Redefining Precision Management of r/r Large B-Cell Lymphoma

Subjects: Hematology

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The treatment paradigms for patients with relapsed large B-cell lymphoma are expanding. Chimeric antigen receptor technology (CAR-T) has revolutionized the management of these patients. Novel bispecific antibodies and antibody–drug conjugates, used as chemotherapy-free single agents or in combination with other novel therapeutics, have been quickly introduced into the real-world setting. With such a paradigm shift, patients have an improved chance of better outcomes with unpredictable complete remission rates.

Keywords: large B-cell lymphoma ; LBL ; CART ; bispecific antibodies ; antibody–drug conjugate

1. Introduction

In the recently updated “5th Edition of the World Health Organization Classification of Hematolymphoid Tumors”, large B-cell lymphoma (LBCL) has been included as a group of lymphomas that encompasses 18 different entities [1]. It represents the most common types of non-Hodgkin lymphoma (NHL) with aggressive behavior and distinct histopathological and clinical features, with diffuse large B-cell lymphoma (DLBCL) being the most common subtype. The annual incidence in the United States of America during 1992–2001 was around 7 cases per 100,000 persons [2], and this is projected to increase by 4% by 2025. The median age at diagnosis is 66 years with 52% of newly diagnosed patients having advanced stages (stage III and IV). The 5-year relative survival rate has improved from 61% (2002–2007) to 64% (2008–2013) [3]. This slight numerical improvement is statistically significant ($p < 0.0001$) and is related to several contributing factors, such as fewer patients being diagnosed with human immunodeficiency virus and DLBCL, increased usage of intensive chemotherapy regimens, and improved supportive care, including advances in the management of infectious complication [3]. However, despite all of our achievements, researchers are still left with 40% of patients who will experience primary refractory disease or eventually relapse, with only around 50% of these patients qualifying for autologous stem cell transplantation (ASCT) [4]. More recently, the treatment landscape of LBCL has been enriched by the endorsement of chimeric antigen receptor T-cell therapy (CAR-T) in earlier lines. Its approval has been expanded to include patients with primary refractory disease or relapses (r/r) within 12 months.

Treatment decisions for patients with r/r LBCL have become more complex and should take into account several factors, including the duration of remission, individual patient characteristics, and available treatment options (**Figure 1**).

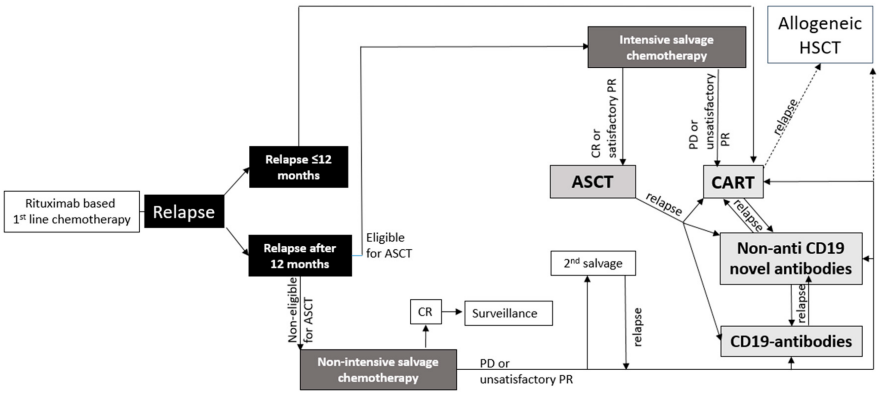

Figure 1. Model for possible treatment algorithm for patients with LBCL.

