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Checkpoint Inhibitors and Other Immune Therapies for Hodgkin and Non-Hodgkin Lymphoma

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Abstract

Opinion statement

Treatment for relapsed/refractory (R/R) Hodgkin and non-Hodgkin lymphoma remains challenging. The introduction of rituximab to B cell non-Hodgkin lymphoma (B-NHL) treatment significantly improved patients' response rate and survival; however, approximately one third of patients with diffuse large B cell lymphoma, the most common B-NHL subtype, still have a relapse or become refractory after first-line therapy. More recently, antibody therapies and small-molecule inhibitors were approved for treating R/R lymphomas; these agents include brentuximab vedotin, ibrutinib, and idelalisib. Immune checkpoint inhibitors and other immune therapies are emerging treatments currently being evaluated in various clinical trials for their efficacy against lymphoid malignancies. Striking results from these treatment modalities have been observed in solid tumors, and evidence is accumulating to support their use in various lymphomas. The most exciting results from immune checkpoint inhibitor therapy have been seen in patients with R/R Hodgkin lymphoma, in whom the overall response rate has reached 60–80 %. Results in NHL are more similar to those seen in other solid malignancies, ranging between 20 and 40 %, depending on the histology. Formal approval of these drugs is being awaited, as are the results of combination therapy with checkpoint inhibitors and other treatment modalities, including conventional chemotherapy, small-molecule inhibitors, and other immune therapies. Although response rates have been promising, attention must be paid to the management of unique immune-related adverse events, which warrant close monitoring in some cases. Identification of biomarkers that predict response or severe adverse events using either the tumor specimen or peripheral blood would aid in selecting patients suited for these types of treatment as well as determining the ideal sequence of treatment within the realm of immune therapies.

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Compliance with Ethical Standards

Conflict of Interest

Eri Matsuki declares that she has no conflict of interest.

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Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Keywords

Hodgkin lymphoma; Non-Hodgkin lymphoma; Checkpoint inhibitor; Nivolumab; Pembrolizumab; CAR T cell

Introduction

The concept of harnessing the human immune system to eradicate malignant diseases emerged almost a century ago, and graft-versus-leukemia effect following allogeneic hematopoietic stem cell transplantation (HSCT) is one of the compelling evidences showing the effect of immune therapy against hematologic malignancies [1, 2]. Recent understanding of the interaction between the immune system and tumors has greatly moved the field forward [3]. Unleashing the breaks on the host immune mechanism via checkpoint inhibition to restore T cell effector function has proven to be an effective treatment strategy for various cancers, including lymphomas (Fig. 1) [4–12, 13••]. Blocking the cytotoxic T lymphocyte-associated protein 4 (CTLA-4) and programmed death 1 (PD-1) pathways thus far has been the most promising approach approved for melanoma, non-small cell lung cancer, and renal cell carcinoma, with ongoing clinical trials in many other cancers, including hematologic malignancies.

CTLA-4 is a coinhibitory receptor expressed mainly in the cytoplasm of resting naïve T cells. Upon antigen stimulation, it is mobilized to the T cell surface, is incorporated into the immunologic synapse, and binds with its ligands, CD80 and CD86, resulting in downregulation of T cell activation [14, 15]. PD-1, another checkpoint molecule, is expressed on the surface of various immune cells, including activated T cells, B cells, and natural killer (NK) T cells. Upon T cell activation, PD-1 expression on the cell surface is induced and persists as the T cell infiltrates the peripheral tissues [16]. Within the tissue, cells in the microenvironment express the PD-1 ligands PD-L1 and PD-L2, leading to T cell suppression upon cellular contact [17, 18]. Recent understanding of various cancers has led to the invention of monoclonal antibodies (mAbs) directed against the receptors of ligands involved in the CTLA-4 and PD-1 pathways, making it possible to reverse the tumor-induced downregulation of T cell function and to augment antitumor immune activity at the priming or tissue effector phase [19].

