RITUXIMAB AND OTHER NEW ANTI-CD20 MABS FOR NON-HODGKIN'S LYMPHOMA TREATMENT

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ABSTRACT

Non-Hodgkin's lymphomas (NHLs) are a heterogeneous group of different haematological cancers with a wide range of aggressiveness. NHLs represent >80% of lymphomas and the majority of NHLs involve B cells. CD20 represents a good target for NHL immunotherapy because it is largely expressed on B cell NHL and not on B cell precursors and plasma cells. The anti-CD20 monoclonal antibody (mAb) rituximab (RTX) was the first antibody approved by the FDA for lymphoma therapy and has revolutionised B cell lymphoma treatment. Several clinical trials have demonstrated the high efficacy of RTX, resulting in a significant improvement in overall response rates and in NHL patient survival. However, RTX, both as a single agent and in combination with chemotherapy, induces several side-effects and resistance mechanisms. Remarkable efforts have been made to improve RTX efficacy, including conjugation to an active moiety (radionuclide, toxin, enzyme, or drug) and the development of new anti-CD20 mAbs. This review summarises the characteristics of RTX and other anti-CD20 mAbs for NHL treatment; the results of the main clinical trials are reported.

Keywords: Non-Hodgkin's lymphoma, CD20, rituximab, immunotherapy, monoclonal antibodies.

INTRODUCTION

Lymphoma is the general term used to define blood cancers that develop mainly in the lymphatic system. Lymphoma is not a single type of cancer but a group of related tumours. There are approximately 30 different types of lymphoma that are divided into two main categories: Hodgkin's lymphoma (HL; or Hodgkin's disease) and non-Hodgkin's lymphomas (NHLs), which are the most common (approximately 80%). HL is a specific type of cancer characterised by the presence of Reed-Sternberg cells in the cancerous tissue; these are large and multinucleated cells, usually derived from B lymphocytes, and their presence is required for HL diagnosis. NHLs are a heterogeneous group of different haematological cell malignancies with a wide range of aggressiveness; >80% of NHLs are B cell lymphomas. NHLs usually occur in adults and can be further classified by growth rate; fast-growing subtypes are defined as aggressive, slow-growing NHLs are defined as indolent. The two most common forms of NHL are diffuse large B cell lymphoma (DLBCL), an aggressive type accounting for 30% of NHL cases, and follicular lymphoma (FL), an indolent type that accounts for 25-30% of cases.[1] NHLs are often cured by combined therapies including chemotherapy and radiotherapy and, rarely, surgery and transplants (autologous or allogeneic). However, indolent lymphomas, when in advanced clinical stages, are incurable in most cases. The classic chemotherapeutic approach is CHOP therapy (cyclophosphamide, doxorubicin, vincristine, and prednisone). Chemotherapy's efficiency is limited by non-specific toxicity to normal tissues and by the development of resistance to therapeutic agents. Moreover, a percentage of patients treated

with chemotherapy and radiotherapy develop secondary malignancies due to the lowering of immunosurveillance induced by conventional antiblastic agents and radiation and to the therapies' transformative actions. Approximately 50% of NHL patients either relapse or become refractory to conventional therapy.[2] For these patients with poor outcomes, the use of new therapeutic strategies, such as immunotherapy, is required.

The use of monoclonal antibodies (mAbs) for anti-cancer therapy has been widely explored since mAbs were initially developed by Kohler and Milstein. The specificity of immunotherapy is based upon characteristics (surface antigens) that are completely independent from the parameters that allow for the differential toxicity of chemotherapy and radiotherapy. This specificity results in a non-superimposition of side-effects and unimpaired cytotoxicity towards cell clones resistant to chemotherapy and radiotherapy. The choice of the target antigen for antibody-based therapy should take into account important factors; the antigen should be easily accessible, highly expressed on unwanted cells and possibly restricted to these cells, and the antigen should not be shed into the blood. Because most lymphomas have vascular accessibility, they are a favourable setting for this treatment modality. Furthermore, haematological cells represent the ideal target for antibody-based immunotherapy due to the presence of clusters of differentiation (CD) on their surface. CD are well-characterised molecules against which a multitude of mAbs are available. In fact, the first successful use of mAbs for cancer treatment was demonstrated in lymphoma, and mAbs are now employed to benefit thousands of patients with NHL.[3,4]