2. First Salvage Treatment Options in r/r Large B-cell Lymphoma

Diffuse large B-cell lymphoma (DLBCL) represents by far the most common subtype of LBCL, and approximately 30–40% of patients with DLBCL will experience a relapse, with an additional 10% having primary refractory disease. The data for other LBCL subtypes are not significantly different [5][6]. Relapsed and especially primary refractory disease behaves aggressively, and untreated patients may die within 3–4 months [7]. Historically, there have been various second-line treatment options, ranging from well-tolerated to more intensive regimens. However, the outcome of patients with primary refractory and early-relapsed LBCL treated with salvage conventional chemotherapy remains poor, with only 7% of patients achieving complete remission (CR) [8]. Several novel oral agents have been explored with none achieving approval. Ibrutinib, an oral covalent Bruton's tyrosine kinase inhibitor, led in a phase I/II trial to 14/38 and only 1/20 responses in patients with the activated B-cell (ABC) and germinal center B-cell (GCB) subtypes of DLBCL, respectively [9]. A retrospective study from Italy on lenalidomide, an oral immunomodulatory agent, found an overall response rate (ORR) of 45.5% [10]. The combination of lenalidomide, ibrutinib, and the CD20 antibody, rituximab, in a phase Ib study, resulted in responses in 44% of patients with r/r DLBCL [11]. Everolimus, an oral novel agent inhibiting the raptor mammalian target of rapamycin (mTORC1) pathway, produced in a phase II study an ORR of 30% [12]. However, for all of these agents, the responses are not long-lasting, ranging from a few weeks to a couple of months. Therefore, more efficacious agents targeting new pathways are desperately needed.

3. Novel Antibodies

For several decades, rituximab has been the sole antibody approved for treating patients with CD20-positive lymphomas. Although rituximab leads to a significant improvement in the outcome of patients in first and subsequent lines of treatment, a considerable number of patients eventually become refractory to it, underscoring the need for new CD20-targeting antibodies. However, despite targeting different epitopes of the CD20 receptor than rituximab, newer antibodies, such as ofatumumab and obinutuzumab, have not shown any significant improvement over rituximab in DLBCL [13][14]. Multiple resistance mechanisms for anti-CD20-directed therapy have been proposed, and one of the primary mechanisms responsible for resistance in B-cell NHLs is the development of CD20-negative cells following treatment with anti-CD20-containing therapy. Scientists are continuously striving to improve the outcomes of patients with relapsed or refractory DLBCL by developing novel agents that target new molecules on the surfaces and inside the malignant B lymphocytes. Therefore, new surface antigens are being targeted (**Figure 2**), such as CD19, CD22, CD37, and CD79B. CD19 is considered a particularly promising target for the development of novel agents as it is highly expressed in all stages of B-cell maturation and in a majority of B-cell lymphoma types [15].

Figure 2. Overview of different novel antibodies and their targets.

4. Tafasitamab

CD19 plays a crucial role in B-cell development, activation, and differentiation. Compared to CD20, the expression profile of CD19 is wider, and CD19 is expressed at an earlier pre-B stage, making it an attractive target in B-cell lymphomas [15]. CD19 shedding from the cell surface is not a common occurrence and is not typically observed, given that CD19 is a transmembrane protein that is typically anchored to the surface of B cells with regulated expression [16]. Therefore, antibodies targeting CD19 are less likely to be depleted or exhausted due to an absence of soluble CD19 in the circulation compared to antibodies targeting other B-cell surface markers. Although the native Fc CD19 antibodies displayed promising results in preclinical studies, they did not yield significant clinical success in the treatment of B-cell lymphomas. Clinical trials showed limited efficacy of this first generation of unmodified Fc CD19 antibodies. As a result, subsequent generations of CD19 antibodies have been engineered with modified Fc regions. Tafasitamab is a humanized monoclonal IgG1 antibody against CD19 that has been modified in its Fc region with two amino acid substitutions to enhance its affinity for Fcγ receptors. Antibody-dependent cellular cytotoxicity is mediated by the binding of tafasitamab's Fc region to FcγRIIIa receptors on immune effector cells, which triggers the cells to release cytotoxic molecules such as perforin and granzyme B when combined with lenalidomide [17]. These molecules enter the lymphoma cells and activate signaling pathways that induce apoptosis, or programmed cell death. This process is a key mechanism of action of the combination of tafasitamab and lenalidomide, and this interaction between the two medications is thought to play a major role in their antitumor activity.

