Journal of BUON **16:** 9-15, 2011

REVIEW ARTICLE

Current standards and future strategies in immunochemotherapy of non-Hodgkin's lymphoma

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Summary

The therapeutic options for B-cell non-Hodgkin's lymphoma (NHL) have dramatically expanded with the advent of immune-based treatments. The monoclonal antibody anti-CD20 rituximab represents the best example of these advances and has quickly become incorporated into the therapeutic armamentarium for this hematological disease. In addition, other antibodies are eventually becoming part of treatment approaches to NHL. Furthermore, the role of therapeutic vaccines continues to be an important ongoing research question. Despite this success, several questions on how to optimize the use of monoclonal antibodies in NHL remain open since the best administration schedules, as well as the optimal duration of immunotherapy still have to be determined. Finally the development of resistance to treatment remains the main limit of this innovative approach, necessitating the development of strategies to circumvent resistance itself. This review will summarize the state of the art of antibody-based immunotherapy of NHL and discuss prospective approaches to improve the benefit of these treatments in patients.

Key words: apoptosis, chemotherapy, lymphoma, monoclonal antibodies, rituximab

Introduction

NHL is the most common form of hematological malignancy in adults. Although extremely chemosensitive, most of NHL are incurable with current therapeutic approaches. Additionally, a fraction of the patients, especially those with poor risk features, experience refractory or relapsed disease with a dismal outcome.

The potential importance and effectiveness of the immune system in killing lymphoma cells has always kept promise. The graft-versus-lymphoma effect observed in patients undergoing allogeneic stem cell transplantation is well documented and corroborated this hypothesis [1]. However, the high treatment-related toxicity of this type of immunotherapy has limited its application to a minority of the patients. *Vice versa*, monoclonal antibodies (mAbs), such as rituximab, have found broad applications in the treatment of NHL (and in other conditions), truly revolutionizing the field of lymphoma therapy.

In this review we will focus on the use of the anti-CD20 mAb rituximab, by summarizing and updating the data on the clinical issues associated with its use. Additionally, we will review the most innovative antibody-based therapeutic strategies for NHL.

What is rituximab and how does it work?

Cell-surface proteins, such as CD19, CD20, and CD22, are highly expressed on B-cell lymphomas and represent key targets for treatment. Perhaps the most important advance in the treatment of NHL is the approval by the US FDA in 1991 of rituximab for the treatment of relapsed or refractory, or CD20+ follicular (FL) NHL. Rituximab is a chimeric (mouse and human) anti-CD20 monoclonal antibody, derived from the mouse mAb 2B8. It is directed against the B-cell antigen CD20. Significantly, rituximab is cytotoxic to both normal and malignant CD20+ B-lymphocytes [2,3].

The cell surface protein CD20 is a 33-kDa protein expressed by mature B-cells and by most malignant B-cells, but not by pre-B cells or by differentiated plasma cells [2,4-6]. *In vitro* studies have revealed that CD20,

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Received 25-10-2010; Accepted 16-11-2010

through its ability to associate with the B-cell receptor acts as an ion channel [7], in particular as a calcium channel [8,9] that also activates intracellular signaling. Finally CD20 is not shed, modulated, or internalized significantly upon antibody binding, thus making it an ideal target for passive immunotherapy [10].

The exact *in vivo* mechanisms of action of rituximab are not completely understood. Rituximab depletes B-cells by several mechanisms, including direct antibody-dependent cellular cytotoxicity (ADCC), complement-mediated cell death (CDC), and signaling apoptosis [11]. Finally, rituximab has also been reported to inhibit B-cell proliferation, to enhance the activity of chemotherapeutic agents, and to directly induce apoptosis [12].

More recently, in the light rituximab successes, newer mAbs have been developed. In the next sections, we will discuss the current therapeutic applications of rituximab in indolent NHL, diffuse large B-cell NHL (DLBCL) and in chronic lymphocytic leukemia (B-CLL), as well the newer immunotherapeutic approaches for this haematological disorder. It is noteworthy that, due to its capacity to affect the B-cell compartment, rituximab was also shown to be effective in autoimmune disorders such as rheumatoid arthritis [13]. However, these applications will not be the focus of this review.

