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REVIEW ARTICLE

A Comprehensive Review of Polatuzumab vedotin: Mechanisms, Clinical Applications, and Future Prospects

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Abstract

A novel antibody-drug conjugate (ADC), Polatuzumab vedotin has emerged as a promising player in the oncology field. This comprehensive review aims to elucidate the intricate details of Polatuzumab vedotin, encompassing its molecular structure, mechanisms of action, clinical applications, therapeutic efficacy, and ongoing research endeavors. With a focus on precision and targeted therapy, Polatuzumab vedotin stands as a beacon of hope in the battle against various malignancies. It has been regarded as a significant advancement in the field of targeted treatment of diffuse large B-cell lymphoma. As research continues to expand, our understanding of Polatuzumab vedotin, it is evident that its potential to improve patient outcomes and reduce the burden of cancer will remain a topic of great interest for the medical community.

Keywords: Antibody-drug conjugate (ADC), Polatuzumab vedotin, Diffuse large B-cell lymphoma (DLBCL), Relapsed/refractory, CHOP

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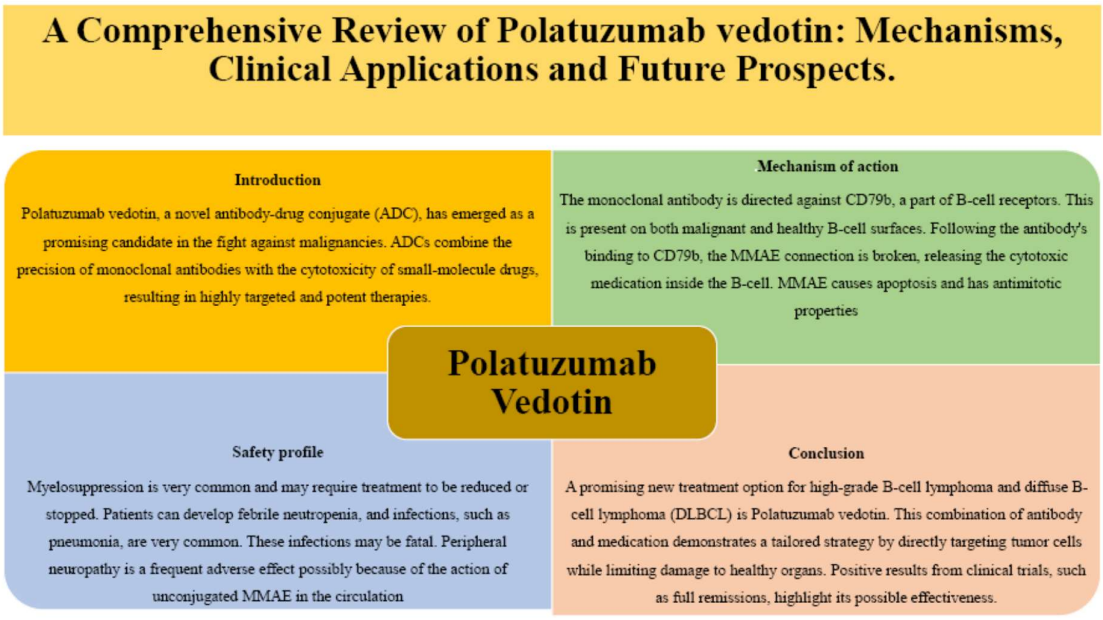
Graphical Abstract



Introduction

Cancer remains a global health challenge, demanding innovative treatment strategies. diffuse large B-cell lymphoma (DLBCL) is the most prevalent form of Non-Hodgkins lymphoma. Until 2000, the main chemotherapeutic agents used in the treatment of DLBCL and other aggressive NHL was cyclophosphamide, doxorubicin, vincristine, and prednisone every 21 days (CHOP-21); however, the treatment's cure rates was only 35%. Then, they could be given transplant consideration for stem cells [1].