5. Checkpoint Inhibitors

Checkpoint inhibitors (ChIs) showed high efficacy in classic Hodgkin lymphoma. However, studies with single-agent nivolumab or pembrolizumab in combination with RCHOP or post-ASCT failed to show significant outcome improvement in aggressive lymphomas [18][19][20]. Nonetheless, pembrolizumab seems to be effective in patients with primary mediastinal B-cell lymphoma (PMLBCL). In a phase Ib trial, KEYNOTE-013, 21 patients had an objective response rate of 48% (CR: 33%), while in a phase II trial, KEYNOTE-170, 53 included patients had an objective response rate of 45% (CR: 13%). Median PFS and OS were 5.5 and 22.3 months, respectively [21]. During the 2021 ASH annual meeting, the final analysis of KEYNOTE-170 showed a prolonged DOR, with a median DOR that was not reached after a median follow-up of 48.7 months [22].

6. Magrolimab

CD47 is highly expressed on numerous types of cancer cells, including lymphoma cells, where it serves as an antiphagocytic molecule. CD47 enables cancer cells to avoid being phagocytosed and destroyed by macrophages, thereby facilitating their evasion of the immune system. The overexpression of CD47 has been identified as an independent predictor of an unfavorable prognosis in patients with different types of cancer, such as lymphoma [23]. CD47 is emerging as a promising and potent macrophage immune checkpoint. Magrolimab is a humanized anti-CD47 IgG4 antibody that inhibits the CD47 signaling pathway. It induces phagocytosis of tumor cells via the blockade of CD47 and its ligand SIRPα [24].

7. Antibody–Drug Conjugates

Antibody–drug conjugates (ADCs) are a group of monoclonal antibodies directed against a specific cell surface structure which is usually overexpressed on malignant cells. They are designed to be a carrier to deliver the cytotoxic agent to the target cells with the least off-target effects. ADCs are composed of antibodies conjugated through a chemical linker with a toxic drug. The linker must maintain the balance between stability and lability to ensure that the cytotoxic payload is released only inside targeted malignant cells, while minimizing damage to healthy tissue. Once the antibody binds to the targeted receptor on the surface of malignant cells, it induces endocytosis of the receptor with the adherent antibody, including the poison. With this approach, researchers are able to smuggle higher concentration of chemotherapy inside the malignant cells and minimize systemic side effects. Examples of receptors which are currently being targeted in hematological malignancies are CD19, CD22, CD33, CD30, BCMA, and CD79b [25].

8. Polatuzumab Vedotin

Polatuzumab vedotin (polatuzumab) is a so-called third-generation ADC. It is a fully humanized IgG1 antibody targeting CD79b which is part of the B-cell signaling pathway and expressed exclusively on B lymphocytes. It is overexpressed on different B-cell lymphomas. Polatuzumab is linked to the microtubule polymerization inhibitor, the highly toxic monomethyl auristatin E (MMAE). Polatuzumab was tested in combination with rituximab in a phase II trial (ROMULUS) in difficult-to-

treat patients with r/r DLBCL with four median prior lines, showing an ORR and a CR rate of 54% and 21%, respectively [26].

9. Pinatuzumab Vedotin

Pinatuzumab vedotin (pinatuzumab) is a humanized IgG1 ADC which is directed against CD22 and linked with MMAE via a protease-cleavable peptide. CD22 is expressed on mature B-cell lymphocytes and plays a role in B-cell receptor signaling [27]. Pinatuzumab has demonstrated encouraging clinical activity as a single agent and in combination with rituximab. Patients with r/r DLBCL treated with 2.4 mg/kg pinatuzumab in a phase I trial had an ORR of 36% (9/25). The CR rate of patients treated with single-agent pinatuzumab and pinatuzumab in combination with rituximab (R-pinatuzumab) was 16% and 25%, respectively [27]. In another phase I/II study, R-pinatuzumab induced in the r/r DLBCL cohort a 60% ORR and 26% CR rate. Median OS, PFS, and DOR were 16.5, 5.4, and 6.2 months, respectively. Grade 3–5 AEs were frequent (78.6%), leading to treatment discontinuation in 42.9% of patients and dose reduction in 14.3% [26]. The abovementioned ROMULUS study showed the greater efficacy and better tolerability of polatuzumab over pinatuzumab, and therefore, the manufacturer opted for further development of polatuzumab and ceased conducting tests with pinatuzumab.