Indolent NHL

The first line therapy in symptomatic low-grade NHL until the early 90's was chlorambucil and prednisone [14]. Subsequently, several randomized trials showed the efficacy of rituximab (R) in combination with other chemotherapeutic agents such as fludarabine (R-F), fludarabine and cyclophosphamide (R-FC), fludarabine, cyclophosphamide and mitoxantrone (FCM-R), cyclophosphamide, vincristine, and prednisone (R-CVP), cyclophosphamide, vincristine, doxorubicin and prednisone (R-CHOP), CVP plus mitoxantrone (R-CNOP), fludarabine, dexamethasone, and mitoxantrone (R-FND) [15-18]. All these trials showed an overall response (OR) rate that was consistently around 95%, with complete response (CR) and partial response (PR) rates ranging from 45 to 100%, and from 0 to 52%, respectively. Therefore, the clinical response rates of rituximab-containing regimens were encouraging.

Subsequently, rituximab was first used in monotherapy in patients with relapsed or refractory indolent B-cell NHL. In those treated with rituximab 375 mg/m^2 once weekly for 4 weeks, OR rates ranged from 40 to 60%. Fifty to 70% response rates were observed in patients who had not previously received chemotherapy. CR rates ranged from 3 to 23% in patients with relapsed or refractory disease and from 7 to 37% in those treated with rituximab as first-line therapy [2]. However, the efficiency of rituximab appeared to be higher when used in combination with other agents, such as fludarabine or CHOP chemotherapy [19].

Currently the main therapeutic indication of rituximab remains the treatment, in combination with standard chemotherapy, of patients affected by stage III-IV indolent B-cell NHL, and at first relapse. Additionally, rituximab is recommended as monotherapy for stage III-IV chemoresistant FL or at subsequent relapse after chemotherapy.

Aggressive NHL

Rituximab plus chemotherapy is also approved for the treatment of patients with aggressive CD20 positive B-cell NHL. In this setting, two clinical trials have been conducted in order to assess the usefulness of rituximab in the management of diffuse large B-cell lymphoma (DLBCL): the Mabthera International trial (MInT) involving young patients [20], and the Groupe d'Étude des lymphomes de l'Adulte study (GELA) involving elderly patients [21]. Both the MInT and GELA phase II multicenter trials showed an increased overall survival (OS) at 2 years in rituximab "adding regimen" (R-CHOP) compared to standard therapy (93 vs. 84% and 70 vs. 57%, respectively). These results led to FDA approval of rituximab in combination with CHOP chemotherapy for previously untreated patients with diffuse large B-cell NHL.

Several others trials, conducted in pretreated patients with aggressive forms of B-cell NHL, showed similar results. Therefore, rituximab has been approved for previously untreated DLBCL patients in combination with CHOP and in salvage therapy in relapsed/refractory patients [22].

B-cell chronic lymphocytic leukemia (B-CLL)

Rituximab is active in CLL as a monotherapy [23,24] and in combination with chemotherapy [25,26]. However, since the use of rituximab as monotherapy was found to be associated with a risk of immediate responses followed by appearance of relapsed or refractory disease, the combination therapy is usually preferred to treat B-CLL.

The best results were observed when rituximab was added to fludarabine and cyclophosphamide (R-CF) in previously treated patients [27] and in the treatment-naïve ones [28,29]. In both types of patients the CR rates

and survival were significantly better with R-FC than with FC alone in a retrospective comparison with historical controls. In the light of this data, two randomized multicenter open-label trials were conducted which changed the way this hematological malignancy is treated. The first, known as CLL8, was conducted on 817 previously untreated CLL patients by the German CLL Study Group (ClinicalTrials.gov number, NCT 00281918). The other trial, REACH, enrolled 552 patients with relapsed or refractory CLL following prior systemic therapy [30]. Both studies showed a benefit in the OS rates in the R-FC arm vs. FC arm (86 vs. 73% in CLL8 and 54 vs. 45% in REACH). These clinical trials showed that the addition of rituximab to FC greatly improves the outcome in many CLL patients. OS follow-up for these patients is still ongoing. Based on these results, in February 2010 the FDA approved the use of rituximab in combination with FC for the treatment of both previously untreated and previously treated patients with B-CLL [National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: non Hodgkin's lymphomas (v.1.2010)].