CD20 ANTIGEN AS A TARGET FOR IMMUNOTHERAPY

CD20 (B1) is a highly expressed transmembrane surface antigen with a molecular weight of approximately 35 kDa. The function of CD20 is not completely understood; however, this antigen seems to be involved in the regulation of B cell growth and differentiation via intracellular signalling or by functioning as a calcium channel in association with antigen stimulation of the B cell receptor. The CD20 molecule has been studied extensively as an appealing target for mAb-based immunotherapy due to several favourable properties: 1) CD20 is expressed on nearly 90% of B cell NHLs and on normal B cells, but neither on B cell precursors and plasma cells nor on other tissues; 2) the antigen is highly expressed on the cell surface; 3) CD20 is not normally shed from the cell; and 4) CD20 is internalised after antibody binding.[5] Anti-CD20 mAbs cause cell death through different pathways. After binding to the antigen, these mAbs can activate complement-dependent cytotoxicity (CDC) and antibody-dependent cell-mediated cytotoxicity (ADCC), which are mediated by the Fcγ receptors on effector cells, such as granulocytes, macrophages, and natural killer (NK) cells. Moreover, some antibodies can directly kill the target cell by triggering the apoptotic pathway, thus having a direct cytotoxic effect.[6] These effects make anti-CD20 antibodies essential tools in lymphoma therapy, both alone and in combination with chemotherapy.[7]

Clinically active anti-CD20 mAbs can be divided into two groups based on the triggered cell death pathway. Type I antibodies (rituximab [RTX], ofatumumab [OFA], veltuzumab, ocrelizumab, ocaratuzumab, and rhumAb v114) induce CD20 translocation into lipid rafts with consequent ADCC, CDC, and weak apoptosis. Type II mAbs (tositumomab and obinutuzumab) do not redistribute CD20 on the cell surface and induce strong ADCC and apoptosis but weak CDC.[8]

RTX

RTX, a mouse-human chimeric mAb, was the first anti-CD20 mAb showing clinical effectiveness for lymphoma patients. This mAb is composed of a human immunoglobulin G1 (IgG1) Fc region and human kappa constant regions with variable regions derived from the 2B8 murine Ig.[8] RTX was the first antibody approved by the FDA for use in cases of relapsed or indolent NHL. The primary cell death mechanism induced by RTX is CDC, but RTX can also lead to ADCC and apoptosis. In addition, RTX is able to raise the T cell response against malignant clones.[9] RTX treatment improves response rates in several types of B cell NHL, including DLBCL, FL, and mantle cell lymphoma. The treatment has also resulted in a significant increase of progression-free survival (PFS) and overall survival (OS), unlike the combination of different chemotherapies.[10] RTX has been investigated both as a single agent and in association with standard chemotherapy. The combination of RTX with CHOP treatment has been evaluated in patients with

aggressive NHL (MabThera International Trial); 824 patients with DLBCL were randomly selected to receive six cycles of either CHOP + RTX (R-CHOP) or standard CHOP alone. After a 3-year follow-up period, R-CHOP-treated patients had a 79% improved rate of PFS versus 59% of those treated with CHOP alone. The 3-year OS rates were 93% (R-CHOP) versus 84% (CHOP).[11]

In indolent NHL, such as FL, RTX has been investigated both as a single agent and combined with standard chemotherapy.[12] First, RTX was investigated as a single agent in a 166-patient clinical trial; the response rate was 48%, which was similar to chemotherapy alone.[13] In a larger Phase III trial, 428 patients with advanced FL were randomly treated with either R-CHOP or CHOP alone. Significant increases in OS rates (96% for R-CHOP versus 90% for CHOP alone) and estimated survival rates at 2 years (95% for R-CHOP versus 90% for CHOP alone) were reported.[14]

