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Novel monoclonal antibodies for diffuse large B-cell lymphoma

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Abstract

Novel immunotherapeutic approaches to the treatment of diffuse large B-cell lymphoma (DLBCL), including recent approvals of chimeric antigen receptor T-cell therapy, the antibody-drug conjugates polatuzumab vedotin (PV) and loncastuximab tesirine-lpyl, and the anti-CD19 antibody tafasitamab, provide efficacious new treatment options for patients with relapsed and refractory disease.

PV was the first novel therapy approved in combination with bendamustine/rituximab (BR) for relapsed/refractory (r/r) DLBCL patients after two or more lines of treatment who are ineligible for high-dose chemotherapy and autologous hematopoietic cell transplantation. This approval was based on a randomized phase II study comparing PV-BR versus BR arms, resulting in significantly improved rates of complete metabolic response, progression-free survival, and overall response (OS). Remarkably, this was the first randomized study in DLBCL demonstrating OS benefit to an experimental arm to have been conducted in several years. The promising activity of PV-BR in rrDLBCL may be a result of the use of innovative target CD79b that enables the bypassing of resistance mechanisms related to the CD20 molecule.

Two other recently approved antibodies are directed to CD19 antigen, the other attractive alternative target in lymphoma. Although these agents are generally approved for use as third- or second-line therapy, studies are in progress exploring their value in earlier treatment lines including induction treatment.

While we still await the successful incorporation of other targeted agents into the treatment of DLBCL, R-CHOP prevails as the standard of care for DLBCL, regardless of immunohistochemical or molecular subtype at diagnosis.

Key words: diffuse large B-cell lymphoma, monoclonal antibodies, clinical trials

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Introduction

The monoclonal anti-CD20 antibody rituximab initiated the era of anti-cancer immunochemotherapy more than two decades ago, starting with R-CHOP for DLBCL and subsequently in other B-cell lymphomas. The cure rate and long-term disease-free survival increased markedly across the B-cell lymphoma entities, but DLBCL patients with recurrent or progressive disease were more difficult to treat due to reduced response rate and duration to second-line therapies [1].

Immunochemotherapy R-CHOP21 has been a standard of care for two decades, and results in long-term disease-free survival or cure of 60% of DLBCL patients. But efficacy in an individual patient depends on their age and on other International Prognostic Index (IPI) clinical risk factors, and ranges from 30% to 90%+. The National Comprehensive Cancer Network and the British Columbia Cancer Agency recently validated the prognostic value of the IPI in DLBCL patients treated with R-CHOP in 2000–2010 [2]. The prognostic value of all five factors: age, performance score, disease

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stage, elevation of LDH, and extranodal involvement, was confirmed. Age and LDH level were subdivided into ranges to account for a continuous negative influence of these variables on survival. In addition, there is a confirmed negative prognostic influence of particular extranodal sites (E) including the bone marrow, central nervous system, the GI tract, the liver, and the lungs, but not the E number itself.

Attempts to make R-CHOP better

There have been a number of attempts to improve the outcomes of initial immunochemotherapy, including modifications of the anti-CD20 antibody itself such as glycoengineering and fine tuning of the epitope specificity in obinutuzumab or modifying antigen complementarity and mechanism of action in ofatumumab. Disappointingly, substituting rituximab with the new compound has failed to improve treatment outcome in DLBCL [3, 4].

Obinutuzumab is a type II antibody with a glycosyl moiety engineered by means of fructose deletion that demonstrates increased ability to induce antibody-dependent cellular cytotoxicity (ADCC) and lyzosome-dependent cell death with attenuated activation of complement-dependent cytotoxicity (CDC).

The recently published GOYA randomized study [3] in patients with advanced DLBCL with two or more IPI risk factors and/or the presence of bulky disease, directly comparing PFS of patients treated with obinutuzumab or rituximab to both combined with CHOP showed no difference: 3-year PFS of 70% and 67% for G (obinutuzumab)-CHOP and R-CHOP, respectively.

Other attempts to improve the efficacy of R-CHOP have been based on the concept of targeted agents that were expected to switch off pathogenic signaling and increase the cytotoxic effect of standard immunochemotherapy. Prospective randomized trials were designed to provide a proof of concept including bortezomib, ibrutinib, and lenalidomide, but these studies failed to show a statistically significant improvement in outcome, even in patients selected on the base of detecting appropriate pathways (i.e. ABC or non-GCB-subtype) [1]. The immunomodulatory agent lenalidomide was tested in several B-cell lymphoma types based on a mechanistic rationale including reduction of IRF-4 (interferon regulating factor) needed for plasmablastic differentiation and cell survival as well as derepression of IL-2 (interleukin-2) synthesis.

In addition, some phase II data has suggested that lenalidomide may reverse the negative prognostic impact of the ABC phenotype in DLBCL. Although a randomized phase II trial evaluating the addition of lenalidomide to R-CHOP in unselected patients suggested an improvement in PFS and OS, a phase III trial involving patients with the ABC subtype of DLBCL identified with gene expression profiling showed no benefit to lenalidomide added to R-CHOP [5, 6].