Lymphoid malignancies treatment was certainly changed with the advent the first anti-CD20 monoclonal antibody, Rituximab. In 1997, rituximab was licensed for the treatment of follicular B-NHL; however, its use with CHOP-21 (Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone) extended to include newly diagnosed DLBCL. More than twenty years later, rituximab (R) is still the gold standard for treating DLBCL; A significant number of patients experience initial refractory illness or recurrence following R-CHOP treatment, eventhough there was initial high cure rates [2,3]. Role of prognostic biomarkers in the identification of highrisk cases has been highlighted in many studies. Polatuzumab vedotin, a novel antibody-drug conjugate (ADC), has emerged as a promising candidate in the fight against malignancies. ADCs combine the precision of monoclonal antibodies with the cytotoxicity of small-molecule drugs, resulting in highly targeted and potent therapies. This review examines Polatuzumab vedotin's pharmacological and therapeutic attributes, encompassing its mechanism of action, clinical applications, safety profile, and ongoing research efforts [4].

Mechanism of Action

Immunoconjugates also called as antibody-drug conjugates (ADCs) are made up of a monoclonal antibody and a cytotoxic drug, which is referred to as the payload (toxic at their therapeutic dose

levels in untargeted form are highly active molecules) connected by a chemical linker. The purpose of the ADC is to target cancer cells directly with an extremely toxic payload that is delivered selectively. Cytotoxicity and cell death occurs when the ADC/antigen combination binds to the appropriate antigen of tumor cell surface, after which internalization occurs and its payloads are released. At the moment, loncastuximab tesirine, brentuximab vedotin, polatuzumab vedotin, and inotuzumab ozogamicin are the four ADCs that are licensed for the treatment of lymphoid malignancies; numerous more compounds are being studied in clinical studies [5,6].

Polatuzumab vedotin (PolaV) is an ADC targeting, a component of the B-cell receptor, CD79b invariably expressed in B-NHL; A monoclonal antibody and monomethyl auristatin E (MMAE) which is cytotoxic combined to form Polatuzumab vedotin. Following the antibody's binding to CD79b, the MMAE connection is broken, releasing the cytotoxic medication inside the B-cell. MMAE causes apoptosis and has antimitotic properties [7,8].

In the treatment of adult patients with refractory DLBCL who are not eligible for hematopoietic stem cell transplant (as a second line treatment) European Medicines Agency (EMA) approved PolaV in combination with Bendamustine and Rituximab (BR). FDA granted PolaV accelerated approval in June 2019 when used in conjunction with BR,for the treatment of refractory DLBCL after at least two previous therapies [9,10].

Polatuzumab vedotin's influence on the tumor immunological microenvironment is quite significant apart from its direct cytotoxic effects. Immune microenvironment, a complex network of immune cells, cytokines, and signalling chemicals inhibit or stimulate the tumor growth. New research highlights the complex interplay between immunotherapeutic drugs' ability to modify this immune milieu and how well they work, such as Polatuzumab vedotin.

Studies have shown that the targeted administration of monomethyl auristatin E by Polatuzumab vedotin to B-cells expressing CD79b not only induces the demise of cancer cells but also may affect immunological responses. Polatuzumab vedotin may lessen the immune suppression brought on by tumors by eradicating malignant B-cells, and enhance the tumor antigens presentation to immune cells. This might then set off a series of immunological activation events, such as improved T-cell recruitment and recognition, which would ultimately strengthen and prolong the antitumor immune response [11].

Furthermore, there is strong evidence to support the conduct of clinical trials combining immune-stimulating antibodies or checkpoint inhibitors with Polatuzumab vedotin. These combos take use of the medication's ability to alter the immunological milieu, which may lead to increased response rates and extended illness control. Examining how immune cells and Polatuzumab vedotin interact in the context of tumors may provide important new insights into therapy approaches that use the immune system to improve patient outcomes [12].

Pharmacokinetics

The administration of Polatuzumab vedotin must be intravenous. The medication is diluted and infused after it has been reconstituted. Over ninety

minutes pass during the initial infusion. If this is well tolerated more infusions may be administered over a 30-minute period. Dose of Polatuzumab vedotin is 1.8mg/kg IV. The majority of MMAE in the bloodstream is coupled to an antibody. The half-life of this conjugated form is roughly 12 days.

Antibody degradation is anticipated to occur akin to that of other proteins, with the majority of the dosage likely to be excreted in the faeces. MMAE concentrations can be altered by cytochrome P450 3A4 inducers and inhibitors, because unconjugated MMAE is a substrate for cytochrome P450 3A4.Pharmacokinetics of Polatuzumab vedotin is not well-documented in liver and kidney disease patients [13].

