Review Article

An update on newer monoclonal antibodies in lymphoma therapy

ABSTRACT

In 2014, an estimated 9.4% of all new cancers in the US were accounted to hematological cancers. Most of these cancers have a B-cell origin and on the cell surface express antigen CD20-known to restrict B-cells. Considering the intrinsic immune status of the patients receiving chemotherapy, monoclonal antibodies (mAbs) are designed to provide active or passive immunotherapy. Clinical success of rituximab-anti-CD20 mAb in the treatment of lymphoma has led to the development of newer generations of mAb to increase the anti-tumor activity. Hence, recent advances in lymphoma therapy are being built on the conventional prototype of anti-CD20 mAb-rituximab. Our review is an update on the advances in lymphoma therapy using mAb against CD20 including the second generation-ofatumumab, veltuzumab, ocrelizumab, and the third-generation mAbs-ocaratuzumab and obinutuzumab.

Key words: CD20 monoclonal antibody; lymphoma therapy; recent advances

Introduction

Various monoclonal antibodies (mAbs) target different epitopes namely as CD19, CD20, CD22, CD40, CD52, and CCR4 that are present on the lymphoma surface.[1] Encoded by the gene MS4A1 gene located on the chromosome 11q12.2, CD20 molecule is a 297 amino acid phosphoprotein with four transmembrane domains.[2] It plays a crucial role in B-cell development and has been a reliable biomarker for immunotherapies targeting B-cell derived diseases.[3] The malignant cells have known to surpass the initial immune-surveillance and gradually develop resistance to medications through polymorphism of the target Fc receptors.

After its approval in 1997, rituximab a mAb against CD20 is being effectively used for the follicular lymphoma (FL) – B-cell cancer. Consequently, many studies conducted showed significant improvement upon addition of rituximab to initial chemotherapeutic regimens for non-Hodgkin's lymphoma (NHL) namely-diffuse large B-cell lymphoma and FL.[4-9] Since this success with rituximab, newer, and enhanced mAbs were developed to be used in place of rituximab or in diseases refractory to it. The gradual expansion of mAbs to unblock the immune checkpoints by targeting program death ligand-1 as well as the concept of bispecific T cell engagers has opened newer options in lymphoma chemotherapy. Few of the novel mAb are being used in the present clinical practice or have the potential to revolutionize lymphoma treatment options in the future [Table 1].

Subhashini Archana Kadavakolan, Sonam Puri[1], Sandeep Sahay[2], Jitesh Joshi[3]

Department of Internal Medicine, Sir Seewoosagur Ramgoolam Medical College, University of Mauritius, Mauritius, [1]Department of Internal Medicine, University of Connecticut, CT, [2]Department of Medicine, Baylor College of Medicine, Houston, TX, [3]Department of Internal Medicine, Arkansas Cancer Institute, Little Rock, AR, USA

Address for correspondence: Dr. Sandeep Sahay, Department of Internal Medicine, Baylor College of Medicine, 6620 Main St, 11B.12, Houston, TX, USA.
E-mail: sandeep.sahay@bcm.edu

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Table 1: Anti-CD20 monoclonal antibodies currently approved or being investigated in clinical trials for B-cell lymphomas

mAb	Type of CD20 antibody*	Generation**	Structure	Mechanism of action (ADCC/CDC/PCD)	Comparison to rituximab	References
Rituximab	I	1	IgG1 human mouse chimeric	++/++/+	-	[7]
Ofatumumab	I	I1	Fully human IgG1	+++/++++/++	Superior CDC, decreased PCD	[19]
Veltuzumab	I	II	Humanized IgG1	++/++/+	Longer "off-rate," more avid CD20 binding can be given subcutaneously	[21]
Ocrelizumab	I	II	Humanized fusion IgG1	+++/+/+	Enhanced binding to FCγRIIa	[22]
Obinutuzumab (GA101)	II	III	Murine bly-I derived humanized IgG1	++++/−/++++	Superior PCD/ADCC; no CDC	[23]
BM-ca	I/II		Humanized IgG	++++/+++/++++	Different epitope, superior ACDD, CDC and PCD	[34-36]
Alemtuzumab	NA (target CD52)		Humanized IgG1	++++/+++/+++	Anti CD52, increased toxicities	[30,31]