Lymphomas are malignancies of lymphocytes in which malignant cells, arrested at different stages of differentiation, expand in lymph nodes, bone marrow, and often other tissues and organs. They often arise from genetic alterations, such as chromosome translocations that bring an oncogene under the control of an immunoglobulin locus. The genetic changes, as well as activation of certain upstream signaling pathways and viral infection, often lead to mechanisms that evade immune surveillance by re-educating the cells in the microenvironment through cytokine and chemokine signaling as well as aberrant expression of checkpoint proteins such as PD-1 and its ligands [20–22]. In classic Hodgkin lymphoma (cHL) and primary mediastinal large B cell lymphoma (PMBCL), amplification and translocation of the 9p24.1 region—the location of PD-L1 and PD-L2, as well as JAK2, an upstream signaling of the JAK–STAT pathway—have been reported and lead to the

overexpression of PD-L1 and PD-L2 [23]. Moreover, recent data show that the tumor microenvironment in lymphoma is highly immunosuppressive, with cells within the immune microenvironment expressing PD-L1 and many of the intratumoral T cells with an exhausted immune phenotype expressing PD-1, making lymphoma an attractive target for immune checkpoint blockade and other immune therapies [24]. This immunophenotype may be responsible in part for the very high response rate of Hodgkin lymphoma (HL) to PD-1 blockade compared with other tumor types.

In this article, we review the current available data on immune checkpoint inhibitors and other immune therapies currently being evaluated for treating HL and non-Hodgkin lymphoma (NHL).

Checkpoint inhibitors

Pidilizumab (CT-011)

Pidilizumab, a humanized IgG1 mAb directed against PD-1, was the first agent in this class to be tested in lymphoid malignancies. The phase I study included 17 patients with various hematologic malignancies, eight of whom had lymphoid malignancies (one with HL, four with NHL, and three with chronic lymphocytic leukemia [CLL]). The patients were treated with a single dose of pidilizumab at five different dose levels (0.2, 0.6, 1.5, 3, and 6 mg/kg) after premedication with an antihistamine, pain relief medication, and corticosteroids; no dose-limiting toxicity was observed. Overall, six patients responded to treatment, including a complete response (CR) in a patient with follicular lymphoma (FL) and stable disease (SD) in two patients with CLL and one patient with HL [25]. In light of these promising results, two phase II studies were conducted, one study in previously treated, chemosensitive de novo or transformed diffuse large B cell lymphoma (DLBCL) or PMBCL after autologous HSCT and the other in combination with rituximab in patients with relapsed, rituximab-sensitive FL [26, 27].

The international phase II study [26] included patients with DLBCL, PMBCL, or transformed indolent B cell lymphoma after autologous HSCT. They were treated with intravenous pidilizumab at a dosage of 1.5 mg/kg every 42 days for three cycles, beginning 30 to 90 days after undergoing autologous HSCT. The patients received premedication with acetaminophen or ibuprofen and diphenhydramine or promethazine. Seventy-two patients received at least one dose of the drug, 66 of whom were evaluable. The most frequently reported grade 3 to 4 adverse events (AEs) were neutropenia (19 %) and thrombocytopenia (8 %). There was no evidence of significant autoimmune toxicity, infusion reactions, or treatment-related mortality; however, one patient died of disseminated zoster after the third dose of pidilizumab, but this was deemed unrelated to the study treatment. The 16-month progression-free survival (PFS) and overall survival (OS) of the 66 evaluable patients were 0.72 (90 % CI, 0.60–0.82) and 0.85 (90 % CI, 0.74–0.92), respectively.

Another single-institution phase II study evaluated pidilizumab in combination with rituximab in patients with relapsed, rituximab-sensitive FL [27]. Patients received pidilizumab 3 mg/kg every 4 weeks for four infusions; those with SD or better were given the option to receive up to a total of 12 infusions. Rituximab was given at 375 mg/m²

intravenously weekly for 4 weeks, starting 17 days after the first pidilizumab infusion. Thirty-two patients were enrolled, 29 of whom were evaluable for activity. The treatment was well tolerated, with no autoimmune or treatment-related AEs of grade 3 or 4. The most common grade 1 AEs were anemia (44 %) and fatigue (41 %); the most common grade 2 AE was respiratory infection (16 %). CRs were noted in 15 patients (52 %) and partial responses (PRs) in 4 (14 %), leading to an objective response in 19 (66 %). Median PFS for all patients was 18.8 months (95 % CI, 14.7–not reached). No deaths occurred during the trial.