RTX as single agent or in combination with chemotherapy has revolutionised lymphoma therapy. Unfortunately, RTX is not effective in all cases, and some patients experience severe side-effects; the main side-effects reported for RTX treatment are listed in Table 1. The frequency of side-effects may vary among the first and subsequent infusions (for a complete list of these rates see the web page http://www.rxlist.com/rituxan-side-effects-drug-center.htm). In addition, acquired resistance to RTX is another observed clinical problem. The mechanism of RTX resistance is not completely clear. Alterations in host immunologic factors could be implicated in tumour resistance to RTX, such as: 1) CDC resistance due to the alteration of expression of complement-regulatory proteins (CD46, CD55, and CD59) on tumour cells; 2) ADCC resistance due to changes in the lipid raft causing failed recognition of the CD20/antibody complex by effector cells and FcγRIIIa polymorphisms; 3) selection of apoptosis resistant clones as a consequence of repeated exposure to RTX; and 4) selection of CD20-negative tumour clones.[15] For these reasons, different strategies have been explored to obtain higher response rates and remission duration for mAb-based immunotherapy. For example, mAb efficacy can be augmented by conjugation to an active moiety, such as radionuclide (radioimmunoconjugate),[16] toxin/enzyme or drug (immunotoxin).[17-19]

Table 1: Main adverse effects of rituximab treatment.

Side-Effects	Symptoms
Infusion reactions	Headache, breathing difficulty, urticaria, angioedema, chills, and fever. Rapid onset respiratory failure, heart attack.
Skin and mouth reactions	Painful sores or ulcers on skin, lips, or in mouth; blisters, peeling skin, pustules. Acute whole-body allergic reaction.
Progressive multifocal leukoencephalopathy (infection caused by John Cunningham virus)	Death or severe disability.
Reactivation of hepatitis B virus	Serious liver problems and death.
Tumour lysis syndrome	Kidney failure, altered heart rhythm.
Cytopaenias and hypogammaglobulinaemia	Late-onset neutropaenia, leukopaenia, thrombocytopaenia, lymphopaenia, anaemia, hypogammaglobulinaemia.
Others	Bowel obstruction and perforation.

RTX-Containing Radioimmunoconjugates

Immunoconjugate toxicity is based on the involvement of different pathways that only minimally depend on ADCC and CDC. The response rates observed in Phase I/II trials have often been higher than those reported for unconjugated antibodies and conventional drugs. Radioimmunoconjugates can kill not only the target cells but also surrounding cells. This can represent an advantage because tumour cells not expressing the antigen or expressing a mutated antigen can also be eliminated, but it represents also a disadvantage due to the non-specific toxicity towards normal cells near the tumour. Two radioimmunoconjugates, ^{90}Y-ibritumomab tiuxetan and ^{131}I-tositumomab, have been approved by the FDA to treat relapsed/refractory FL and low-grade lymphomas. Compared to RTX, in clinical trials radioimmunotherapy (RIT) increased complete responses (CR) in low and intermediate-grade refractory NHLs, while the addition of RIT after chemotherapy in maintenance therapy produced effects comparable to or better than RTX. Several Phase III clinical trials have been conducted with these two radioimmunoconjugates and many others are still ongoing in lymphoma patients.[20] The most common side-effects are hypothyroidism and marrow suppression, but there is also a risk of acute myeloid leukaemia and myelodysplastic syndrome. In other experimental approaches, RTX has been conjugated to a toxic moiety to obtain immunotoxins. For this purpose, plant toxins[21] and chemotherapy agents[22] have been utilised.

SECOND-GENERATION ANTI-CD20 MABS

The second generation of anti-CD20 mAbs (OFA, veltuzumab, and ocrelizumab; see Table 2) are humanised or fully human molecules developed with the purpose of reducing immunogenicity. These mAbs have often been tested in contemporary clinical trials on NHL and chronic lymphocytic leukaemia (CLL) patients; better results were reported in the latter patients. As a consequence, in some cases, second-generation anti-CD20 mAbs have been approved by FDA for CLL therapy.

