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Invited review

Targeting B-cell non Hodgkin lymphoma: New and old tricks

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ABSTRACT

The management of B-cell malignancies continues to pose a clinical challenge. In the past years, rituximab (anti-CD20) emerged as the standard of care in the induction treatment of follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), chronic lymphocytic leukemia (CLL), and mantle cell lymphoma (MCL), as well as in other subsets. Since the benefits of immuno-chemotherapy have been clearly demonstrated in a whole range of lymphomas, several innovative approaches are being explored to achieve significant responses, particularly in refractory B-cell non-Hodgkin lymphoma (NHL) cases. Studies of the comparative effectiveness and structure/function relationship of therapeutic monoclonal antibodies, together with an increased understanding of the molecular features of NHLs, have led to the development of a range of novel therapies, many of which target the tumor in a tailored fashion. Although several molecules can help clinicians to dissect the pathological mechanisms acting in the natural history of the disease, the main purpose of this review emphasize the recent developments in targeting the B-cell NHLs surface. These novel approaches are illustrated, and the new intriguing opportunities offered by bispecific antibodies and antibody-associated immune modulation are addressed.

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1. Introduction

In the past decade, advances in molecular medicine have provided exciting insights into the biology of non-Hodgkin lymphomas (NHLs). Cell surface antigens have been defined, that may be targets for therapy with monoclonal antibodies and radioimmunotherapy. Moreover, a better knowledge of critical cell signaling pathways and the results of gene expression analyses have demonstrated the importance of the malignant microenvironment in the neoplastic process, revealing opportunities for targeted therapy with novel molecules. Thanks to these advances, an improved survival has been observed in patients with both indolent and aggressive B-cell NHLs [1]. A broad spectrum of targeted therapies seeks to capitalize

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Table 1
Clinical subsets in NHLs after rituximab introduction. Adapted from Ref. [1].

Improved outcomes with addition of rituximab in indolent and aggressive NHL
Indolent lymphoma
First-line (chemotherapy + rituximab)
Second-line (chemotherapy vs chemotherapy + rituximab)
Maintenance after second-line (rituximab vs observation)
High-dose chemotherapy as second-line (salvage regimen vs rituximab-containing salvage regimen)
Aggressive lymphoma
First-line (chemotherapy vs chemotherapy + rituximab)
Maintenance after first-line (rituximab vs observation)
High-dose chemotherapy as second-line (salvage regimen vs rituximab-containing salvage regimen)

NHL: non Hodgkin lymphoma.

on the biology underlying the aberrant cellular behavior as a basis for therapeutic effects. This review will focus on the most important antibody-based therapeutics, that have become important components of the B-cell NHL therapeutic armamentarium [2]. Although several molecules can help clinicians to dissect the pathological mechanisms acting in the natural history of the disease, such as Bruton tyrosine kinases (BTK) inhibitors, phosphoinositide-3-kinase (PI3K) inhibitors and other molecular targets, the main purpose of this review emphasize the recent developments in targeting the NHLs surface. Additional therapeutic strategies and the approach to the patients with Hodgkin lymphoma (HL) are mentioned here only indirectly and are reviewed elsewhere [1,2].

Rituximab was the first monoclonal (mAb) antibody to target the CD20 molecule (anti-CD20), a receptor present on the membrane of most lymphoma B-cells. Anti-CD20 antibodies had a major impact on the natural history of all B-cell NHLs. Since the early 2000s, NHL mortality has decreased in most countries [1]. Although the reason for this decline is not completely understood, advances in treatment, and especially rituximab, have likely played an important role. Rituximab has shown efficacy as a single agent, especially in indolent lymphoma, where it has been suggested to postpone the need for chemotherapy.

A further step forward has been the combination of rituximab with chemotherapy ("Immuno-chemotherapy"), which is the standard of care in the induction treatment of follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), chronic lymphocytic leukemia (CLL), and mantle cell lymphoma (MCL), as well as in other pathologies under study in this context (Table 1) [1].