Rituximab maintenance therapy for indolent (FL) and aggressive (DLBCL) NHL

Despite the success of rituximab-combined treatment, residual lymphoma cells frequently remain the cause of disease relapses. Therefore, several randomized trials have been done to analyze the benefit of maintenance therapy with rituximab. These studies compared the survival of patients who received rituximab maintenance therapy with that of patients who did not receive such treatment. Importantly, all these studies indicated that rituximab maintenance extends OS in patients with indolent NHL. However, additional studies are warranted to identify the optimal dosing and schedule, as well as those patients who are most likely to benefit from prolonged rituximab administration [31,32]. Unlike in indolent NHL, in DLBCL rituximab maintenance has failed to demonstrate benefit in all published clinical trials [33].

Rituximab and autologous stem cells transplantation (ASCT)

The current standard of care for young high-risk DLBCL patients is salvage chemotherapy followed by high-dose chemotherapy with ASCT. Several studies are assessing the role of rituximab as a part of high-dose regimens pre-ASCT. When incorporated into salvage chemotherapy regimens such as ICE (ifosfamide, carboplatin, and etoposide) and DHAP (dexamethasone, high-dose cytarabine, and cisplatin), rituximab may improve the OR rate [34]. Khouri and colleagues found that using rituximab in combination with high-dose BEAM (BCNU, etoposide, ara-C and melphalan) and ASCT, increased the OS from 53% for the control group to 80% for the study group [35,36].

The use of rituximab plus ASCT in indolent lymphoma has also been extensively evaluated. Overall, these studies suggested that rituximab-based chemotherapy followed by ASCT might provide superior disease control in comparison to either modality alone in relapsed FL and that it could have curative potential in a subset of patients [37].

Tolerability

In 84% of patients receiving rituximab during therapy or within the first 30 days following treatment some adverse events were reported [38]. More than 95% of these events were mild to moderate in severity, of brief duration, and observed during the first infusion. Typically they occurred within the first 30 min to 2 h of starting the first rituximab infusion and were usually resolved by interrupting or slowing down the infusion and providing supportive care [2].

The most common of these adverse effects were infusion-related reactions and lymphopenia. Ten percent of patients reported chills, infections, or high-grade fever. More serious effects included severe infusion-related reactions, tumor lysis syndrome, mucocutaneous reactions, hypersensitivity reactions, cardiac arrhythmias, angina, bronchospasm, hypotension, angioedema, hypoxia, and renal failure [39].

Adverse events were noted less often during the subsequent rituximab administrations. The reduction in peripheral B-lymphocyte counts is one possible hematological adverse event and can last up to 6 months with a recovery period of 9-12 months [38]. Rarely, cases of transient aplastic anaemia, haemolytic anaemia, and prolonged pancytopenia and marrow hypoplasia have also been reported with rituximab [2]. However, there appears to be a much lower risk of serious opportunistic infections than that reported by conventional therapy [2].

Resistance

Although the combination of rituximab plus chemotherapy represents the standard treatment for both FL and DLBCL, a resistance develops in about 50% of previously sensitive patients through tumor and host re-

lated mechanisms. Additionally, despite the expression of CD20 on their lymphoma cells, not every patient responds to the same extent to antibody therapy (primary resistance) and an initially responsive lymphoma can subsequently become resistant to rituximab (secondary/acquired resistance). The molecular understanding of the underlying mechanisms of resistance facilitates the development of pharmacologic strategies to overcome this event. Rituximab exerts its activity on CD20-expressing B-cells by indirect antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cell-mediated cytotoxicity (CDC) and direct (induction of apoptosis and chemosensitization) mechanisms. Moreover, the relative contribution of CDC, ADCC and direct mechanisms to the activity of rituximab *in vivo* is unclear. Downregulation of CD20 and expression of complement inhibitors have been described as escape mechanisms in B-NHL [40]. Recent reports suggest that deregulated phosphoinositide-3-kinase (PI3K)/Akt, mitogen-activated kinases (MAPK) and nuclear-factor kappaB (NF-kappaB), as well as upregulation of antiapoptotic proteins may determine the efficacy of rituximab to kill B-NHL cells *in vitro* and *in vivo* [41-43]. The latter signaling pathways are attractive targets for pharmacologic modulation of resistance. The newer generation of anti-CD20 mAbs under development should be able to induce considerably less CD20 downmodulation than rituximab and thus could possibly be more effective therapeutically. Therefore, CD20 downregulation, regardless of the underlying cause, appears to be an important mechanism that affects rituximab efficacy since antigen loss by malignant cells will prevent rituximab activity.

