CD20-Targeted Therapies Remain Central to NHL Management

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Non-Hodgkin lymphoma (NHL) treatment relies heavily on CD20-directed therapies, a strategy that has evolved significantly since the introduction of rituximab. The ongoing challenge is to improve efficacy and overcome resistance mechanisms in diverse NHL subtypes, particularly in relapsed/refractory settings.

KEY TAKEAWAYS

- The Pivot: CD20 remains a foundational target, with newer modalities like bispecific antibodies and ADCs enhancing its utility.
- The Data: While specific trial data are not provided, the established efficacy of rituximab in combination regimens (e.g., R-CHOP) demonstrates a significant improvement in overall survival and progression-free survival compared to CHOP alone.
- The Action: Clinicians should continue to integrate CD20-targeted agents into first-line and relapsed/refractory NHL regimens, considering newer options based on patient-specific factors and disease biology.

The CD20 antigen, a non-glycosylated phosphoprotein expressed on the surface of pre-B and mature B lymphocytes, but not on hematopoietic stem cells or plasma cells, has been a critical therapeutic target in B-cell non-Hodgkin lymphoma (NHL) for over two decades. The initial success of rituximab, a chimeric monoclonal antibody, transformed the treatment landscape, particularly when combined with chemotherapy regimens such as CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone). This combination, known as R-CHOP, demonstrated superior outcomes compared to CHOP alone in diffuse large B-cell lymphoma (DLBCL), establishing CD20 targeting as a standard of care.1

Subsequent developments have focused on enhancing CD20 targeting through various mechanisms, including glycoengineered antibodies, antibody-drug conjugates (ADCs), and bispecific antibodies. Glycoengineered antibodies, such as obinutuzumab, are designed to improve antibody-dependent cell-mediated cytotoxicity (ADCC) and direct cell death compared to rituximab. Obinutuzumab, for example, has shown improved progression-free survival (PFS) in combination with chemotherapy for follicular lymphoma and chronic lymphocytic leukemia.2

Non-Hodgkin lymphoma represents a diverse group of hematologic malignancies, with B-cell lymphomas accounting for approximately 85% of all NHL cases. DLBCL is the most common aggressive subtype, while follicular lymphoma is the second most common indolent subtype. The incidence of NHL varies globally but has generally increased over the past few decades, particularly in older adults. The prognosis for NHL patients has significantly improved with the advent of CD20-targeted therapies, moving from a largely palliative approach for advanced disease to curative intent for many. However, a substantial proportion of patients still experience relapse or refractory disease, necessitating the

continuous development of novel therapeutic strategies. The consistent expression of CD20 on malignant B-cells across various NHL subtypes makes it an ideal target for therapeutic intervention, as its absence on hematopoietic stem cells allows for selective targeting with manageable myelosuppression.

Evolving CD20-Targeted Strategies

The utility of CD20 has expanded beyond naked monoclonal antibodies. Antibody-drug conjugates (ADCs) deliver cytotoxic payloads directly to CD20-expressing cells. Polatuzumab vedotin, an ADC targeting CD79b (a component of the B-cell receptor complex often co-expressed with CD20), has demonstrated improved outcomes when combined with bendamustine and rituximab (BR) in relapsed/refractory DLBCL, leading to a higher complete response rate and overall survival compared to BR alone. While not directly targeting CD20, its efficacy underscores the principle of targeted delivery to B-cells.3

Bispecific antibodies represent another significant advancement, designed to simultaneously bind to CD20 on B-cells and a T-cell activating receptor, such as CD3. This dual engagement brings T-cells into proximity with lymphoma cells, inducing T-cell mediated cytotoxicity. Mosunetuzumab, a CD20xCD3 bispecific antibody, has shown durable responses in heavily pretreated relapsed/refractory follicular lymphoma and DLBCL patients, with manageable safety profiles.4 Glofitamab, another CD20xCD3 bispecific, has demonstrated high complete response rates in relapsed/refractory DLBCL, particularly in patients who have failed prior CAR T-cell therapy. These agents offer off-the-shelf alternatives to CAR T-cell therapy, addressing accessibility and manufacturing challenges.5

The mechanisms of action for these diverse CD20-targeted agents vary. Rituximab primarily acts through ADCC, complement-dependent cytotoxicity (CDC), and direct induction of apoptosis. Glycoengineered antibodies like obinutuzumab enhance ADCC and direct cell death by optimizing Fc region glycosylation, leading to stronger binding to $Fc\gamma RIIIa$ receptors on immune effector cells. Bispecific antibodies, by engaging both CD20 on tumor cells and CD3 on T-cells, redirect T-cell cytotoxicity specifically to lymphoma cells, bypassing the need for major histocompatibility complex (MHC) presentation. This T-cell redirection leads to potent anti-tumor activity, even in patients with heavily pretreated disease or those who have developed resistance to other therapies. The selection of appropriate patients for these therapies often involves considering prior treatment history, disease burden, and specific lymphoma subtype, as well as potential comorbidities that might influence tolerability.

Ongoing research at conferences like EHA 2026 continues to explore optimal sequencing, combination strategies, and patient selection for these diverse CD20-targeted agents. The focus remains on identifying biomarkers that predict response and resistance, as well as mitigating toxicities, particularly cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) associated with bispecific antibodies. The development of novel CD20-targeting agents aims to overcome mechanisms of resistance, such as CD20 antigen loss or modulation, and to improve outcomes in high-risk patient populations.6

For further comprehensive information on the diagnosis and management of haematological malignancies, including lymphomas, readers may consult the excellent Oxford Handbook of Clinical Haematology.

CLINICAL IMPLICATIONS

The enduring relevance of CD20 as a therapeutic target in non-Hodgkin lymphoma is a testament to its foundational role in B-cell biology and oncology. While rituximab established the initial benchmark, the subsequent evolution into glycoengineered antibodies, ADCs, and bispecifics reflects a continuous refinement of precision medicine. Clinicians now have a broader armamentarium, allowing for more tailored approaches in both frontline and relapsed/refractory settings. The challenge lies in navigating the increasing complexity of treatment algorithms, particularly with the emergence of off-the-shelf bispecifics that offer alternatives to CAR T-cell therapy, which itself is a significant advancement but comes with logistical hurdles.

From an industry perspective, the sustained investment in CD20-directed therapies indicates a recognition of its market potential and clinical utility. Companies like Roche, Genentech, and AbbVie have been at the forefront of developing these agents, and the competitive landscape is driving innovation. However, the cost-effectiveness of these newer, often more expensive, therapies will undoubtedly come under scrutiny by healthcare systems and payers. Demonstrating superior long-term outcomes and quality of life improvements will be critical for widespread adoption, especially as these agents move into earlier lines of therapy.

For patients, the expansion of CD20-targeted options translates to improved prognosis and, for many, a better quality of life. The availability of bispecific antibodies, in particular, offers hope for those with heavily pretreated or refractory disease, providing an alternative when CAR T-cell therapy is not feasible or has failed. However, the potential for novel toxicities, such as cytokine release syndrome, necessitates careful monitoring and patient education. The ongoing research into optimal sequencing and combination strategies will be vital to ensure that patients receive the most effective and safest treatment pathways, ultimately extending survival and enhancing their well-being.

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