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Review

Immunotherapy for diffuse large B-cell lymphoma: current use of immune checkpoint inhibitors therapy

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Abstract: Patients diagnosed with diffuse large B-cell lymphoma (DLBCL) have high cure rates with current treatment options including immuno-polychemotherapy. However, around 30% of cases do not respond or develop relapse disease. For this, it is necessary to search for new therapeutic options. In recent years, therapy using chimeric antigen receptor (CAR) T-cells has been a strategy for those patients with LBDCG in progression or relapse, although only 30–40% of cases achieve durable remissions. The programmed death-1 (PD-1) receptor regulates the T-cell-mediated immune response through binding to its ligands (PD-L1). Some tumor cells present high expression of PD-L1, which down-regulates T-cell activation. The beneficial antitumor activity of PD-1 and PD-L1 has been widely demonstrated in certain solid organ malignancies. However, their utility in the treatment of lymphomas is complex. To date, different clinical trials have demonstrated its usefulness as an innovative therapeutic alternative in these tumors. In this review article, we evaluate the literature on the role of the PD-1/PD-L1 pathway in DLBCL and describe future strategies involving these new anticancer agents in this lymphoid neoplasm.

Keywords: diffuse large b-cell lymphoma; target therapies; immunotherapy; anti PD-1; anti PD-L1

1. Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most frequent form of non-Hodgkin's lymphoma (NHL) in adults, with a peak incidence in the 60s, representing approximately 25–35% of the total, being even higher in developing countries. It is a large B-cell lymphoid neoplasm, which can occur

both in the lymph nodes and in extranodal locations, with diffuse proliferation that blurs the pre-existing architecture.

There is marked clinical and biological heterogeneity in this group of lymphoid neoplasms, with more than 18 different clinicopathologic entities. However, most do not have specific clinical or pathologic features so they are placed in the DLBCL not otherwise specified (NOS) category [1,2].

New molecular findings in the genetics of these lymphoid neoplasms have provided further insight into the disease. At least two molecular variants of DLBCL NOS are recognized, based on the gene expression profile according to Hans' algorithm, which refers to the cell of origin (COO): the GCB (germinal center B-cell) type, the ABC type and unclassifiable cases (~10%), which are grouped as non-GCB (non-germinal center B-cell).

The GCB and non-GCB subtypes account for 40% and 60% of de novo DLBCL, respectively. In comparison to patients with the non-GCB subtype, individuals with the GCB subtype experience better results. To date, there is insufficient clinical evidence to make a therapeutic decision other than conventional immunochemotherapy based on this result, outside of a clinical trial setting [1,2].

Subgroups of DLBCL with poor prognoses have been connected to several molecular disorders. It is known that MYC translocation occurs in 10 to 15 percent of DLBCL, and in a subset of cases there are concurrent MYC, BCL2 and BCL6 rearrangements, giving rise to so-called double hit and triple hit lymphomas [1].

The standard treatment of patients with DLBCL has been CHOP-type polychemotherapy (cyclophosphamide, doxorubicin, vincristine and prednisone) for many years, which, despite the aggressive clinical course of this pathology, achieved a long-term survival of 40%, whether or not followed by RT. The combination of CHOP with rituximab (anti-CD20 monoclonal antibody) has improved patient survival and is now considered the standard treatment for DLBCL with an overall long-term survival of 60–70%. 30 to 40% of patients with DLBCL have refractory disease or relapse after the first line of treatment [3].

To improve the results of R-CHOP, new therapies have been compared in recent decades. DA-EPOCH-R (dose adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin and rituximab) has also been proven to be a good therapeutic option, with adequate OS and DFS, although with greater haematological toxicity. Given the emerging molecular and prognostic characterization, DA EPOCH R seems to be especially useful in advanced stages and specific subtypes of poor prognosis, establishing itself as a potential replacement for RCHOP in high-risk DLBCL [4,5].

Subtypes of DLBCL with a less favorable prognosis require a choice of treatment appropriate to its characteristics. For lymphomas with rearrangement of MYC and additional rearrangements of BCL-2, BCL-6 or both (DH/TH), standard immunochemotherapy has shown worse results than with the rest of DLBCL and intensive regimens such as DA-EPOCH-R or R-hyper CVAD/MA (fractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone alternating with high-dose methotrexate and cytarabine) or others such as those used in the treatment of Burkitt lymphoma [6,7].