CAR-T cell therapy

More success has been achieved with new approaches to recurrent DLBCL. Anti-CD19 CAR-T cell therapy is now approved, with three distinct second-generation products becoming commercially available: axicabtagene ciloleucel (axi-cel), tisagenlecleucel (t-cel), and lisocabtagene maraleucel (liso-cel). Overall and complete remission rates were within the ranges 52–82% and 40–54% respectively, despite most of the patients having refractory disease [1, 7–9]. Toxicity is substantial and careful supportive care is needed including ICU admission, tocilizumab administration, and short-term corticosteroids treatment. Recent updates on the registration study or standard-of-care use of axi-cel showed a sustained complete remission rate, after two years of follow up, of 37% [7, 10].

Approved indications for use of these CAR-T cell products include relapsed/refractory adult DLBCL after two or more lines of treatment. The product t-cel is also indicated for children and adults aged under 25 with refractory ALL relapsed after transplantation or in second or more relapse. The products axi-cel and liso-cel are also indicated in primary mediastinal large B-cell lymphoma and transformed follicular lymphoma.

The approvals of axi-cel, t-cel, and liso-cel were based on extremely encouraging phase I/II studies including ZUMA-1 [7, 10], JULIET [8], and TRANSCEND NHL 001 [9] that demonstrated significant improvements in outcomes, if not cures, in a proportion of patients compared to the results of conventional salvage therapy evaluated in the SCHOLAR-1 study [11]. Acute toxicity of CAR-T cell therapy including CRS (cytokine release syndrome) and ICANS (immune effector cell associated neurotoxicity syndrome) is of concern with grade 3/4 CRS and ICANS rate of 2–22% and 10-28% respectively, but treatment-related mortality is rare. This extremely beneficial therapeutic index applies to all CAR-T cell products even though they differ in costimulatory domains, method of lymphocyte procurement, wait time for cell infusion, permission for bridge therapy, cell doses, timing of adverse events, as well as cytotoxic potential.

Currently, accessibility to CAR-T therapy is limited due to toxicity, non-satisfactory activity of salvage/bridging therapy, rapid disease progression, and financial burden. In addition, most patients eventually progress [1].

Tafasitamab

An alternative promising approach to targeting CD19 is tafasitamab, a novel Fc-engineered, humanized monoclonal antibody. CD19 is an attractive target as it is not only upfront expressed on malignant B cells, but also remains present in the case of CD20 downregulation as a result of prior rituximab exposure. Fc domain engineering leads to decreased binding affinity to inhibitory receptor FcγRIIa and

increased binding to stimulatory FcγRIIIa on the effector cells, resulting in more potent ADCC (antibody dependent cell mediated cytotoxicity). A phase IIa trial of tafasitamab monotherapy in 35 patients with r/r DLBCL resulted in ORR of 26% and median duration of response (DOR) of 20 months in nine responders including five patients with a response sustained ≥12 months [12].

The combination of tafasitamab and lenalidomide is the first therapy approved by the FDA for second-line treatment of DLBCL based on the results of a phase II trial (L-MIND) in 80 patients with r/r DLBCL ineligible for aHCT [13]. ORR was 60% with CR of 43% and DOR of 21.7 months and median progression-free survival (PFS) of 12.1 months. Responses were seen across risk categories including cell of origin subtype, and refractory status. Toxicity was tolerable, and the most common adverse event was neutropenia or grade 1–2 diarrhea and rash. With additional follow up, median DOR was 34.6 months, and median overall survival (OS) 31.6 months demonstrating the durability of responses to this immunologic chemo-free combination [14].

Tafasitamab is currently undergoing a randomized study in combination with bendamustine compared to bendamustine plus rituximab in r/r DLBCL [15] and a phase I frontline study in combination with R-CHOP or R-CHOP plus lenalidomide [16].

Loncastuximab tesirine-lpyl

CD19 is also a target to the antibody-drug conjugate loncastuximab tesirine (lonca), a humanized anti-CD19 antibody conjugated to a pyrolobenzodiazepine dimer designed to bind irreversibly to DNA to create highly potent interstrand cross-links that block DNA strand separation, therefore disrupting essential DNA metabolic processes such as replication and ultimately resulting in cell death.

In a phase I study involving 183 patients, ORR was 45.6% and CR 26.7% with median DOR of 5.4 months. Adverse events were mostly hematologic plus fatigue [17]. The compound is undergoing further evaluation in phase II and III studies. Recently, the FDA granted accelerated approval to loncastuximab tesirine-lpyl as therapy for patients with relapsed or refractory large B-cell lymphoma following two or more prior lines of therapy, including DLBCL not otherwise specified, DLBCL arising from low-grade lymphoma, and high-grade B-cell lymphoma. The approval was based on data from the pivotal phase II multi-center, open-label, single-arm, LOTIS-2 clinical trial [18], evaluating the efficacy and safety of the antibody-drug conjugate in patients with relapsed or refractory DLBCL following two or more lines of prior therapy (n =145). Loncastuximab tesirine demonstrated an objective response rate (ORR) of 48.3% and a complete response rate of 24.1%. The median duration of response in 70 responders was 10.3 months, with a median time to response of 1.3 months.