Both studies also investigated correlative biomarkers from peripheral blood or lymph node specimens. In the international phase II study, pidilizumab treatment resulted in a significant increase in the absolute number of PD-L1-bearing activated helper T cells (CD4⁺/CD25⁺/PD-L1⁺), which was sustained until at least 16 weeks after treatment [26]. A higher level of PD-L1 expression was observed on peripheral blood T cells and monocytes at baseline in responders to treatment in the other study, suggesting the utility of PD-L1 as an effective biomarker. Changes also were seen in the genetic signature in cells of peripheral blood or the tumor microenvironment, as well as a unique genetic signature predicting response to pidilizumab; however, these findings must be confirmed in larger samples and in response to other PD-1-targeting drugs [27].

Overall, these studies provide proof of concept that blocking the PD-1 axis in lymphoma is an effective treatment strategy. A phase II study being conducted in patients with DLBCL following first remission is using peripheral blood lymphocyte proportion as a response marker (NCT02530125).

Nivolumab (BMS-936558, MDX1106)

Nivolumab, a fully human IgG4 anti-PD-1 mAB, currently is approved by the US Food and Drug Administration (FDA) for the treatment of melanoma, non-small cell lung cancer, and renal cell carcinoma. The results of a phase I study against lymphoid malignancies have been reported, with the most abundant experience in patients with HL. In this study, an independent cohort of 23 patients with relapsed/refractory (R/R) cHL received nivolumab at a starting dosage of 1 mg/kg, escalated to 3 mg/kg; the results show that nivolumab was well tolerated and yielded an overall response rate (ORR) of 87 % [13•]. Overall, drug-related AEs were reported in 18 patients (78 %), the most common of which were rash (22 %) and thrombocytopenia (17 %). Drug-related grade 3 AEs were reported in five patients (22 %); these included myelodysplastic syndrome (MDS), pancreatitis, pneumonitis, stomatitis, colitis, gastrointestinal inflammation, thrombocytopenia, increased lipase levels, decreased lymphocyte levels, and leukopenia. There were no drug-related grade 4/5 AEs. Three patients had one serious drug-related AE each: one grade 3 pancreatitis, one grade 3 MDS, and one grade 2 lymph node pain.

A follow-up report recently was presented, with the median observation period extended to 101 weeks [28]. The ORR remained at 87 % (CR, 5; PR, 15; SD, 3 patients), with one patient previously with a PR improving to a CR. Among responders, the time to CR after starting nivolumab ranged from 3 to 88 weeks. Neither the median duration of response nor the median PFS had been reached. OS was 91 % at 1 year and 83 % at 1.5 years. Among the

20 responding patients at the time of data cutoff, three were still receiving nivolumab treatment, with ongoing responses. Some of these patients surpassed the 2-year treatment mark; one patient who discontinued treatment after initial response and subsequently experienced disease progression was re-treated with nivolumab and achieved a second response. This report highlights not only a high response in cHL but also the safety, tolerability, and durable response with long-term treatment.

The activity of nivolumab in other lymphoid malignancies also has been presented [29]. Patients with R/R NHL were treated at the same dose escalation of 1 to 3 mg/kg of nivolumab every 2 weeks for up to 2 years. The expansion cohort was treated at a single-dosing schedule of 3 mg/kg every 2 weeks. Among the 31 patients with B-NHL enrolled in the study, an ORR of 26 % (CR, 10 %; PR, 16 %) was observed, with 52 % of the patients achieving SD. Patients with more common disease subtypes were more likely to respond, with an ORR in DLBCL of 36 % (CR, 18 %; PR, 18 %) and in FL of 40 % (CR, 10 %; PR, 30 %). The median duration of response was 22 weeks in patients with DLBCL and was not reached in patients with FL. Responses also were seen in 23 patients with T cell NHL (T-NHL), with superior response seen in patients with peripheral T cell lymphoma (PTCL). The ORR for patients with T-NHL was 17 % (all PRs). The ORR in patients with PTCL was 40 % and was 15 % in those with cutaneous T cell lymphoma (CTCL). Sixty-nine percent of the patients with CTCL had SD; therefore, the median duration of response was not reached for both PTCL and CTCL.