OFA (Arzerra, HuMax-2F2) is a completely human Type I anti-CD20 mAb that binds a different epitope than that recognised by RTX. OFA targets CD20 with greater avidity than RTX, causing similar ADCC but stronger CDC in both RTX-sensitive and RTX-resistant cells.[23,24] The first Phase I/II clinical trial for OFA conducted with 40 relapsed/refractory FL patients showed an overall response rate (ORR) ranging from 20-63%.[25]

Table 2: Cytotoxic mechanisms of RTX and other new anti-CD20 mAbs.

	Cytotoxic Mechanisms Compared To RTX	Clinical Trials	FDA Approval
First Generation			
RTX	CDC, ADCC, apoptosis	I, I/II, II, III, IV	Yes
Second Generation			
Ofatumumab	↑CDC	I/II, II, and III	In development
Veltuzumab	↑CDC	I/II	In development
Ocrelizumab	↑ADCC, ↓CDC	I/II	In development
Third Generation			
RhumAb v114	↑affinity to FcγRIIIa (↑ADCC)	I	Terminated
Ocaratuzumab	↑affinity to FcγRIIIa (↑ADCC), ↑CDC	I	In development
Obinutuzumab	↑affinity to FcγRIIIa (↑ADCC)	I, I/II, II, III, and IV	Yes
TRU-015	Apoptosis	I/II	Terminated
EMAB-6	↑affinity to FcγRIIIa (↑ADCC)	I and I/II	In development

RTX: rituximab; mAbs: monoclonal antibodies; CDC: complement-dependent cytotoxicity; ADCC: antibody-dependent cell-mediated cytotoxicity.

In a further Phase II study, OFA was evaluated in 116 patients with RTX-refractory FL, but only a limited response was reported with an ORR of approximately 11% and a median PFS of 5.8 months.[26] When OFA was used in combination with CHOP in untreated advanced-stage FL patients, OFA showed greater efficacy (ORR of 90%).[27] The most common side-effects reported with OFA were neutropaenia, thrombocytopaenia, and anaemia. In response to the good results reported in Phase III clinical trials in CLL patients, OFA was approved by the FDA in 2009 for fludarabine and alemtuzumab-refractory CLL treatment.

Veltuzumab (IMMU-106, hA20) is a Type 1 humanised anti-CD20 mAb with a single amino acid difference in the CDR3 variable region of the heavy chain compared to RTX. This substitution causes a significant improvement in CDC and the off-rate reduction in different preclinical models.[28] Veltuzumab was evaluated in a Phase I/II trial in 82 patients with relapsed/refractory NHL (55 with FL) that showed high tolerance to weekly infusions. The FL patients showed an ORR of 44% (CR/CR unconfirmed rate 27%) despite the failure of previous RTX treatment. Interestingly, objective responses were obtained for marginal zone lymphoma and DLBCL with ORRs of 83% and 43%, respectively.[29] The most commonly observed adverse events included transient infusion-related reactions.

Ocrelizumab (PRO70769, rhuH27) is a Type 1 humanised anti-CD20 mAb with different amino acids at several positions within CDRs of variable heavy and light chains compared to RTX. These differences allow ocrelizumab to bind to a different but overlapping epitope. In contrast to RTX and most Type 1 mAbs, ocrelizumab causes stronger ADCC and lower CDC. Ocrelizumab's efficacy was evaluated in a Phase I/II trial in FL patients previously treated with RTX. The ORR was 38% with a median PFS of 11.4 months; Grade 3/4 toxicity was observed in 9% of patients. In many cases, infusion-related reactions were reported (74%).[30]