Among the risk criteria for the administration of intrathecal prophylaxis in DLBCL is the presence of MYC rearrangement. Dose-adjusted EPOCH-R could also be more effective, especially in cases with risk factors unfavorable, in primary b-cell lymphoma of the mediastinum, managing to avoid radiotherapy and its side effects.

However, 30–40% of patients with DLBCL have refractory disease or relapse after the first line of treatment. In this regard, the choice of a second line of treatment begins with assessing whether the patient is a candidate for autologous hematopoietic stem cell transplantation (ASCT) [8]. This

procedure has demonstrated superiority over consolidation chemotherapy in cases of chemosensitive relapse. In patients who are candidates for ASCT, no salvage regimen that has demonstrated superiority over others in terms of efficacy, especially in patients previously treated with rituximab and in those with early relapse after first-line treatment. This group of patients could benefit from inclusion in clinical trials that have demonstrated less toxicity, less need for hospitalization and maintain the patient's quality of life, with similar efficacy to more toxic regimens such as R-ESHAP, R-DHAP or R-ICE, which can also be used depending on the clinical experience of the center and the individual assessment of each patient [9,10].

In patients who are not candidates for ASCT, outpatient regimens that do not present very high toxicity such as R-GEMOX, R-bendamustine-polatuzumab or tafasitamab-lenalidomide can be used.

The encouraging results obtained in the ZUMA-7 and TRANSFORM clinical trials, which have compared the use of standard second-line therapy with the use of CART in patients with refractory DLBCL or early relapse, could change in the short term the management of these patients in favor of CAR-T. For the moment the approval of the CAR-T is maintained in subsequent lines of treatment [11,12].

There are currently three types of treatment available for patients who relapse or are refractory to the second line of systemic treatment: CAR-T cell therapy, conventional treatment with immunochemotherapy and/or radiotherapy and another group of new therapeutic strategies. The latter present different mechanisms of action on the disease and some of them are currently under investigation to improve the results of conventional treatment.

Today, the high efficacy and curative potential shown by CAR-T cells, even in patients with chemo refractory disease, has changed the paradigm of treatment of DLBCL, and should be considered in every relapsed or refractory patient after two lines (with or without TAPH), with two CAR-T constructs currently available and approved by the FDA and the EMA: tisagenlecleucel and axicabtagene ciloleucel, both second-generation and directed against CD19 [13–15].

Within the previously mentioned group of new drugs and therapeutic strategies, small molecules, new CAR-T therapies and monoclonal antibodies stand out. We will make special mention of immune checkpoint blockers because they are the central theme of this review.

Inhibitors of PD-1, PD1 ligand and CTLA-4 act by increasing the antitumor capacity of the patient's T lymphocytes, attempting to prevent immune evasion of tumor cells and constitute a new type of antitumor therapy. Different subtypes of LCGBD express PD-1 with intensity and produce promising data in the few trials available.

The use of immunotherapy presents clinical efficacy documented in several trials, obtaining outstanding therapeutic effects with an adequate safety profile, especially when PD-1 or PDL1 blockade is used in numerous solid tumors. The importance of this pathway has been demonstrated in the treatment of various solid tumors such as melanoma, non-small cell lung cancer, colorectal cancer, nasopharyngeal carcinoma and urothelial carcinoma, among others. Preliminary data has also demonstrated the therapeutic activity of PD-1 blockade in certain lymphoid hematologic malignancies, including classical Hodgkin's lymphoma (cHL) and follicular lymphoma (FL), as well as potential utility in diffuse large B-cell lymphoma (DLBCL). However, PD-1/PD-L1 expression levels in neoplastic cells and in the tumor microenvironment vary between subtypes and its prognostic implications remain unclear.

2. PD1/PDL1 structure

PD-1 is a glycoprotein of the immunoglobulin superfamily, composed of an IgV extracellular domain, a stalk of approximately 20 amino acids separating the plasma membrane IgV domain and a cytoplasmic tail containing tyrosine-based signaling motifs [16,17]. The PDCD1 gene, composed of 5 exons, responsible for its encoding, is located on the long arm of chromosome 2 (2q37.3). The cytoplasmic tail of PD-1 contains two structural motifs, an immunoreceptor tyrosine-based inhibitory motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). The SHP-2 tyrosine phosphatase SHP-2 has been reported to constitutively interact with ITSM and is involved in PD-1-mediated inhibitory function [18]. The similarity between the structure of PD-1 with both CD28 and CTLA4 suggests that it is a member of the CD28 superfamily, albeit with properties that differentiate them. PD-1 is predominantly expressed on activated T cells, B cells, macrophages and natural killer (NK) cells.