Other mAbs for NHL

Drawing from the therapeutic success of rituximab, considerable efforts have been made to identify other therapeutic monoclonal antibodies (Figure 1).

Several attempts have been conducted to improve rituximab efficacy and to avoid the development of resistance and side effects.

1. Ofatumumab

Ofatumumab (HuMax-CD20) is a fully human IgG1κ monoclonal antibody targeting a novel epitope of CD20. In preclinical studies, this novel anti-CD20 showed greater activity than rituximab, presumably because of greater interaction with the complement. Clinical trials confirmed this increased antitumor effects of ofatumumab compared to rituximab [44].

Another recently identified anti-CD20, humanized antibody, IMMU-10, is highly effective at depleting CD20+ cells through ADCC and CDC mediated mechanism, resulting in objective clinical response [45]. Several additional anti-CD20 mAbs under development include antibodies with enhanced binding to Fc receptors and augmented antibody-dependent cellular cytotoxicity.

2. Alemtuzumab

It is a humanized monoclonal antibody against CD52 (an antigen expressed by normal and malignant B and T lymphocytes, monocytes, and natural killer

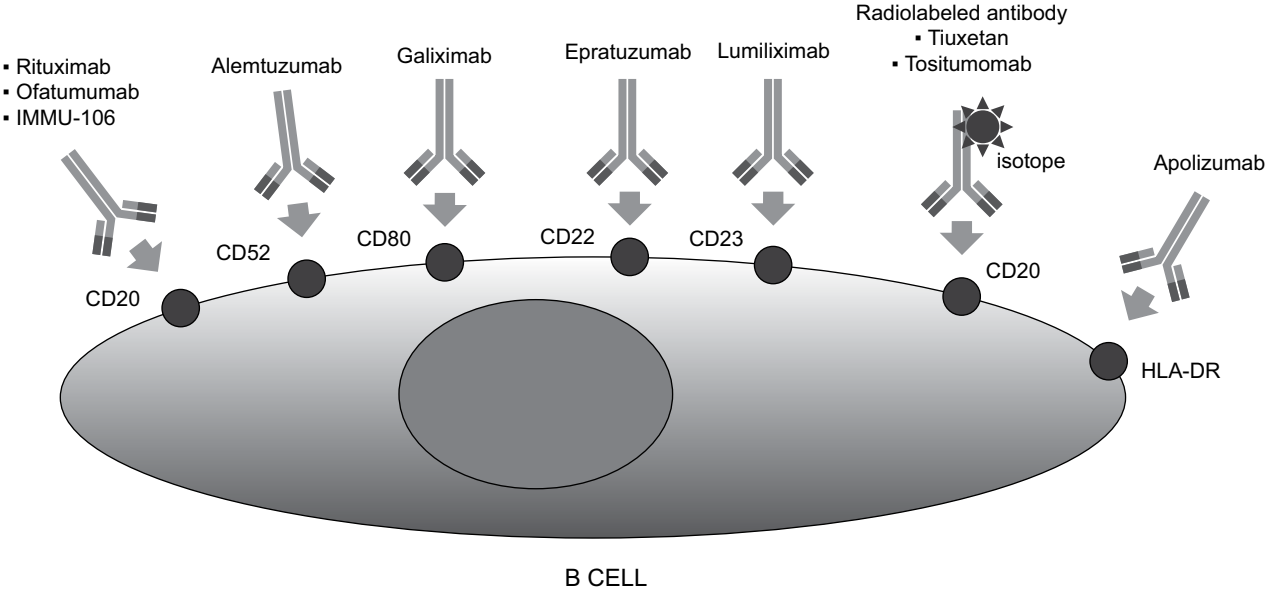

Figure 1. mAbs for B-cell NHL. Cell-surface proteins, such as CD20, CD22, and CD52 etc. are expressed on B-cell NHL and represent promising targets for the treatment of these malignancies. Their mechanism of action includes ADCC, complement activation, and direct cytotoxic activity on the target cells. Antibodies that are conjugated to radioisotopes allow the local delivery of radiation for "local radiotherapy".

[NK] cells). It is indicated for the treatment of patients with B-CLL that is refractory to fludarabine (OS rate of 56%) [46], for advanced-stage mycosis fungoides/ Sezary syndrome [47], and for relapsed or refractory peripheral T-cell lymphomas [48]. Although clinically effective, this mAb induces a dramatic decrease in CD4+ and CD8+ T lymphocytes and thus strongly increases the risk of infections.

