monoclonal antibody rituximab is inarguably the most commonly used agent in patients with Waldenström macroglobulinemia (WM). In addition to its efficacy, the favorable toxicity profile of rituximab has allowed a broad use in WM. Rituximab is used alone or in combination with chemotherapy, such as cyclophosphamide and bendamustine, and proteasome inhibitors, such as bortezomib and carfilzomib.

New monoclonal antibodies have also been shown to be safe and effective in patients with WM, including the anti-CD20 monoclonal antibody ofatumumab, while

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obinutuzumab is currently being evaluated in clinical trials. Other targets for monoclonal antibody therapy include surface antigen CD38, of great success in patients with myeloma, and CXCR4, which is of interest given the presence of CXCR4 mutations in approximately 40% of patients with WM.

In this article, the authors review the mechanism of action of monoclonal antibodies, the available data supporting the use of these agents in WM, as well as ongoing clinical trials.

MECHANISMS OF ACTION OF MONOCLONAL ANTIBODIES

The fundamental basis of antibody-based therapy dates back to the original observations of antigen expression by tumor cells through serologic techniques in the 1960s. The definition of cell surface antigens that are expressed by human cancers has revealed a broad array of targets that are overexpressed, mutated, or selectively expressed compared with normal tissues.[1]

Monoclonal antibodies have a fixed effector cell binding (Fc) region and a variable region with affinity toward a specific antigen. Antibodies can mediate cytotoxicity toward tumor cells via both direct and indirect mechanisms based on the target. Direct cytotoxicity of tumor cells can occur through transmembrane signaling, and recruitment of effector cells (ie, natural killer [NK] cells, macrophages, neutrophils) that mediate antibody-dependent cell cytotoxicity and phagocytosis (ADCC and ADCP, respectively), and complement that mediates complement-dependent cytotoxicity (CDC). Indirect cytotoxicity can occur by interfering with both the interaction of a tumor cell with the microenvironment-generated survival signal and its binding to soluble factors that enhance tumor cell survival.[2]

ADCC, ADCP, and CDC are promoted when the variable region of the monoclonal antibody binds to its specific antigen, and the Fc region of the monoclonal antibody interacts with the Fc receptor of an effector cell (eg, NK cell or cytotoxic T cells) or macrophage.[3] Fc receptor crosslinking activates effector cells and mediates the release of enzymes and peptides, by the effector cell, that mediates target cell killing. Through a similar mechanism, Fc receptor crosslinking also activates monocytes and macrophages promoting ADCP.[4] The Fc portion of the monoclonal antibody may interact with C1q and initiate the classical pathway of complement activation, specifically through C3b and subsequent formation of the membrane attack complex, inducing cell killing through osmotic stress.[5] C3b also acts as an opsonizing molecule further inducing ADCC and ADCP. Most of tumor cells have an overexpression of growth receptors that give them intracellular signals for proliferation and survival. Monoclonal antibodies can diminish signaling through modulation of membrane-bound receptors, which in turn slows the rates of growth, activates intracellular apoptosis pathways, and/or sensitizes cells to cytotoxic agents.[2]

RITUXIMAB

Rituximab is a chimeric murine/human monoclonal antibody directed against the surface antigen CD20, which is expressed selectively on B-cells from the pre-B-cell stage until postgerminal center cells that differentiate to become plasma cells.[2] CD20 seems to be an excellent target for antibody-based therapy in mature B-cell malignancies, unlike other antigens, because it is not shed or internalized in resting normal B cells.[6] As with other immunoglobulin G1 (IgG1) antibodies used in clinical practice, rituximab mediates it effects by CDC, ADCC, and direct apoptosis. Rituximab was the first approved therapeutic monoclonal antibody for the treatment of cancer. CD20 is a