THIRD-GENERATION ANTI-CD20 MABS

The third-generation anti-CD20 mAbs (rhumAb v114, ocaratuzumab, obinutuzumab, TRU-015, EMAB-6; see Table 2) have humanised CDR and engineered Fc regions, resulting in enhanced binding affinity for the FcγRIIIa receptor expressed on NK cells with a consequent augmentation of ADCC. RhumAb v114 (PRO131921) is a Type 1 humanised anti-CD20 mAb. This mAb is derived from ocrelizumab and has better binding affinity for FcγRIIIa than RTX. A Phase I trial was conducted with dose escalation in 24 patients with relapsed/refractory indolent lymphoma previously treated with RTX. The maximum tolerated dose was not determined but the study showed a correlation between drug exposure and tumour reduction. A partial response (PR) was observed in 6 out of 22 evaluable patients. Infusion-related reactions were the most frequently reported side-effects. In addition, three patients had temporary neutropaenia.[31]

Ocaratuzumab (LY2469298, AME-133v) is an anti-CD20 mAb used to treat NHL and other B cell malignancies. Ocaratuzumab is a Type 1 humanised IgG1 mAb that binds CD20 more efficiently than RTX. This mAb has been optimised by protein engineering to improve both CDC and ADCC with respect to RTX. In a Phase I study, ten patients with relapsed/refractory FL received the mAb with dose escalation; three patients had a CR, one patient had an unconfirmed response, and one patient had a PR.[32] Another Phase I clinical trial with ocaratuzumab in 23 patients previously treated with FL showed that ocaratuzumab is well tolerated. A CR was observed in 2 out of the 23 patients, and the median PFS was 25.4 weeks. The main side-effects were chills and fatigue and transient tumour lysis syndrome; one patient showed a dose-limiting toxicity.[33]

Obinutuzumab (GA101, RO5072759) is a Type II humanised anti-CD20 mAb. Compared to RTX, obinutuzumab recognises CD20 antigen on a larger surface area, binding a different epitope. The Fc region has been engineered with a consequent higher ADCC compared to that of RTX. Obinutuzumab induces cell death more efficiently than other anti-CD20 mAbs. In a Phase I study, obinutuzumab was administered to 22 patients with relapsed NHL or CLL that had received a median of 4 prior regimens; 86% of the patients had received at least 1 RTX treatment. No dose-limiting or unexpected adverse effects were observed. At the end of induction, 5 patients achieved PR and 12 patients had stable disease; 8 patients received maintenance therapy, and the ORR was 32% (6 PR/1 CR). Injection reactions were the most common adverse event, followed by infection, neutropaenia, headache, and nausea.[34]

Obinutuzumab is currently being evaluated in several clinical trials, one of which (NCT00576758) has recently been completed. In this Phase II trial, 175 patients with relapsed indolent NHL were randomised to receive either obinutuzumab or RTX given as four weekly infusions. Many other clinical trials with this mAb are ongoing or recruiting patients, and it has been approved by FDA for the treatment of CLL (Phase IV clinical trial: NCT01868893).

TRU-015 (CytoxB20G) consists of a single-chain Fv specific for CD20 linked to the human IgG1 hinge domain and the heavy-chain constant region domains CH2 and CH3. TRU-015 has shown pro-apoptotic activity against B lymphoma cells.[35] Clinical development efforts for the treatment of lymphoma and inflammatory disease are ongoing. The first Phase I/II dose escalation study (NCT00521638) of TRU-015 in subjects with relapsed or refractory B cell NHL was recently terminated, but no data are available. EMAB-6 (LFB-R603) is a novel chimeric anti-CD20 mAb that is able to induce similar apoptosis and CDC but higher ADCC compared to RTX.[36] A Phase I clinical trial (NCT01098188) involving 33 CLL patients was completed in 2012, and other clinical trials for the treatment of NHL, CLL, and other B cell lymphomas are ongoing. To date, the clinical results have not been made available. Some other Phase I/II trials are ongoing.

CONCLUSIONS

The above summarised clinical trials show the efficacy of RTX and the clinical potential of the other new anti-CD20 mAbs in NHL therapy. The availability of a panel of new human mAbs will surely lead to a reduction in the side-effects associated with RTX. Moreover, the clinical efficacy of these new mAbs has not yet been completely explored because the results of several clinical trials have not been disclosed and many trials are ongoing. In the near future, it will be possible to match the more effective and tolerated agents to a single lymphoma subtype to obtain personalised therapies for each patient.

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