PD-1 has two different ligands, PDL1 (CD274, B7-H1) and PD-L2 (CD273, B7-DC). They are members of the B7 family, with 37% sequence homology, generated by gene duplication mechanisms [19]. Both differ in their affinity for PD-1 and in their expression patterns. It has a transmembrane sequence, IgV and IgC extracellular domains, but no discernible intracellular signaling region. The CD274 gene on the short arm of chromosome 9 generates PD-L1 [20]. In addition to binding to PD-1, PD-L1 can bind to CD80/B7, and PD-L2 can bind to RGMb, promoting tolerance. However, the function of PD-L1 through interaction may be context-dependent and there may be other co-stimulatory receptors for PD-L1/PD-L2 [21].

Expression analysis of these molecules showed that both B7-H1 and B7-DC are abundantly induced in dendritic cells and macrophages, although B7-H1 appears to be more widely inducible in activated T. B cells, epithelial cells and endothelial cells. PD-L1 is widely expressed in both hematopoietic (T and B cells and macrophages) and non-hematopoietic cells, whereas PD-L2 is expressed in activated dendritic cells and some macrophages. PD-L1 is expressed in malignant lymphoid cells, but PD-L2 appears to have low expression in NHL cell lines.

In circulation, PL-1 may exist as a soluble form after membrane cleavage by matrix metalloproteins, retaining the IgV ligand-binding domain to interact with T-cell PD-1. Several studies have also studied the association of soluble levels with disease prognosis [17].

3. Mechanism of immune evasion

New lines of DLBCL research highlight the importance of the tumor microenvironment (TME) in its pathogenesis. TME is understood as the interactions between tumor cells and the different elements of the stroma (fibroblasts, blood and lymphatic vessels), as well as with the extracellular matrix and with immune cells (mast cells, macrophages and T or B lymphocytes). It appears that there may be great heterogeneity in the role of SMT depending on the type of lymphoma or the tissue or organ in which the lymphoma arises. This web of interactions may influence important aspects such as the prognosis of the disease or the response to standard therapy, so it may be useful to know more about it [22].

In the tumor microenvironment of lymphomas, there are many mechanisms involved in the suppression of the tumor immune response, including the presence of immune regulatory cells, the production of immunologically active molecules by the tumor, the role of monocytes and macrophages

as immune suppressors, the loss of the major histocompatibility complex and the secretion of immunosuppressive cytokines [23].

Some of the best-known mechanisms of this immune regulation are the immune checkpoints, among which CTLA-4 or the PD-1/PDL-1 axis, whose increased expression exerts a negative regulation of the immune system, stand out. PD-L1 is expressed in lymphoid cells, which is part of the basic escape strategies in lymphoid pathology.

The antitumor immune response requires the participation of TCD8+ and TCD4+ lymphocytes, which are activated by antigenic presentation through major histocompatibility complex (MHC) class I and II molecules. B-cell lymphoma cells constitutively express major histocompatibility complex (MHC) class II and functionally active CD80/CD86 co-stimulatory molecules, allowing these lymphoma cells to act as antigen-presenting cells themselves, a mechanism that would contribute to an enhanced immune response against neoplastic cells. However, it has been observed that in 41–60% of NHL cases there is decreased expression of MHC I and II, which seems to play an important role in the genesis and progression of lymphoma by allowing escape from immune surveillance [21]. A high frequency of genetic mutations (up to 29% of cases) that determine the lack of surface HLA has been documented. Alterations in the CD58 gene, the receptor of natural killer (NK) cells or CD2+ T cells also play an important role, implying the loss of recognition of tumor cells by these cells [22].