10. Naratuximab Emtansine

Naratuximab emtansine (naratuximab) is a humanized IgG1 ADC recognizing CD37 that is conjugated via a thioether-based linker to a cytotoxic maytansinoid, DM1. CD37 is a surface antigen overexpressed on B-cell lymphocytes. Its function has not been fully elucidated. However, it plays a significant role in immune regulation and tumor suppression. In a phase II trial with 80 patients with r/r DLBCL, naratuximab and rituximab produced an ORR of 43.2% and a CR rate of 32.4%. However, 82% experienced grade ≥ 3 AEs, with neutropenia (54%), anemia (17%), and thrombocytopenia (11%) being the most-documented higher-grade AEs [28].

As of the time of writing this manuscript, there are no ongoing clinical trials of naratuximab for the treatment of lymphoma registered on clinicaltrials.gov. It is important to note that this does not necessarily mean that there are no ongoing clinical trials of naratuximab for other indications or in other countries that may not be included on this database.

11. Zilovertamab Vedotin

Zilovertamab vedotin (zilovertamab) is a humanized ADC that is conjugated to MMAE and targets extracellular receptor tyrosine kinase-like orphan receptor 1 (ROR1). ROR1 is a cell surface protein on fetal cells which is usually not expressed on normal cells after birth. However, some solid and hematological cancer cells regain the ability to express ROR1, which promotes the migration and survival of malignant cells. A phase I study with 13 patients with r/r DLBCL proved its efficacy as a single agent, obtaining an ORR of 38.5% and a CR rate of 23.1%. Treatment-related AEs were observed in 47.1% of the cohort. The most commonly observed ≥3 AEs were neutropenia (29.4%), anemia (15.7%), febrile neutropenia (7.8%), peripheral neuropathy (7.8%), platelet count decrease (7.8%), diarrhea (5.9%), and pneumonia (5.9%) [29].

Zilovertamab is currently being tested in a phase II/III study in combination with R-CHP for participants with untreated DLBCL (NCT05139017) and as a single agent in two phase II studies on patients with r/r DLBCL (NCT05406401 and NCT05144841).

12. Loncastuximab Tesirine

Loncastuximab tesirine (loncastuximab) is an ADC composed of a humanized monoclonal IgG1 antibody, a linker, and a potent cytotoxic agent. The antibody is directed against the CD19 receptor and conjugated to a pyrrolobenzodiazepine dimer cytotoxin (PBD), SG3199 [30]. The short half-life of this payload reduces the risk of excessive systemic toxicity [31]. CD19 has emerged as an attractive target in several B-cell malignancies as it is highly present on the surface of B-cell lymphocytes throughout all stages of their maturation [32].

13. Bispecific Antibodies (BsAbs) and Bispecific T-Cell Engagers (BiTE)

BsAbs are immunoglobulins that are directed against two different antigens. They are designed to bring CD3-positive T cells nearby to malignant cells through binding to a tumor-specific antigen, resulting in T-cell activation and death of the cancer cells. BsAbs are composed of a combination of various antibody fragments joined together by flexible linker. BsAbs can vary in their structure and may include full-sized IgG and other, more intricate formats. Bispecific T-cell

engagers (BiTEs) are a subclass of BsAbs that are composed of two single-chain variable fragment (scFv) regions, which are derived from monoclonal antibodies [33]. The two scFvs are joined by a flexible peptide linker. BiTEs are not fully antibodies. They are smaller and simpler than other BsAbs.

14. Glofitamab

Glofitamab is a fully humanized IgG1-bispecific antibody that has a unique binding pattern of two CD20 binding domains and one CD3 binding domain. By binding to both CD20 on B cells and CD3 on T cells, it brings the two cell types closer together, triggering the activation of T cells. This activation leads to a release of cytotoxic molecules and cytokines, which further enhance T-cell migration and proliferation, ultimately promoting the elimination of malignant CD20-expressing B cells [34]. The intensity of CD20 expression does not appear to be a reliable predictor of response to glofitamab [34].

15. Mosunetuzumab

Mosunetuzumab is a bispecific full-length humanized IgG1 antibody that targets CD20 and CD3. The variable domains of the heavy and light chains are responsible for binding to CD3 and CD20, respectively. By targeting both proteins, mosunetuzumab can recruit T cells to the B-cell lymphoma tissue facilitating T-cell-mediated killing of the lymphoma cell. The altered Fc region lacking glycans leads to the loss of its effector function [35][36].