*Type of mAb - compared to a Type I mAb, a Type II mAb does not evoke a complement response, however, may have increased PCD/ADCC, **Generations of mAB - First generation - originally approved mAB against a clinically validated target, Second generation - follow-up antibodies with improved variable domains that target the same epitopes with higher or lower affinity, or have different antibody formats, e.g., pegylation and Fc-fusion proteins, Third generation - target different epitopes or trigger other mechanisms of action. ADCC - Antibody dependent cellular cytotoxicity; CDC - Complement dependent cytotoxicity; CLL - Chronic lymphocytic leukemia; mAB - Monoclonal antibody; PCD - Programmed cell death; NA - Not available; ++++ /+++/++/+ - It is the relative strength of the antibody towards the mechanism of action in comparison to rituximab

First-generation CD20 Monoclonal Antibody

Rituximab

It is a first generation chimeric mAb targeting CD20 on the B-cell surface. Even though the primary mechanism of cell-killing for rituximab is complement dependent cytotoxicity (CDC), it can also induce antibody-dependent cell mediated cytotoxicity (ADCC) and direct cellular effects that eventually leads to apoptosis of lymphoma cells.[10] It has boosted the response rates and progress-free survival in first-line as well as refractory cases and significantly improved the overall survival in lymphoma patients.[7,11,12] Various studies conducted showed that approximately 60% of previously untreated lymphoma patients and 40–50% of those with refractory/relapsed disease respond to rituximab monotherapy.[13] Remission periods with maintenance therapy are significantly prolonged in patients with FL.[4,5]

There are some lymphoid cells (about 10%) that are resistant to CDC because of lower levels of complement activation or decreased cytotoxicity of activated complements.[14] Hence, novel methods were developed to increase the antitumor activity and Fc binding for the low – affinity FcγRIIIa receptor (CD 16) on immune effector cells.[15]

Second-generation CD20 Monoclonal Antibody

Ofatumumab (HuMax-CD20; Arzerra)

It is a human Type I anti-CD20 IgG1 kappa mAb that binds loop domains of the antigen at an epitope different from that of rituximab.[14,16] It is Food and Drug Administration-approved, as combination chemotherapy for treatment of chronic lymphocytic leukemia (CLL) in patients with contraindication to fludarabine therapy or resistance to fludarabine and/or alemtuzumab therapy.[17] Furthermore, the combination of ofatumumab with pentostatin and cyclophosphamide had better treatment outcomes compared to the older fludarabine, cyclophosphamide and rituximab regimen.[18] An international phase-II trial contrasted the present chemoimmunotherapy regimen (CHOP) with combined treatment with ofatumumab (O-CHOP) for FL therapy.[19] In 59-patients tested, it had an overall response rate (ORR) of 90–100% with significant clinical improvement in treatment outcomes. Common adverse effects encountered with ofatumumab include infections, rash, urticaria, pruritis, neutropenia, anemia, and thrombocytopenia.[19]

Veltuzumab (IMMU-106, hA20)

It is Ig1 humanized mAb structurally different from rituximab by only one amino acid targeting the CD20 with therapeutic effects greater than that of rituximab mainly due to its higher CDC and longer retention on the cellular surfaces.[20] This conclusion was drawn through extensive Phase I/II studies carried out using veltuzumab on patients with FL, who were initially treated with rituximab. In these 82 patients with relapsed/refractory B-cell NHL, veltuzumab infusions were well-tolerated with only infusion-reactions.[21]

Ocrelizumab (PRO70769)

It is a Type I second generation anti CD20-mAb derived with a different prototype of human Fc that binds firmly to low affinity variants of FcγRIIIa receptor (CD16). It uses a separate complement determining region from that of rituximab with an increased ADCC and lower CDC activity. To oversee the

safety profiles of ocrelizumab, a brief study with relapsed/refractory cases of Follicular lymphoma (FLL) on monotherapy were analyzed. This showed results comparable to that of rituximab monotherapy with an ORR of 38%.[22] Adverse effects include infusion reaction, nasopharyngitis, asthenia, lymphopenia, and infections.[22]

Third-generation Monoclonal Antibody

The three third generation humanized CD20 mAbs are AME-133 v, PRO131921, and GA101 that have been engineered Fc region to increase their binding affinity for the FcγRIIIa receptor.