CD20 first appears in the late pro-B-cell phase of normal B-cell differentiation, continues to be expressed through development to immunoblasts, but it is absent on plasma cells. It is also expressed by memory B cells, and by more than 90% of malignant B cells. As a calcium channel, its main function is to activate B-cells, allowing their proliferation and differentiation. CD20 is a target for a whole range of mAb therapies because it is not shed, not secreted, and the degree of internalization is generally minimal [2]. As it is present on most mature B-cell NHL cells, it offers an ideal therapeutic target. While mAbs against CD20 target mature B-cells, they spare B cell progenitors, allowing normal B cell regeneration [2]. The following sections will integrate the information regarding mAbs employed in the treatment for patients with B cell NHLs and consider how it might best be used in clinical development.

2. Type I antibodies

Monoclonal antibodies that target CD20 is subdivided into type I and type II antibodies: type I, including rituximab and ofatumumab, bind to CD20. Then CD20 is redistributed into lipid rafts, and antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) are activated (Fig. 1). Moreover, these antibodies induce apoptosis as a consequence of a down-regulation of antiapoptotic proteins, including Bcl-2 and Bcl-XL [2].

The most important mechanisms of action in terms of the effector function of rituximab are mediated through the interaction of the Fc-gamma receptor with the Fc, the portion of the antibody that interacts with effector cells. The Fc-gamma receptor is strongly expressed by macrophages, as well as by natural killer cells, and neutrophils [3]. Fc-gamma receptors and in C1q may be responsible for different outcomes in patients [3].

In studies conducted to better understand the comparative effectiveness and structure/function relationship of therapeutic mAb in B-NHL, patients with a high-affinity receptor due to a valine/valine polymorphism (158 v/v) were shown to have a superior outcome to patients who had a polymorphism resulting in a phenylalanine at site 158. These findings demonstrate that antibody Fc domain::Fc receptor interactions underlie at least some of the clinical benefit of rituximab, and indicate a possible role for ADCC stemming from these interactions [3,35].

Moreover, patients with polymorphisms in C1q that result in lower levels may potentially have a prolonged clinical response, as compared to patients lacking those polymorphisms and hence with higher C1q levels [3]. Programmed cell death may also be a direct mechanism of action deriving from the use of type I mAbs such as rituximab, either through modulating antiapoptotic proteins or influencing intracellular $Ca2^{+}$concentrations [2].

Nevertheless, the role of complement in the mechanism of action of rituximab has been somewhat disputed. It is probably far less important than ADCC. In fact, it may even account for some of the infusion-related reactions that we see in patients given rituximab and other CD20 mAbs. Additionally, some interesting data have shown that the activation of complement may affect those effector cells that induce ADCC, and so this activation may have negative effects on the function and effector mechanisms of rituximab action.

The benefits of immuno-chemotherapy have been clearly demonstrated in a whole range of lymphoma subtypes. In DLBCL, a clear benefit from immuno-chemotherapy has been shown. The LNH-98.5 study by the GELA group investigated the effect of the addition of rituximab (R) to CHOP [cyclophosphamide, doxorubicin, vincristine, and prednisone]. The updated 10-year progression-free survival (PFS) was 36.5% in the R-CHOP-treated arm compared to 20% in the CHOP-treated arm. The overall survival (OS) in the R-CHOP-treated arm was 47.5% compared to 27.6% in the CHOP-treated group [4].

The MInT study was conducted in younger patients and showed a 6-year event-free survival in 55.8% of patients treated with chemotherapy vs 74.3% of those treated with immuno-chemotherapy (Fig. 2) [4,5]. In FL, immuno-chemotherapy results in improved response rates, event-free survival, time to treatment failure, and OS (Table 2) [6–9].

As regards maintenance rituximab strategy, a number of studies was centered on the role of maintenance B-cell depletion therapy. For instance, the PRIMA study in FL patients showed that PFS was significantly improved in the maintenance rituximab-treated group. Nevertheless, there was an increased rate of grade 2–4 infections in the rituximab group compared with the observation-only arm and no improvement in OS (Fig. 3) [10].

Changing the antibodies formulation has had a major impact on the effects and side effects of these important components of lymphoma treatment. A subcutaneous preparation of rituximab has been developed, that offers advantages in terms of faster administration, and use in the outpatient setting [21,22]. In this preparation at a fixed dosage, established at 1400 mg flat, hyaluronidase is added to rituximab [23]. The SparkThera and SABRINA studies were the first clinical experiences of subcutaneous administration of rit-