Biomarkers of response also have been investigated. In a subgroup of 10 patients with HL whose tumor samples were available, tumor cells exhibited increased copy numbers of PD-L1 and PD-L2 genes, and all expressed PD-L1 and -L2 proteins. Tumor cells also were positive for nuclear phosphorylated STAT3, suggesting activation of JAK–STAT signaling in the tumor cells. The infiltrating T cells in the microenvironment largely expressed low levels of PD-1 receptors [13•]. Although these findings have not been confirmed in patients with lymphoid malignancies, data from other solid tumors suggest the following as potential biomarkers of response to nivolumab and other anti-PD-1 antibodies: expression of PD-L1 on tumor cells, PD-L1 expression in the microenvironment, the presence of tumor-infiltrating cells, the existence of somatic mutations as assessed by mismatch repair deficiency, and an increased mutational landscape of tumors [8, 11, 30•, 31•]. We await the results of ongoing phase II studies to evaluate the utility of these biomarkers in patients with lymphoma.

Multiple phase II studies of nivolumab as a single agent are underway to evaluate its efficacy in patients with FL (NCT02038946), DLBCL (NCT02038933), and HL (NCT02181738). Many ongoing studies also are evaluating the efficacy of this drug in combination with agents such as brentuximab vedotin (NCT02572167), ipilimumab (NCT01896999), urelumab (NCT02253992), ibrutinib (NCT02329847), and indoleamine 2,3-dioxygenase 1 (IDO1) inhibitor (INCB24360; NCT02327078). Combinations with ibrutinib or INCB24360 are especially attractive because of their biologic mechanism in enhancing antitumor T cell immune responses [32, 33•].

Pembrolizumab (MK-3475, lambrolizumab)

Pembrolizumab, formerly known as lambrolizumab, is a humanized IgG4 antagonistic anti-PD-1 mAb. The use of IgG4 limits Fc receptor engagement and does not result in antibody-dependent cell-mediated cytotoxicity (ADCC) of PD-1-positive cells. Therefore, the predominant mechanism of pembrolizumab is enhancement of antitumor immune responses [34]. A multicohort open-label phase Ib clinical trial (KEYNOTE-013) is ongoing to assess the safety and efficacy of pembrolizumab in patients with hematologic malignancies. Results already were reported from a cohort of patients with HL in whom brentuximab vedotin treatment had failed [35, 36].

Thirty-one patients received pembrolizumab 10 mg/kg intravenously every 2 weeks until tumor progression, excessive toxicity, or completion of 2 years of therapy. Altogether, 68 % of the patients presented with AEs of any grade; however, none had a grade 4 or fatal AE. AEs leading to treatment discontinuation were pneumonitis and nephrotic syndrome. The ORR was 65 % (CR, 16 %; PR, 48 %); 23 % of patients achieved SD, with 90 % exhibiting a reduction in target lesions. Seventy-one percent of the patients had a sustained response of more than 24 weeks. With a median follow-up of nearly 18 months for survivors, the PFS at 24 weeks was 69 % [36].

A patient subset was evaluated for biomarkers [36]. Fifteen patient samples (94 %) were positive for PD-L1 and nine (90 %) for PD-L2. Nine patients had peripheral blood samples available for pretreatment and posttreatment comparison after cycle 7, and changes in circulating lymphocyte subsets were assessed by flow cytometry. CD4, CD8, NK, and total T cell counts all showed significant increases compared with baseline. Blood from 19 patients also was available for RNA analysis performed on a NanoString platform (NanoString Technologies, Seattle, WA) at baseline and after cycle 7. No specific signature or single gene expression was identified that predicted response to treatment; however, on a 794 immune-related gene panel, previously identified gene signatures (i.e., expanded immune score, T cell receptor signaling, and IFN- γ score) [37] were significantly upregulated after pembrolizumab treatment.