Polatuzumab vedotin

Another new target proven to be successful in overcoming resistance to initial therapy of B-cell lymphomas is CD79b, an essential component of the B-cell receptor signaling pathway expressed on normal and lymphoma B cells, but not on hematopoietic stem cells.

Polatuzumab vedotin (PV) is a humanized anti-CD79b monoclonal antibody linked to a microtubule poison MMAE (monomethyl auristatin E). Linker chemistry was refined in this particular antibody to ensure a consistent drug-to-antibody ratio of 2:1 and resulting consistency in pharmacological properties. In addition to MMAE-mediated cell death, PV can induce target cell death by antibody-mediated opsonization, and antibody-dependent cellular cytotoxicity. PV was the first novel therapy approved in combination with BR (bendamustine/rituximab) for r/r DLBCL patients after two or more lines of treatment who are ineligible for aHCT [19]. This approval was based on a randomized phase II study enrolling 80 patients, 40 per arm (PV +BR vs. BR), resulting in significantly improved rates of complete metabolic response, PFS, and OS, compared to BR alone. End of treatment and best ORR was 45.0% vs. 17.5% and 62.5% vs. 25.0%, and CR was 40.0% vs. 15.5% and 50.0% vs. 22.5%, respectively. Median OS was 12.4 vs. 4.7 months, p =0.002. This was the first randomized study in DLBCL demonstrating OS benefit to experimental arm for several years. Efficacy was evident across risk groups independent of cell of origin, expresser status, IPI score, refractory status, and number of prior treatments. Responses were best in patients receiving PV+BR as second-line treatment and those with non-refractory disease. Toxicity was more pronounced in the PV arm with higher rates of grade 3–4 neutropenia without excess rate of infection. There was a grade 1–2 peripheral neuropathy in 44% of patients reversible in the majority of patients.

Updated results from this study including the phase Ib safety run-in cohort, phase II randomized arms, and results from an extension cohort (n =106), confirmed the response rates from the phase II PV+BR arm and sustained a significant survival benefit over a longer follow up [20]. 2-year PFS and OS was 28.4% and 38.25%, respectively, in the randomized PV+BR cohort. Ten patients (25%) from the randomized PV+BR cohort had an ongoing response of >25 months (range: 26–49). No new safety signals were identified with longer follow-up or in additional patients. Recently, a phase III trial evaluating PV in place of vincristine in R-CHOP in previously untreated DLBCL patients with an IPI score of 2–5 completed recruitment, with results pending.

Magrolimab

Another promising target for DLBCL patients is CD47, an anti-phagocytic protein with increased expression on lymphoma compared to normal B cells. Overexpression of

CD47 protects lymphoma cells from antitumor macrophages and has been shown to be an independent predictor of poor outcome in DLBCL. Anti-CD47 antibodies block the interaction between CD47 and its ligand signal-regulatory protein alpha (SIRPα) on macrophages and enhance recognition and phagocytosis of lymphoma cells. Magrolimab, a humanized anti-CD47 antibody, was tested in a phase Ib/II study and demonstrated an ORR of 50% and a CR rate of 36% in combination with rituximab in a heavily pretreated population of DLBCL and FL patients with no clinically significant safety event [21].

Bispecific antibodies

Bispecific antibodies are designed to target molecules on both tumor cells and T cells with the aim of inducing T-cell activation and cell mediated cytotoxicity. Blinatumumab, a bispecific construct directed against CD3 and CD19 approved for recurrent CD19 positive acute lymphoblastic leukemia, is also active in DLBCL but its use is problematic due to neurotoxicity and a need for continuous infusion schedule [22]. There are four different full-length bispecific antibodies targeting CD3 and CD20 in development that have a longer half-life and can be administered every 3–4 weeks.

A phase I/Ib study of mosunetuzumab showed promising results with durable responses in patients with r/r DLBCL including patients who progressed on CAR-T cell therapy [23]. Additional agents targeting CD3 and CD20 that showed preliminary efficacy are glofitamab, odronextamab, and epcoritamab. A potential adverse event with these agents is cytokine release syndrome [1, 24].

Conclusions

There are three recently approved monoclonal antibodies for relapsed/refractory DLBCL: two are conjugated with the toxin, and one is Fc-fragment engineered. They are labeled for use in third- or second-line treatment based on documented substantial clinical activity including improved overall survival in the case of polatuzumab vedotin, which is unusual for randomized trials in r/r DLBCL. It is likely that these agents may eventually find a role in earlier lines of treatment. Several other antibodies, including bispecific CD3/CD20 full length agent, are in advanced stages of clinical research.

Author's contributions

JW — sole author.

Conflict of interest

JW — advisory role: Roche, Takeda, Abbvie, Novartis, Gilead; research funding: Roche, GSK/Novartis; lecture honoraria: Roche, Takeda, Servier, Amgen, Abbvie, Gilead; conference travel support: Roche.

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform requirements for manuscripts submitted to biomedical journals.

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