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A review of monoclonal antibody therapies in lymphoma

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ABSTRACT

Monoclonal antibodies (moAb) represent a novel way of delivering therapy through specific target antigens expressed on lymphoma cells and minimizes the collateral damage that is common with conventional chemotherapy. The paradigm of this approach is the targeting of CD20 by rituximab. Since its FDA approval in 1997, rituximab has become the standard of care in almost every line of therapy in most

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B-cell lymphomas. This review will briefly highlight some of the key rituximab trials while looking more closely at the evidence that is bringing other antibodies, including next generation anti-CD20 moAbs, and anti-CD30 moAbs, among others to the forefront of lymphoma therapy.

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1. Introduction

Antibodies play a role in the adaptive immune system by recognizing foreign antigens and triggering its elimination. The ability to specifically target a cognate antigen and the observations of antigenic expression by malignant cells led to the development of monoclonal antibodies (moAbs) which have become a standard of care in many lymphoid malignancies. These moAbs take advantage of tumor-related targets, including cell surface molecules, soluble effectors, and cell signaling machinery which may be selectively expressed, overexpressed, or mutated.

MoAbs are generally 'bare' antibodies which carry no effector 'payload' or antibody conjugates which consists of an antibody (or antibody fragment) covalently linked to cytotoxic compounds, like drugs, immunotoxins or radioisotopes. These home in on the target antigen to deliver the cytotoxic agent directly. In this review, we will discuss the most clinically relevant moABs used for the treatment of lymphoma.

2. CD20

The CD20 molecule is a transmembrane protein comprising a large loop and smaller loop that serves as a calcium channel initiating intracellular signals (Tedder and Engel, 1994). It is present during all stages of B-cell development except in pro-B cells and antibody-producing plasma cells. Monocytes, T-cells, non-lymphoid cells and stem cells are devoid of CD20 (Stashenko et al., 1980). The antigen is expressed at high density (90,000 molecules/cell) on 90% of all B-cell non-Hodgkin lymphomas (NHL), although in chronic lymphocytic leukemia (CLL), the antigen density is lower at approximately 8000–15,000 molecules/cell (Rossmann et al., 2001). CD20 is not internalized or down-modulated following antibody binding, thereby rendering it an excellent therapeutic target for most B-cell malignancies (Liu et al., 1987).

MoAbs to this molecule are classified as type I or type II. Type I antibodies translocate CD20 into detergent-insoluble fractions, or 'lipid rafts' which function as platforms for cell signaling and receptor trafficking (Beers et al., 2010; Cragg et al., 2003). They are most effective in activating complement directed cytotoxicity (CDC). Type II antibodies do not induce lipid rafts but efficiently induce antibody dependent cellular toxicity (ADCC) via the recruitment of cells displaying FC gamma receptor (FcγR) such as FcγRIII-expressing NK-cells and macrophages. They also play an important role in the induction direct cell death via apoptotic or non-apoptotic mechanisms (Fig. 1).

The first experimental treatment with monoclonal murine 'anti-idiotype antibody' was published in 1982. Miller et al. reported a dramatic anti-tumour response in a patient with lymphoma who had failed conventional chemotherapy (Miller et al., 1982). Rituximab was subsequently constructed as a chimeric antibody with a murine variable region derived from monoclonal anti-CD20 antibody IDEC-2B8, and a human IgG_1-kappa constant region. This construct ensured high affinity and strong ADCC, and was a thousand times more cytotoxic compared to its wholly murine equivalent (Liu et al., 1987). In vivo studies demonstrated this chimeric antibody to selectively deplete CD 20-positive B-cells in the lymph nodes and bone marrow of cynomolgus monkeys when administered weekly (Reff et al., 1994). Based on these pre-clinical studies, rituximab went into clinical testing under the name IDEC-C2B8.

2.1. Rituximab

Rituximab was the first moAb to be approved for treatment in cancer patients. It is a type I moAb which binds to the large loop of CD20 and induces the formation of a 'cap' comprising the CD20 molecule, intercellular adhesion molecule 1 (ICAM-1), moesin and the microtubule organizing center (MTOC) on the cell surface which causes polarization and enhanced interaction and destruction by NK cells.

2.1.1. Early trials with single-agent rituximab and combination chemotherapy

The first phase I trial, reported in 1994, involved 15 patients with relapsed low-grade B-cell NHL. Single intravenous IDEC-C2B8 administered at escalating doses resulted in tumor regression in half the patients, with the most notable outcome occurring at a dose of 500 mg/m^2. The mean half-life was 209 h and the clearance rate, 9.2 ml/h (Maloney et al., 1994). CD20+ B-cells remained depleted for up to 3 months (Berinstein et al., 1998). Minimal short-term side-effects were observed; therefore trials involving multiple administrations of rituximab as four weekly infusions were initiated, and demonstrated durable remissions in half the patients with indolent but chemotherapy-resistant lymphoma (McLaughlin et al., 1998).

Following these results, Coiffer et al. conducted a phase II trial of single-agent rituximab in more aggressive lymphomas including DLBCL, MCL and other intermediate to high grade lymphomas. They enrolled 54 patients who received 8 weekly infusions of 375 mg/m^2 or 500 mg/m^2. There was no significant difference in overall survival (OS) or overall response rate (ORR) between the two dosage groups, although slightly more infusional reactions manifesting as anaphylaxis, fevers, bronchospasm and hypotension were seen with the higher dose. These were mitigated by premedication with paracetamol, prednisone, diphenhydramine and intravenous fluids (Coiffier et al., 1998). Weekly rituximab was subsequently deemed most tolerable and optimally effective at 375 mg/m^2.

At present, rituximab monotherapy may be offered as first-line therapy for follicular lymphoma (FL) with low tumour burden as well as for maintenance therapy following completion of chemotherapy or high-dose therapy. Colombat et al. demonstrated sustainable responses in 50 untreated FL patients, achieving an ORR of 73% and bcl-2 PCR negativity in 62% at 12 months (Colombat et al., 2001). The PRIMA study was a multicenter study in previously untreated FL patients requiring systemic therapy that had 2 randomization steps. The first was between 3 different immunochemotherapy regimens, and the second between rituximab maintenance and observation in patients whom achieved at least a partial remission (PR) after induction. Rituximab maintenance of 375 mg/m^2 was given ($N = 505$) every 2 months for up to 2 years and resulted in a sustained CR (at 2 years) of 71.5% in the maintenance arm compared to 52.2% in the observation arm ($P = .0001$) with no difference in OS observed (Salles et al., 2011).

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