Regarding the main topic of this review, the mechanism of cancellation of T cell activation signals in the tumor microenvironment through the immune checkpoint of the PD-1/PD-l1 pathway is initiated by the binding of PD-1 expressed on T cells to the corresponding PD-L1/L2 ligand on tumor cells. The structural modification of PD1 as a consequence of the interaction of its exposed domain with its respective ligand leads to the phosphorylation of the previously mentioned structural motifs and the initiation of the participation of protein tyrosine phosphatase-2 (SHP-2) and SHP-1 in the intracellular signaling cascade [24].

The latter are responsible for the dephosphorylation of proximal TCR signaling molecules, most notably the ZAP70 protein, which as mentioned previously was involved in the TCR-mediated T cell activation signaling pathway and this inhibits the phosphatidylinositol-3-kinase/Akt (PI3K/Akt) pathways, which is the main target of the PD-1-mediated inhibitory function, as well as the RAS/MEK/Erk and protein kinase C-9 (PKC-9) pathways [25].

With all this, evasion of the anti-tumor function of the immune system is achieved. In summary, the PD-1-mediated inhibitory pathway is related to decreased T-cell proliferation and increased T-cell apoptosis. It entails the resistance of malignant cells.

In a healthy host, PD-1/PD-L1 signaling regulates effector T cell responses, protecting tissues and generating self-tolerance. PD-L1 expression in the tumor cell is primarily mediated by the JACK/STAT signaling pathway, which in turn is influenced by several factors in the tumor microenvironment [25]. This is shown in Figure1. The following influences could determine the increased expression of PD-L1 in lymphoid neoplasms:

1. Chromosome 9p24.1 structural alterations induce JAK2 amplification, leading to increased JAK/STAT signaling, implying increased PD-L1 expression. In DLBCL, genetic abnormalities or chromosomal alterations were observed on the short arm of chromosome 9 (gain type in 12% of cases, 3% amplifications and 4% translocations), leading to PD-L1 expression in approximately 20% of DLBCLs.

The Ig heavy chain gene may be implicated in further translocations that might result in the expression of PD-L1 in DLBCL [26]. Another genetic alteration favoring PD-L1 overexpression is the

disruption of 3'-UTR, a site of action of microRNAs involved in the regulation of oncogenes. The gene fusion between CIITA and PD-L, which determines that PD-L1 expression is regulated under the transcriptional control of the CIITA promoter (major histocompatibility complex transactivator gene), also favors PD-L1 overexpression, as well as decreased expression of MHC class II, already mentioned previously as an important factor in NHL immune evasion [27].

2. Proinflammatory cytokines: IFNy produced by tumor infiltrating lymphocytes (TILs) and increased IL-10 in the tumor microenvironment increases the JAK/STAT pathway.

3. Mutational status of tumor suppressor genes and genes involved in the immune response including the suppressor of cytokine signaling gene 1 (SOCS1) and myeloid differentiation primary response gene 88 (MYD88). Mutations are detected in about one third of DLBCL cases with the non-GC form. The MYD88 L265P mutation is the most frequent oncogenic change.

4. Epstein-Barr virus (EBV) infection, through the expression of EBV latent membrane protein 1 (LMP-1), which induces activation of the transcription factor, activator protein 1 (AP-1), by activating the N-terminal kinase (JNK) cascade c-Jun. In this way, the JAK/STAT pathway is activated. This has been especially important for several lymphoma subtypes, including HL where larger percentages of PD-L1 expression have been seen and in certain DLBCLs caused by or related to EBV. Immunodeficiency has been considered a key factor in the development of EBV+BCL, as well as immune escape from tumor cells [27].

5. Epigenetic regulation. MicroRNAs (miRNAs) are single-stranded non-coding RNAs of between 20 and 24 nucleotides that bind directly to the untranslated region 3 (3UTR) of the target gene's messenger RNA to degrade that mRNA or inhibit its translation. They play a crucial role in regulating oncogene expression, functioning as suppressor genes, such that increased miRNA levels prevent uncontrolled tumor cell growth. The relationship of miRNA with certain specific types of cancer has been described. For hematological malignancies, miR-135a is associated with the regulation of classical Hodgkin's lymphoma cells and miR-195 is associated with cell growth in several types of cancer including DLBCL. Reduced miRNA levels could be a clinical predictor of disease progression or cancer relapse. miR-195 binds to the 3UTR region of PD-L1 protein and inhibits its expression, so there appears to be a correlation between the down-expression of miR-195 and the up-regulation of PD-L1 in DLBCL cell lines [28,29].