3. Galiximab

It is a primatized anti-CD80 (IgG1λ) mAb with human constant regions and primate (cynomologous macaque) variable regions [49]. CD80 is a molecule involved in the regulation of T-cell activation. It is transiently expressed on the surface of activated B cells, dendritic cells and T cells of healthy individuals [50]. Additionally, a variety of lymphoid malignancies constitutively express CD80, making this antigen a suitable target [51]. A phase I/II study showed that galiximab is able to enhance rituximab antitumor activity in NLH [52].

4. Epratuzumab

A humanized IgG1 anti-CD22 antibody. It induces ADCC and CDC in preclinical studies. Phase I/II studies demonstrated objective responses in relapsed/ refractory FL (24%) [53] and in DLBCL (15%) [54].

5. Lumiliximab

A genetically engineered primatized chimeric macaque-human anti-CD23 monoclonal antibody with a macaque variable region and a human IgG1 constant region. Preclinical data showed that lumiliximab enhances the antitumor effect of fludarabine or rituximab in B-CLL [55].

6. Hu1D10

Apolizumab (Hu1D10) is a humanized anti-HLA-DR antibody that induces CDC, ADCC and apoptosis. HLA class II antigens are expressed at the surface of B cells. They are involved in antigen presentation and in promoting cell proliferation. Consequently, mAbs against HLA-DR inhibit B-cell proliferation and induce apoptosis. Recently, apolizumab has shown promising activity for the treatment of B-cell malignancies [56].

Radioimmunotherapy

It is a therapeutic approach which consists in the administration of an antibody linked to a radioisotope. Namely, this approach permits to target the radioactive isotopes to the cancer tissues and is especially interesting since it allows to kill neighboring cancer cells that are either inaccessible to the antibody or express insufficient antigen for the antibody to bind in adequate amounts. Two anti-CD20 radioimmunoconjugates are approved for use in patients with relapsed or refractory FL and for low-grade lymphoma:

1. Yttrium-90 (90Y)-labeled ibritumomab tiuxetan (Zevalin). It consists of a murine variant of rituximab (ibritumomab tiuxetan) conjugated to 90Y. About 80% of patients with FL or low-grade lymphomas respond to this treatment, including 20-30% CRs. Most responses last for about a year, but the duration of response has exceeded 3 years in about 25% of the patients [57-59]. Interestingly, 90Y-labeled ibritumomab tiuxetan also appears to be effective against some DLBCLs and mantle-cell lymphomas when it is used sequentially with chemotherapy [60].
2. Iodine-131 (131I)-labeled tositumomab (Bexxar). It is a conjugate of the murine anti-CD20 antibody tositumomab and 131I. The response rate to this compound among patients with rituximab-refractory lymphoma has been 63%, with 29% having CRs [61]. This regimen has also been administered after chemotherapy, resulting in durable responses and conversion of PR to CR without serious toxic effects [62]. A recent clinical trial (ClinicalTrials.gov number, NCT00006721) compared the efficacy of CHOP followed by 131I-labeled tositumomab with rituximab plus CHOP as the initial treatment of FL. The final results of this clinical trial might redefine the standard therapy for these haematological malignancies.

Conclusions

Ten years after its introduction in the treatment of NHL, the anti-CD20 mAb rituximab has already become a therapeutic mainstay in these disorders. However, several questions remain still open, including the best dosing and schedule of administration, why its activity as a single agent is limited, and how exactly their B-cell-depleting activity is carried out *in vivo*. Basic cancer cell biology, appropriate *in vivo* models, and well designed clinical trials will hopefully provide an answer to these issues in the very next future. Despite these unresolved questions, cumulative evidence supports the concept of rituximab usefulness in NHL treatment and, in some cases, in maintenance therapy. Additionally, recent data highlight the role of new anti-CD20 radioimmunoconjugates and, possibly, of newer mAbs target-

ing different NHL-associated antigens as novel treatment options. In summary, the positive results obtained with rituximab herald the advent of a new era in NHL treatment based on molecularly targeted agents which will hopefully be less toxic and more effective than traditional chemotherapy-based approaches.

Acknowledgement

Alessio Nencioni and Eva Moran are supported by the Associazione Italiana per la Ricerca sul Cancro (AIRC) and by the University of Genoa.

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