16. Epcoritamab

Epcoritamab is a subcutaneously IgG1-bispecific antibody redirecting CD3-positive T lymphocytes to CD20-positive B-cell lymphoma tissue. In the EPCORE NHL-1 phase II trial with 157 patients with r/r LBCL, the ORR of patients treated with single-agent epcoritamab was 63.1%, with 38.9% achieving CR. The median DOR was 12 months, with a DOR of 9.7 months in the post-CAR-T cohort. Additionally, 45.8% achieved MRD negativity, as determined using a ctDNA NGS assay [37].

17. Odronextamab

Odronextamab is a fully human IgG4-bispecific antibody which targets both CD20 on B cells and CD3 on T cells, leading to the activation and engagement of T cells against malignant B cells.

18. Blinatumomab

Blinatumomab is a first-in-class BiTE which consists of anti-CD19 and anti-CD3 domains allowing T cells to recognize CD19-positive lymphoma cells and destroy them. Blinatumomab is not a full-length antibody and lacks, like other BiTEs, the Fc region. Therefore, the half-life of blinatumomab is as short as 2–4 h. This is in contrast to the longer half-life observed with full-length monoclonal antibodies, which is attributed to the recycling process mediated by Fc receptors [38].

19. Resistance Mechanisms, Challenges, and Future Perspectives

To date, our understanding of the mechanisms underlying resistance to novel antibodies is limited due to the paucity of available research in this area. However, recent data, primarily consisting of those from preclinical studies, suggest that LBCL cells have the ability to evade the effects of novel antibodies including ADCs, BsAbs, and BiTEs through various mechanisms (**Table 1**).

Table 1. Challenges of novel antibodies and future perspectives in management of LBCL.

	Challenge	Possible Future Management
ADCs	Loss of CD79 b expression	BsAbs
	Overexpression of efflux pumps	Drug efflux pump inhibitors
	Activation of compensatory signaling pathways	Novel payloads
	Downregulate immune checkpoint proteins or upregulate inhibitory proteins	Combination with checkpoint inhibitors
	Hypoxia and vascularization	HIF-1α inhibitors
	Neurological AES	Inhibitors of nicotinamide phosphoribosyl-transferase
	Shedding of CD20	Pretreatment with anti-CD20-directed therapy
	Loss of CD20	ADCs
BsAbs and naked antibodies	Hypoxia and vascularization	HIF-1α inhibitors
	P53 mutation	MDM2 inhibitor
	Downregulation of CD3	Combination with checkpoint inhibitors
	ICANS	Lenzilumab
	CRS	Tocilizumab
	Complement activation	Avoid type IgG1 and 3 and use IgG4/IgM

Abbreviations: BsAbs: bispecific antibodies; ADCs: antibody–drug conjugates; HIF-1α: hypoxia-inducible factor-1α; MDM2: mouse-double-minute-2, ICANS: immune-effector-cell-associated neurotoxicity syndrome; CRS: cytokine release syndrome.

For instance, in vitro, downregulation, loss of expression, or mutation in CD79b may reduce the efficacy of polatuzumab [39]. However, other in vitro studies in animals and humans found no strong correlation between a high density of expression of CD79b or CD22 and the cytotoxic activity of ADCs, suggesting that there may be other factors than target overexpression that play a role in conferring sensitivity to ADCs [40][41]. Another way of escaping ADCs is the development of efflux pumps that can expel various toxic compounds. The overexpression of the multidrug resistance pump (MDR1) can reduce the effectiveness of payloads such as MMAE, resulting in resistance of lymphoma cells. This has led to investigations into several drug efflux pump inhibitors to address this issue [42]. Furthermore, activation of compensatory signaling pathways that bypass the targeted pathway reduces the effectiveness of ADCS. Some DLBCL cells may downregulate immune checkpoint proteins or upregulate inhibitory proteins, making them resistant to immune-mediated cytotoxicity induced by the novel antibody [25]. Resistance can also arise from the tumor microenvironment through processes such as hypoxia and vascularization, which can restrict the penetration and distribution of ADCs in lymphoma tissue.

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