6. Transcription factors that are involved also in the escape of cancer cells from the immune system are HIF-1, STAT3, nuclear factor kappa, TGF-y, GATA 3 and T-bet [17].

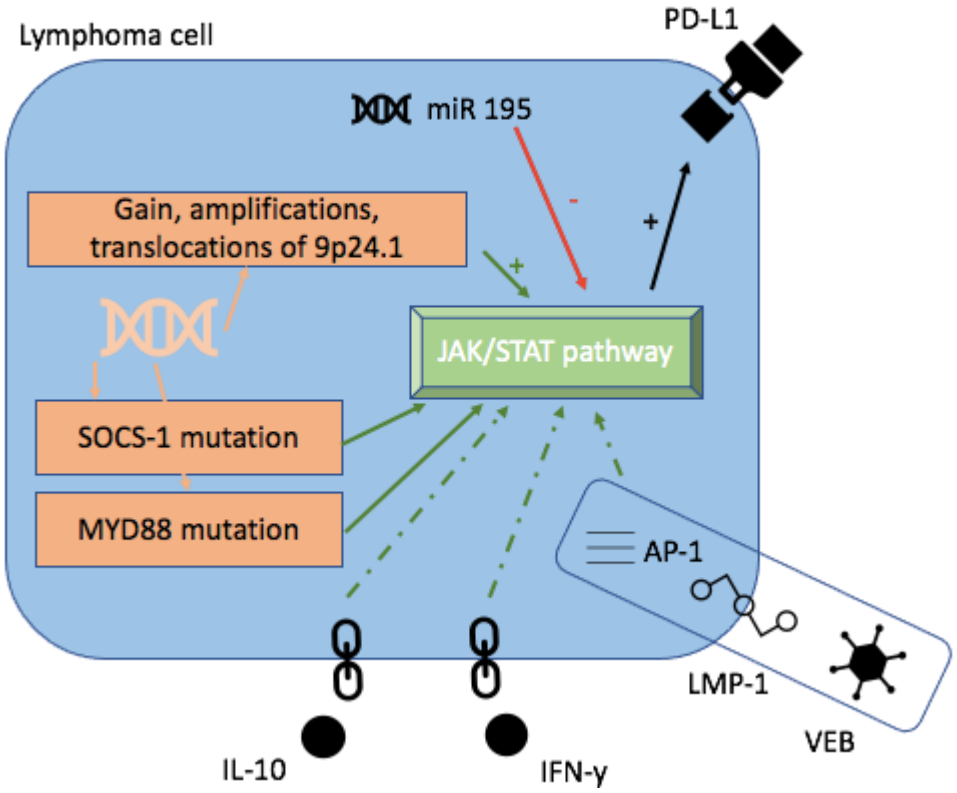

Figure 1. Mechanisms of escape of DLBCL from the control of immune system and possibly involved in the regulation of PDL-1 expression.

4. Clinical data on the use of PD1/PD-L2 inhibitors in DLBCL

Although most patients with DLBCL have cure rates of about 80% with standard immunochemotherapy like R-CHOP regimen, a percentage of them die from disease progression (40%) [25,30]. Although PD1 and PD-L1 expression is not usually a striking feature of patients with this type of cancer, several reports have shown strong overexpression of PD-L1 in specific subsets of these NHLs [31,32]. The PD-1/PD-L1 pathway contributes to tumor cell survival and inhibition of this pathway may be an effective tool for the treatment of this type of lymphomas [33,34]. Andorsky et al described a PD-L1+ DLBCL cell line that exhibited non-GCB phenotype properties (inhibition of T-cell proliferation and IFN-γ secretion by tumor-associated T cells), suggesting that PD-L1 plays a key role in the tumor microenvironment and results in an aggressive clinical phenotype and worse prognosis [35].

Although the first published data on checkpoint inhibition in B-cell NHL was using ipilimumab (anti-CTL4 antibody), most current clinical trials have been conducted with monoclonal antibodies blocking PD-1 or PD-L1 [36]. Immunotherapy using this pathway has now been shown to have a durable response and improved survival rates in a variety of hematological malignancies.

Nivolumab is a fully humanized IgG-4 monoclonal antibody that targets the PD-1 receptor on human T cells. The blockade of this pathway by this drug increases T-cell proliferation and IFN-γ release [37].