The results of this phase Ib study regarding the other lymphoma subtypes are still pending; however, various phase II studies of pembrolizumab, either as a single agent (NCT02362997, NCT02576990, NCT02684292, NCT02453594, NCT02535247) or in combination with conventional chemotherapy (NCT02541565), rituximab (NCT02446457), or small-molecule inhibitors, such as ibrutinib, idelalisib, and INCB24360 (NCT02332980, NCT02178722), are underway for HL, PTCL, DLBCL, PMBCL, FL, and other indolent B cell lymphomas.

Ipilimumab

Ipilimumab is a fully humanized IgG1 mAb targeting the CTLA-4 pathway. The data on CTLA-4 blockade in hematologic malignancies are limited, as CTLA-4 blockade has been less studied compared with PD-1 blockade.

In a phase I study, ipilimumab was administered in a single dose of 0.1 to 3.0 mg/kg to 29 patients, predominantly with relapsed hematologic malignancies after allogeneic stem cell

transplantation [38]. No dose-limiting toxicity was observed, and ipilimumab did not induce graft-versus-host disease or graft rejection. Three patients with lymphoid malignancy developed objective disease responses, including two patients with HL in CR and one patient with mantle cell lymphoma (MCL) achieving a PR. An ongoing follow-up phase I/Ib is administering ipilimumab at 3 or 10 mg/kg intravenously every 3 weeks for four induction cycles, followed by maintenance dosing every 12 weeks up to 1 year [39]. Preliminary results reported 13 patients treated, including three with NHL and four with cHL, with 36.4 % of patients achieving a clinical benefit (one HL with PR, one HL, and one CTCL with SD).

Another phase I study was conducted to evaluate safety, immunologic activity, and potential clinical efficacy in patients with R/R B cell lymphoma [40]. Treatment consisted of ipilimumab at 3 mg/kg and then monthly at 1 mg/kg for 3 months, with subsequent escalation to 3 mg/kg monthly for 4 months. Among 18 patients treated, two patients showed a clinical response, one patient with DLBCL had an ongoing CR for over 31 months, and one patient with FL had a PR lasting 19 months.

Based on these results, studies are being conducted to evaluate the efficacy of ipilimumab either alone or in combination, both before and after stem cell transplantation (NCT01896999, NCT01729806, NCT01592370, NCT01919619, NCT01822509). Because of the major success of ipilimumab/nivolumab combination checkpoint inhibitor therapy in patients with melanoma, there is much interest in using this combination therapy in lymphoid and other hematologic malignancies.

Agents targeting PD-L1

MEDI4736, an IgG1 anti-PD-L1 mAb, is being evaluated in combination with ibrutinib (Bruton's tyrosine kinase inhibitor) in patients with R/R FL and DLBCL (NCT02401048) and in combination with rituximab for aggressive B cell lymphomas (NCT02205333) [41].

Atezolizumab (MPDL3280A), a humanized engineered IgG1 mAb against PD-L1 [42•], is being developed for use against various hematologic malignancies. A global phase I/II study testing this agent in combination with obinutuzumab in patients with R/R FL or DLBCL (NCT02220842) is currently recruiting patients, as are studies of MPDL3280A and obinutuzumab plus lenalidomide, bendamustine, or CHOP chemotherapy (NCT02596971, NCT02631577).

Urelumab

Urelumab is a fully human IgG4 mAb targeting the CD137 receptor (also known as 4-1BB or TNFRSF9) with potential immunostimulatory and antineoplastic activities [43]. CD137 is a member of the tumor necrosis factor/nerve growth factor family of receptors and is expressed by activated T and B lymphocytes and monocytes. Activation of the molecule may costimulate and enhance the effect of T cells, increasing their cytotoxicity and protecting them from programmed death. It also can enhance NK cell function in ADCC, thus enhancing the antitumor effects of antibodies that target tumor cells directly, such as rituximab. Although it is not a part of the CTLA-4 or PD-1 pathway, its potential to enhance immune response has gained interest in the clinical development of the antibody, and it

currently is being evaluated in combination with rituximab or nivolumab against B-NHL and CLL (NCT02253992, NCT02420938).