Clinical Trials & Studies

Patients with Relapsed/Refractory (R/R) B-cell non-Hodgkin's lymphoma received intravenous Polatuzumab vedotin in cycles of 21 days as part of a Phase I open-label research (NCT01290549). 45 patients with evaluable NHL received 2.4 mg/kg Polatuzumab vedotin during the exacerbation or expansion phase. Among them, objective response (OR) occurred in 23, comprising 7 complete responses (CR) and 16 partial responses (RP).

Patients receiving 2.4 mg/kg of Polatuzumab vedotin experienced 6.2 months as median duration of response (DoR) and 5.7 months as median progression-free survival (PFS). Comparable results is also produced in a Japanese experiment (JO29138) [14].

The main study done in patients not eligible for transplants was an open-label, phase II trial involving 80 participants. The participants were divided into two groups (40 in each group).one group received treatment with bendamustine, rituximab & Polatuzumab vedotin Another group received bendamustine and rituximab. Significant improvements were seen in objective response rate (ORR-45% vs. 18%), complete response rate (CRR- 40% vs. 17.5%), overall survival (OS- median 12.4 vs. 4.7 months), and PFS (median 9.5 vs. 3.7 months) with the addition of PolaV. The Polatuzumab vedotin regimen was a 6 cycles infusion for every twenty one days. Using positron emission tomography, 16 patients showed improvement with Polatuzumab vedotin plus bendamustine and rituximab, while only 7 individuals showed improvement with bendamustine and rituximab.

The three-drug regimen's progression-free survival after a median follow-up of 22.3 months was 9.5 months, while bendamustine and rituximab's was 3.7 months. The chance of dying was decreased by adding Polatuzumab vedotin; the median overall survival was 12.4 months as opposed to 4.7 months when bendamustine and rituximab were used.

The greatest overall response (BOR) was 56.6% in the extension of this research, which involved 106 patients who took PolaV-BR; the ORR was 41.5% with 38.7% CRs. The median response time was 9.5 months, with corresponding PFS and OS times of 6.6 and 12.5 months. Lower PFS and median duration of response were found in a subgroup analysis of patients with primary refractory disease, those who were refractory to the last treatment, and those who had received more than one prior therapy [15].

In fact, PolaV-containing regimens were employed as a bridging therapy to allo-HSCT or CAR T-cell therapy in a recent trial by Liebers et al. The latter was

carried out effectively in 28 out of 41 patients, with an OS of 57.5% at 12 months and 77.9% at 6 months, respectively. By comparison, only 22% of patients who did not advance to CAR T had a 6-month OS There is relatively limited data about the use of PolaV following CAR T-cell treatment. A recent retrospective analysis with 44 patients in relapse following CAR T showed a median PFS of 9 weeks and an ORR of 45% with only 14% CRs.

The first phase III experiment to use PolaV in the treatment of newly diagnosed DLBCL patients is called POLARIX (NCT03274492). In this trial, 440 patients were randomized to receive PolaV-R-CHP whereas 439 received standard R-CHOP. Every patient had six cycles of the prescribed regimen, which were then followed by two more cycles of rituximab monotherapy. Patients treated with PolaV-R-CHP showed a substantially longer PFS (76.7 vs. 70.2% at 2 years, p: 0.02) after a median follow-up of 28.2 months, but no change in OS was seen. Interestingly, despite the fact that the two groups' CR rates were similar, the statistically significant variations in Disease free survival (DFS) imply that PolaV-R-CHP produced more persistent responses. Patients over 60 years old, those with International Prognostic Index (IPI) scores ≥ 3, and those with the activated B-cell–like subtype are those that may benefit more with PolaV-R-CHP [16].

Safety Profile

In terms of tolerability, PolaV-BR was linked to an increased incidence of grade 3–4 cytopenias, but not an increased risk of transfusion requirements or infections. Interestingly, low-grade, reversible peripheral neuropathy was observed in the PolaV arm.

Bendamustine and rituximab become more hazardous when Polatuzumab vedotin is added because CD79b is not only exclusive to cancer cells. Because myelosuppression is so prevalent, medication may need to be lowered or discontinued. Pneumonia and other infections are prevalent, and patients may experience febrile neutropenia. These illnesses could be lethal.