Obinutuzumab (GA101)

It is the first, third-generation Type II glycoengineered CD20 mAb to have gone into Phase II/III randomized clinical trial. The aim was to compare its safety and efficacy with rituximab in relapsed indolent lymphomas.[23] Obinutuzumab has an enhanced direct cell death via a nonapoptotic, caspase-independent mechanism that is independent to Fcγ-receptors. In patients with Fc-dependent tumor mechanisms or tumor resistance to induction, chemotherapy obinutuzumab may be effective.[1] Sehn *et al*. carried this study in 175 patients and found that obinutuzumab had a higher ORR than rituximab (44.6% vs. 33.3%). However, this difference was not converted into improved progression-free survival (PFS).[23]

Ocaratuzumab

Previously referred to as LY2469298 or AME-133 v, Ocaratuzumab is a humanized IgG1 Fc-engineered mAb against CD20 with pharmacokinetics similar to rituximab.[24] FcγRIIIa (CD16) genotyped patients can have a single-gene polymorphism (SNP) on immune mediator cells namely NK cells and macrophages and can activate ADCC and a higher affinity to its ligand (CD20) than rituximab.[24] Since 80% of patients with diagnosed FL are FcγRIIIa F-carrier, an opportunity exists to improve the interaction between CD16 and CD20.[24]

Studies conducted by Cartron *et al*., Weng and Levy and Swiss Clinical Cancer Research showed that rituximab monotherapy is effective in patients with FL and less-effective in F-carriers.[25-27] Bowles *et al*.,[37] conducted preclinical studies *in vitro* showed CD20 enhancing ADCC is more effective than rituximab in activating NK cells. Relapsed FL patients with FcγRIIIa variant treated with rituximab previously, upon receiving treatment with AME-133 v were to found to have an ORR of 50%, according to Tobinai *et al*.[28] In the Phase I trial conducted, ocaratuzumab was safe and well-tolerated in the tested dose range.[24] The most common adverse effects seen in Phase I study were an infusion related reaction, nasopharyngitis, asthenia, lymphopenia, and infection.[14]

PRO131921

A recombinant humanized anti-CD20 mAb that has through various preclinical studies has shown to have greater CDC and ADCC activity than rituximab.[16] Casulo *et al*. carried out a Phase I study to determine the maximum-tolerated dose and the pharmacokinetics of PRO131921.[29] Infusion reactions, joint pain, and fatigue were significant in few of these patients and led to dose-limiting toxicity.[29]

Others

Alemtuzumab

Alemtuzumab (Campath®) is a recombinant mAb against CD 52-a cell-surface protein found on most of the normal and malignant B and T lymphocytes. It is a DNA-derived humanized IgG1 kappa mAb with a significant use in patients with genetically high-risk treatment-resistant CLL.[30] The subgroups that were hypothesized to benefit the most included patients with 17p deletion, bone marrow infiltration and refractory autoimmune cytopenia.[30,31] It received approval in the US for the first time in 2001 and was essentially reserved for patients with CLL who had received fludarabine therapy yet had progressive disease.[30,32] In 2007, it demonstrated an improved PFS over single agent chlorambucil as the first line treatment and received complete approval.[32,33]

The high incidence of Grade 3/4 adverse events including neutropenia (up to 64%) and infusion reactions (up to 35%) has limited the use of alemtuzumab.[33] Studies are being conducted to improve the safety profile of the drug by reducing the dose without affecting its anti-tumor property.[31] In addition, alemtuzumab has been found to be ineffective when used as a single agent, particularly in nodal disease. Hence, combination chemotherapy with other antibodies or with steroids is more effective and less toxic. mAb namely rituximab and steroids – glucocorticoids have been more potent and act in a TP53-independent fashion.[30] Subcutaneous injection has also shown to reduce its serious adverse effects further.[30]

BM-ca

A novel humanized anti-CD20 antibody similar to ofatumumab with regards to its potent effect against rituximab-sensitive SU-DHL-4 cells and rituximab-resistant RC-K8 cells.[34] BM-ca binds to a unique epitope and possesses properties of both Type I and II antibodies. Kobayashi *et al*., study showed that ADCC and anti-proliferative effect of BM-ca was more potent than other anti-CD20 mAb.[34] Vega *et al*. conducted a study

and hypothesized that BM-ca may be superior to rituximab in inhibiting the pathways (NF-kB and p38 MAPK) and are partly responsible for cell growth and response to cytotoxic therapy.[35] This is accounted to the fact that BM-ca binds to a different epitope than rituximab or ofatumumab that results in its higher affinity and exhibits different molecular signaling.[36] To further know about the complete potential of BM-ca, ongoing clinical trials are being conducted to test its therapeutic activity.

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Conflicts of interest

There are no conflicts of interest.

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