Other emerging immune therapies

Chimeric antigen receptor-modified T cells

Chimeric antigen receptor-modified (CAR) T cells are autologous T lymphocytes genetically modified to express CAR constructs. They typically are composed of a single-chain fragment variable (scFv) of an antibody fused to the activating intracellular signaling domain of the T cell receptor, typically the ζ -signaling domain [44]. This construct would allow CAR expressing autologous polyclonal T cells to bind a specific tumor-associated antigen, resulting in major histocompatibility complex-independent activation of T cells [45]. Most published CAR T cell studies used CD19-directed CAR T cells to treat B cell lymphoid malignancies.

Although clinical experience with CAR T cells is more abundant in acute lymphoblastic leukemia, experience in other lymphoid malignancies, such as CLL and NHL, is accumulating. The initial studies of CAR T cells in CLL enrolled patients who had undergone heavy pretreatment and had bulky disease. Without preconditioning chemotherapy, no response was observed; however, modification of the protocol to allow chemotherapy before CAR T cell infusion led to an improvement in clinical response (one CR, one PR, two SD) [46]. In a pilot study of another CAR T cell product, CTL019, 14 patients with R/R CLL were treated, with an ORR of 57 % [47, 48]. A follow-up phase II study presented an ORR of 35 % (CR, 22 %; PR, 17 %) among 23 evaluated patients [49]. A different group tested its construct in a small group of patients with CLL. The initial four patients received fludarabine and cyclophosphamide before CAR T cell infusion, supplemented with IL-2, resulting in an ORR of 75 % [50]. Although a later cohort of four patients did not receive IL-2 supplementation, it presented an ORR of 100 %, including three patients with a CR [51••].

The results of CAR T cell therapy for other B-NHLs also are developing. A team at the National Cancer Institute was the first to evaluate currently used CAR T cell therapy in NHL [52]. According to the report from this study, which included nine patients with DLBCL and two with indolent B-NHL, four of seven evaluable patients with DLBCL obtained a CR, two achieved a PR, and one achieved SD, and one patient with indolent B-NHL also achieved a CR. All patients in this study received cyclophosphamide/fludarabine combination therapy before CAR T cell infusion [51••]. The experience with CTL019 against B-NHL was updated recently [53]. A total of 28 patients (15 with DLBCL, 11 with FL, and 2 with MCL) were treated, with an ORR of 47, 73, and 50 % and a CR rate of 40, 64, and 0 % for DLBCL, FL, and MCL, respectively. A group at the Fred Hutchinson Cancer Center also reported their experience with CAR T cells in B-NHL [54]. They treated 32 patients with R/R CD19-positive B-NHL (18 with DLBCL, 1 with Burkitt's lymphoma, 1 with T cell-rich B cell lymphoma, 2 with PMBCL, 6 with low-grade NHL, and 4 with MCL). Patients received cyclophosphamide and/or etoposide or fludarabine as preconditioning therapy, and the dosage of CAR T cells ranged from 2×10^5 to 2×10^7 /kg. Of the 30 evaluable patients, 19 (63 %) had an objective response. Interestingly, patients who received conditioning

therapy with a combination of cyclophosphamide and fludarabine presented with a higher response rate—72 %—compared with 50 % in those who received cyclophosphamide alone or in combination with etoposide. This observation appears to be a result of reduced transgene immune response following the incorporation of fludarabine. In a different clinical setting, investigators from Memorial Sloan Kettering Cancer Center are evaluating the utility of CAR T cells as a consolidation for high-risk R/R aggressive B-NHL after high-dose therapy and autologous stem cell transplantation [55]. An interim analysis found that 4 of 10 evaluable patients have been in continuous remission at a median follow-up of 14 months after study treatment and up to nearly 2 years in 2 patients.

CAR T cells targeting HL are still under development. Two potential targets are CD123 and CD30, with early results of the latter reported recently in abstract form [56, 57]. Nine patients with either HL or anaplastic large cell lymphoma were treated, with two patients achieving a CR and one patient with a PR. The safety and utility of these CAR T cells, however, warrant further investigation.