One common side effect may be peripheral neuropathy, which could be brought on by unconjugated MMAE acting in the bloodstream. This may also be a reason to cut back on or discontinue treatment. When bendamustine and rituximab are combined with Polatuzumab vedotin, additional side effects that occur more frequently include fever, diarrhea, decreased appetite, hypokalaemia, hypoalbuminaemia, and hypocalcaemia. Hepatotoxicity is a possibility, so liver function should be examined in addition to the patient's blood count. An infusion-related response will occur in about one-third of individuals. Prior to each infusion, each patient should get an antihistamine and an antipyretic [17].

Challenges and Opportunities

Overcoming challenges such as resistance and optimizing dosing regimens are key to maximizing its therapeutic potential. Antibody-based treatments like ADC are thought to be intriguing and promising for enhancing cancer therapy. As others have said, the pharmaceutical industry's interest in funding research and development in the field is reflected in the growth in the number of registered ADCs in clinical trials.

Although an ADC's design may not appear extremely complicated, there are a number of factors that need to be taken into account in order to fully realize an ADC's potential as a cancer therapeutic agent. This could be the primary cause of the situation where just a small number of ADCs have made it to market. The main problems with ADC development appear to have their roots in the things that impede their effectiveness and cause off-target cytotoxicity.

It is not necessary for ADC tumor markers to be connected to tumor growth. As a result, ADC has a wide spectrum of therapeutic applications in malignancies. An ADC tumor marker must, however, satisfy three requirements: it must have a significant expression level in tumor cells relative to normal cells, it must have a cell surface immunogen, and it must be able to internalize ADCs [18].

The main considerations when selecting an antibody are receptor-mediated internalization, sufficient affinity, and high specificity. It would be a fantastic idea to optimize the antibody component to produce better ADCs. Indeed, antibody improvement can solve some of the main drawbacks of ADCs, such as limited internalization, low efficiency, and off-target effect (heterogeneous expression of the target in tumors, and target expression in normal tissues. Numerous preclinical models have demonstrated the efficacy of antibody engineering technology in producing alternative antibodies for the purpose of designing more efficient ADCs.

This technology is justified by the fact that the aforementioned ADC's shortcomings can be addressed by designing better ADCs that function as better antibodies in terms of internalization activity, affinity, and specificity, either by increasing the therapeutic activity or reducing the adverse effects of the ADC [19].

The search for cytotoxic payloads with restricted drug-to-antibody ratio (DAR) 195 that are strong enough to perform therapeutic activity is a major concern in the development of ADCs. Cytotoxic payloads are often selected based on their stable storage and circulation properties, non-immunogenic nature, and acceptable aqueous solubility.

On the other hand, the second fascinating topic is the development of novel techniques to alter the cytotoxic payloads of ADCs with adaptable functional groups (such as amine or thiol groups), which facilitate conjugation. The inability of linking and conjugation chemistry to uniformly bind an optimal number of payloads to the antibody in a predetermined place presents another difficulty for ADCs.

The most promising methods for reaching the objective of site-specific conjugation and homogenous ADCs involve interdisciplinary and multidisciplinary works, as well as associated studies like recombinant DNA technology, bioconjugation, and chemistry. According to promising data from research to synthesize homogenous ADCs, it is possible that the first ADC products created via site-specific conjugation will be made for cancer therapy. This may hold the promise for the future employment of ADCs.

All things considered, despite difficulties with ADC design, the future of ADCs appears to be very bright since additional clinical trials and fundamental research on ADCs now in use will open the door to addressing problems with

tumor marker, antibody, cytotoxic payload, and linkage method [20].

Conclusion

A promising new treatment option for high-grade B-cell lymphoma and diffuse B-cell lymphoma (DLBCL) is Polatuzumab vedotin. This combination of antibody and medication demonstrates a tailored strategy by directly targeting tumor cells while limiting damage to healthy organs. Positive results from clinical trials, such as full remissions, highlight its possible effectiveness. However, the rise of side effects such peripheral sensory neuropathy and neutropenia highlights the need for careful monitoring and all-encompassing management approaches. Polatuzumab vedotin presents a potential breakthrough by bringing hope back to those who have had setbacks with previous treatments. Nonetheless, thorough research is necessary to fully understand its therapeutic environment. With future research, this innovative treatment strategy might reveal further aspects of its efficacy, which would further refine its function in transforming the paradigms around the treatment of high-grade B-cell lymphomas.

Conflicts of interest

The authors declares that they do not have conflict of interest.

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