The results of the Phase 1b dose escalation study of nivolumab involving 81 patients included 11 patients diagnosed with LBDCG. The ORR was 36% (CR = 18% and PR = 18%) and the median PFS was only 7 weeks for this subgroup of patients. Adverse events for this drug were present in 96% of cases, while grade 3 adverse events were observed in 22% of cases [30,37].

The phase II study evaluating the effect of nivolumab administered twice monthly in patients with R/R DLBCL ineligible for transplantation or in those who had failed transplantation, the ORR values were 10% and 3%, respectively. The median PFS and OS were 1.9 and 12.2 months in the cohort of patients in whom autologous transplantation failed and 1.4 and 5.8 months in the group of patients ineligible for transplantation, respectively. Of the total samples in which the 9p24.1 chromosomal alteration was evaluated, 16% of the cases showed a low-level gain, while only 3% of the cases contained amplifications of this chromosomal alteration. The low response rates in LDCBG were attributed to rare genetic alterations on 9p24.1 [30,38].

Another high-affinity humanized IgG-4 anti-PD-1 mAb is Pembrolizumab [37]. This drug was shown to have high antitumor activity and a favorable safety profile in the treatment of different malignancies [39]. In a phase 2 study designed to evaluate the efficacy and safety of this drug, patients with different diagnoses (CLL or transformation to LBDCG) were included. The majority of patients who obtained some response (ORR 44%) was those diagnosed with LBDCG or transformation. After a follow-up period of 11 months, the median PFS was 5.4 months and OS was 10.7 months. Grade 3 or 4 adverse reactions occurred in 60% of cases.

Other studies have evaluated the usefulness of pembrolizumab as maintenance therapy in patients with chemosensitive DLBCL undergoing autologous transplantation. This group of patients showed a PFS at 18 months of 59%. The effectiveness of the association of pembrolizumab with R-CHOP has been studied in 30 cases of newly diagnosed DLBCL and the ORR and CR were 90% and 77%, respectively. With a median follow-up of 25.5 months, 2-year PFS was 83% [39].

Pembrolizumab has also been used in the treatment of primary mediastinal large B-cell lymphoma (PMBL). In this type of lymphoma, the presence of the 9p24.1 rearrangement, which leads to overexpression of the immune checkpoint molecules PDL1 and 2, has allowed the use of these inhibitors [40]. Pembrolizumab, successfully tested as a single agent (KEYNOTE-013) in patients with PMBL relapsed after ASCT has a manageable safety profile and a good overall response rate (ORR) of 48%. However, the good overall response rate observed in the KEYNOTE-013 study was associated with frequent relapses and a median progression-free survival (PFS) of 10.4 months, suggesting the need for combination strategies [41].

Many immune and tumor-infiltrating cells express programmed death-ligand 1 (PD-L1), that negatively regulates the cytotoxic T-lymphocyte activation by binding to the programmed death-1 (PD-1) and B7.1 (CD80) receptors that cause suppression of T-cell migration, proliferation and secretion of cytotoxic mediators leading to inhibited tumor cell killing. Atezolizumab is a humanized monoclonal anti-programmed death-ligand 1 (PD-L1) antibody that inhibits PD-L1–programmed death 1 (PD-1) and PD-L1–B7-1 signaling, thereby resulting in tumor-specific cytotoxic T-cell immunity [42]. The Fc region of atezolizumab is designed to reduce Fc effector function and minimize antibody-dependent cell-mediated cytotoxicity. This prevents hypothetical antibody-mediated loss of PD-L1-expressing T cells and thus anti-tumor activity is enhanced.

The combination of Atezolizumab with 6 cycles of R-CHOP administered for 12 months was assessed in 42 patients with untreated advanced DLBCL. ORR was 87.5%. 2-year PFS and OS were

74.9% and 86.4%, respectively [43]. However, several clinical trials have shown modest activity of atezolizumab in combination with various therapeutic agents in patients with R/R DLBCL [43–45].

Durvalumab, a humanized anti-PD-L1 IgG1 antibody [46], in combination with R-CHOP, has demonstrated a CR rate of 54% in previously untreated patients with DLBCL and has shown acceptable activity in combination with Ibrutinib in patients with R/R DLBCL [47]. Recent various phase-I/II studies in DLBCL were ongoing to investigate the efficacies of durvalumab in monotherapy or combined with other agents (NCT03212807, NCT03241017, NCT03003520 and NCT02401048) [25].