Despite promising results demonstrating the clinical efficacy of CAR T cells, caution must be taken regarding treatment toxicities, the most notable of which are cytokine release syndrome (CRS), encephalopathy, and B cell aplasia. CRS results from the high level of cytokines released by CAR T cells, which stimulates a cascade of cytokine release from the reactive tumor microenvironment. Typical symptoms include fever, tachycardia, capillary leak syndrome, respiratory distress, and hypotension requiring vasopressors, and they manifest within the first 3 weeks of cell infusion. Algorithms have been developed to aid in clinical management of CRS [58]. Despite suggestions that CRS and other AEs associated with CAR T cell therapy may be related to the dosage of infused cells, a clear correlation with the dose or timing of administration has not been identified.

Several challenges exist regarding the further development of CAR T cells, including identification of the ideal CAR construct, cell dosage, cell composition, and manufacturing. So far, different groups have used different constructs and manufacturing procedures, making it difficult to identify a lead compound. Several pharmaceutical companies have joined the market to facilitate large-scale production of the product [59]. While clinical trials of CAR T cells targeting CD19 are underway, combination treatment with small-molecule inhibitors, such as ibrutinib, lenalidomide, or immune checkpoint inhibitors, may be explored to enhance treatment efficacy.

Bispecific antibodies and their derivatives

Bispecific antibodies are recombinantly engineered antibodies that harbor specificities of two antibodies in one molecule, thereby gaining the ability to address different antigens or epitopes simultaneously [60]. They place the two targets close to each other to support protein complex formation on one cell or to trigger contact between cells. Blinatumomab, the first FDA-approved therapy in the class of bispecific T cell engagers (BiTE; Amgen Oncology, Thousand Oaks, CA), consists of two scFvs targeting CD19 and CD3 joined by an amino acid linker [61]. BiTEs work by facilitating the formation of a functional immune synapse between the engaged T cells and the CD19-expressing tumor cells, resulting in IL-2-independent polyclonal T cell activation and apoptotic cell death of target cells.

Blinatumomab has an extremely short half-life; therefore, early dose escalation trials in NHL and CLL, in which the drug was administered at dosages ranging from 0.75 to 13 $\mu\text{g}/\text{m}^2$ up to three times weekly, showed no objective responses. Moreover, troubling AEs, especially neurologic events such as aphasia, ataxia, disorientation, and seizure, were reported, leading to treatment discontinuation in 12 patients [61]. Subsequent studies were conducted with continuous intravenous administration of blinatumomab to increase the exposure to drug.

A phase I dose escalation study was performed to determine the AEs and maximum tolerated dose of blinatumomab in patients with R/R NHL [62••]. Seventy-six patients were treated at seven different dosage levels ranging from 0.5 to 90 $\mu\text{g}/\text{m}^2/\text{day}$ administered over 4 or 8 weeks as a continuous infusion. The maximum tolerated dose was established as 60 $\mu\text{g}/\text{m}^2/\text{day}$, with neurologic events (encephalopathy, seizure, and aphasia) comprising the dose-limiting toxicities. Grade 3 neurologic events occurred in 22 % of patients, with no grade 4/5 AEs reported. No treatment discontinuations occurred among patients who received single-step blinatumomab dosing plus pentosan polysulfate SP54 or double-step dosing with early dexamethasone prophylaxis. Among patients treated at 60 $\mu\text{g}/\text{m}^2/\text{day}$ ($n = 35$), the ORR was 69 % across NHL subtypes (DLBCL, 55 %; MCL, 71 %; FL, 80 %), with a median response duration of 404 days.

The results of a phase II study enrolling patients with R/R DLBCL were reported recently [63••]. This study evaluated a weekly step-up dosing of 9, 28, and 112 $\mu\text{g}/\text{day}$ or a flat dosing of 112 $\mu\text{g}/\text{day}$ of blinatumomab by continuous infusion for up to 8 weeks. The flat-dosing schedule was discontinued because of grade 3 neurologic AEs in both patients treated on this schedule. In the stepwise dosing cohort, grade 3 neurologic events consisted of encephalopathy and ataxia (seen in 9 % of patients) and tremor, speech disorder, dizziness, somnolence, and disorientation (each seen in 4 % of patients). Among 21 evaluable patients, the ORR was 43 %, including 19 % of patients who achieved a CR.

These studies show promising efficacy in heavily pretreated patients with NHL, in whom there is a great unmet medical need. Further studies are needed to confirm these responses as well as to find optimal dosing strategies to avoid AEs leading to treatment discontinuation. Derivatives of this platform, such as dual-affinity retargeting antibodies and tandem antibody-based therapies, also are emerging as treatment strategies with improved dosing schedule and valency, potentially leading to further improvement in efficacy.

Conclusions

Immune therapy with checkpoint inhibitors and other modalities including CAR T cells and bispecific antibodies show a promising treatment result against HL and NHL as summarized in the current article (Table 1). The efficacy of checkpoint inhibitors against HL is striking compared to that against NHL and other solid tumors (Fig. 1), and the result of combination treatment against NHL is anxiously being awaited. While these treatment modalities are effective in R/R HL and NHL where there is yet an unmet medical need, caution needs to be entailed in their unique side effects, especially immune-related AEs. Results from currently ongoing studies will hopefully provide us with better understanding of treatment efficacy as

well as increased information on biomarkers of response that will help guide in patient selection.

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Fig. 1.

Single-agent activity of PD-1/PD-L1 axis blockade in R/R disease across different tumor types. Although the data are preliminary and head-to-head comparison is difficult because of differences in enrollment criteria (e.g., the expression level of PD-L1 in the tumor and methods used to stain PD-L1), response to PD-1/PD-L1 axis inhibition appears especially high in patients with HL compared with those who have other tumor types, including NHLs.

Overview and selected clinical efficiency results on checkpoint inhibitors and others currently being tested in HL and NHL

Table 1

Target	Drug	Construct	Manufacturer	Disease	Number	ORR (%)	CR (%)	PR (%)	SD (%)	DOR	PFS	OS
PD-1	Nivolumab [28, 29]	Fully human IgG4 mAb	Bristol-Myers Squibb	HL	23	87	22	65	13	Median not reached	Median not reached	91 % at 1 year, 83 % at 1.5 years
				B-NHL	31	26	10	16	52			
					DLBCL	11	36	18	18	27	22 weeks	
					FL	10	40	10	30	60	median not reached	
				T-NHL	23	17	0	17	43			
	Pembrolizumab [36]	Humanized IgG4 mAb	Merck		CTCL	13	15	0	15	69	Median not reached	
					PTCL	5	40	0	40	0	Median not reached	
				HL	31	65	16	48	23	71 % had $\geq$ 24 weeks of DOR	69 % at 24 weeks	
				Post autologous SCT for DLBCL, PMBCL, or transformed indolent B-NHL	66	51	34	17	37		72 % at 16 months	85 % at 16 months
				Relapsed FL	32	66	52	14		Median of 20.2 months	Median of 18.8 months	
PD-L1	MPDL3280A	IgG1 mAb with engineered Fc domain	Genentech/Roche									
CTLA-4	MEDI4736	IgG1 mAb with engineered Fc domain	MedImmune/AstraZeneca									
	Ipilimumab	Fully humanized IgG4 mAb	Bristol-Myers Squibb									
	Urelumab	Fully humanized IgG4 mAb	Bristol-Myers Squibb									
CD19	CAR T cells [52–54]	Genetically modified T lymphocytes that express a genetically engineered scFv of an antibody fused to the TCR signaling domain	NCI, U Penn, MSKCC, FHCRC, Baylor, Novartis, Juno Therapeutics, Cellular Biomedicine Group, Bellicum, Celgene/Bluebird, Kite Pharma/Amgen, Collectis/Servier/Pfizer, Opus Bio, TheraVectys	NCI—refractory DLBCL U Penn—DLBCL U Penn—FL FHCRC—NHL	7 15 11 30	57 47 73 63	29 20 36 33	14 27 36 30			Median of 3 months Median not reached	
	Blinatumomab [62, 63]	Two scFvs targeting CD19 and CD3 joined by an amino acid linker	Amgen	Relapsed/refractory NHL	35	69	37	31	14	Median of 404 days		
					DLBCL	11	55	36	18			
					FL	15	80	40	40			
				Relapsed/refractory DLBCL	7	71	43	28			Median of 11.6 months	

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scFv single-chain variable fragment, *TCR* T cell receptor, *NCI*/National Cancer Institute, *U Penn* University of Pennsylvania, *FHCRC* Fred Hutchinson Cancer Research Center