In addition, avelumab as a humanized IgG1 mAb against PD-L1 was shown that leads to potent cell killing in the presence of natural killer cells purified from either healthy donors or cancer patients [32]. Different early phase studies are underway to evaluate the efficacy of Avelumab (NCT03244176, NCT02951156 and NCT03440567) in the treatment of patients diagnosed with high-risk DLBCL [25].

Table 1 summarizes the main clinical trials in the recruitment phase using anti-PD-1 or anti-PD-L1 in combination with other molecules (anti-CTLA-4, PI3K inhibitors, anti-CD27 or CAR T cells) as part of the treatment of patients with DLBCL.

Table 1. Clinical trials of immunotherapy in DLBCL.

Trial	Intervention	Molecular Target	Indication	Primary Endpoint	Status
NCT03305445	Nivolumab plus Ipilimumab	Anti PD-1 and CTLA-4 antibody	RR DLBCL	Safety, CR	Complete
NCT03484819	Copanlisib plus Nivolumab	Anti PD-1 antibody	RR DLBCL, PMBCL	ORR	Active, not recruiting
NCT03401853	Pembrolizumab plus anti CD-20 antibody	Anti PD-1 antibody	RR DLBCL, FL	ORR	Active, not recruiting
NCT03321643	Atzolizumab plus R-GemOx	Anti PD-L1 antibody	RR DLBCL	Safety	Active, not recruiting
NCT03150329	Pembrolizumab plus vorinostat	Anti PD-1 antibody	RR DLBCL, FL, HL	Safety	Active, not recruiting
NCT04476459	Camrelizumab plus Apatinib	Anti PD-1 antibody	RR DLBCL	ORR	Recruiting
NCT04796857	Tislelizumab plus Lenalidomide	Anti PD-1 antibody	RR DLBCL	ORR	Recruiting
NCT03038672	Varlilumab plus Nivolumab	Anti-CD27/anti PD-1 antibody	RR NHL	ORR	Active, not recruiting
NCT03015896	Nivolumab plus Lenalidomide	Anti PD-1 antibody	RR NHL, HL	Safety	Active, not recruiting

Continued on next page

Trial	Intervention	Molecular Target	Indication	Primary Endpoint	Status
NCT03287817	AUTO3 (CD19/CD22 CAR T) with Pembrolizumab	CAR T/anti PD-1 antibody	RR DLBCL	Safety, ORR	Active, not recruiting
NCT04381741	CD19 CAR T expressing IL7 and CCL19 combined with PD1 mAb	CAR T/anti PD-1 antibody	RR DLBCL	ORR	Enrolling by invitation

Note: DLBCL: Diffuse large B-cell lymphoma; RR: Relapsed refractory; NHL: Non-Hodgkin lymphoma; PMBCL: Primary mediastinal B-cell lymphoma; FL: Follicular lymphoma; HL: Hodgkin lymphoma; ORR: Overall response rate; CR: Complete remission; mAb: monoclonal antibody. CTLA-4: cytotoxic T-lymphocyte associated protein 4.

5. Conclusions

In this review, we have discussed the mechanisms of immune evasion and clinical data on PD-1-associated target therapy and its utility in the treatment of DLBCL. The role of the microenvironment and PD-1 expression on T cells as facilitators of tolerance to lymphomatous cells is well known. Blockade of this pathway induces T-cell exhaustion and blockade of malignant B-cell survival. In the case of patients diagnosed with DLBCL, PD-L1 expression in cell lines has been shown to be closely associated with poor prognosis in this neoplasm.

Recently, an improved understanding of the PD-1/PD-L1 pathway has led to the development of immunotherapy in patients with DLBCL. In that sense, different studies have already shown contradictory results with the use of anti-PD1mAbs such as Pembrolizumab or nivolumab in the management of patients with refractory or relapsed DLBCL. New clinical trials with new anti-PD-L1 antibodies are currently ongoing. However, it seems that the results are not entirely satisfactory.

New strategies targeting the immune system such as CAR T therapy and bispecific antibodies seem to be more effective in the treatment of this pathology.

Use of AI tools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

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Conflict of interest

The authors declare no competing interests.

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