Checkpoint inhibition and cellular immunotherapy in lymphoma

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Hodgkin and non-Hodgkin lymphoma are both good targets for immunotherapy, as they are accessible to antibodies and cell-based immunotherapy, express costimulatory molecules, and express lineage-restricted, viral, and unique tumor antigens. Blockade of the programmed-death 1 (PD-1) immune checkpoint has produced very encouraging response rates in patients with Hodgkin lymphoma, whereas adoptive transfer of Epstein-Barr Virus (EBV)-specific T cells has shown clinical activity in patients with posttransplant lymphoma and other EBV-associated lymphomas. T cells can also be genetically modified with chimeric antigen receptors (CARs) to confer specificity for surface antigens, and studies of CD19 CARs in lymphoma also have had encouraging response rates. Future directions include combination of checkpoint blockade and adoptive T-cell studies.

Learning Objectives

- Be aware of current trials with checkpoint inhibitors in lymphoma
- Be aware of cellular immunotherapy approaches being tested in clinical trials

Introduction

Immunotherapeutic strategies including cellular therapies and immune checkpoint inhibitors have produced impressive clinical responses in a broad spectrum of cancers. Lymphomas are a highly attractive target for these therapies because, similar to solid tumors, they employ strategies to actively inhibit endogenous immunity while also harboring targets for clinically tested cellular therapies and expressing ligands responsive to checkpoint inhibition. Programmed-death 1 (PD-1) inhibitors have produced very impressive results in Hodgkin lymphoma (HL) in clinical trials, and now are being tested in other lymphoma subtypes. Moreover, lymphomas are susceptible to immune-based interventions, including allogeneic hematopoietic stem cell transplantation (HSCT), the adoptive transfer of Epstein-Barr Virus (EBV)-specific T cells, and infusion of T cells genetically modified with chimeric antigen receptors (CARs) targeting CD19.1-4 Thus, a number of clinical trials have been implemented to evaluate the safety and efficacy of novel immunotherapies in both patients with HL and patients with non-Hodgkin lymphoma (NHL). The purpose of this review is to provide a basic understanding of the biological and reported clinical effects of these agents in treating lymphomas and to shed light on likely future directions.

Imune checkpoint inhibitors

To evade endogenous antitumor immunity, tumor cells hijack physiologic mechanisms of T lymphocyte inhibition. These mechanisms can include up-regulation of immune checkpoint ligands, such as PD-ligand 1 (PD-L1) and PD-L2, and expansion of regulatory T cells and stroma cells that secrete a number of inhibitory cytokines, such as transforming growth factor (TGFβ) and interleukin 10 (IL-10). Immune checkpoint inhibitors (CPIs) are an exciting class of novel therapies that can reverse tumor-induced T-cell suppression mediated by inhibitory ligands. Antibodies targeting the cytotoxic T lymphocyte antigen 4 (CTLA4) and PD-1 pathways have progressed to regulatory approval. Within the tumor milieu, overexpression of the ligands (B7.1, B7.2, and PD-L1/PD-L2) for CTLA4 and PD-1 can dampen naive and effector T-cell responses, respectively. In patients with metastatic melanomas, blocking these pathways has shown impressive responses in a tumor type that is generally resistant to treatment.5 A key finding in responders is a lymphocytic infiltration at the tumor site, followed by delayed clinical responses. Lymphomas are a logical target for checkpoint inhibition, as they reside in lymphoid organs, tissues that are rife with immune cell infiltrates, and the lymphoma cells themselves possess the machinery to activate strong immune responses, but also express inhibitory ligands.6,7 Indeed, in the case of follicular lymphomas, spontaneous remissions induced by a dense lymphocytic infiltrate have been seen. Therefore, the application of checkpoint inhibition to treat refractory lymphomas is of considerable interest. Table 1 summarizes the outcomes from early-phase clinical trials published to date, using CPIs to treat lymphomas.

CTLA4 blockade

Historically, signaling through CTLA4 has been exploited clinically to induce anergy in naive T cells to treat auto- and alloimmune conditions such as graft-versus-host disease (GVHD) in allogeneic HSCT recipients. In the last decade, however, the anticancer benefits of inhibiting this pathway have become apparent. Ironically, one of the first indicators of clinical benefit to patients with lymphoma was demonstrated by Bashey et al, who gave 1 dose of ipilimumab to patients with relapsed

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hematological malignancies after allogeneic HSCT. Three of 17 patients with recurrent lymphomas showed clinical benefit (2 HL achieved complete remissions [CRs], and 1 patient with mantle cell lymphoma achieved a partial remission [PR]) on this trial. Importantly, none of the patients developed exacerbations of GVHD. More recently, a study was reported in which ipilimumab was infused as an induction course of 4 doses in 28 patients with relapsed hematologic malignancies after allogeneic HSCT, including 7 with HL and 4 with NHL. Of the patients with lymphoma, 1 patient with HL had a partial response, and 3 with HL and 1 with cutaneous T-cell lymphoma had stable disease.

In another trial, multiple escalating doses of ipilimumab were given to patients with refractory lymphomas outside the context of HSCT. Again, in this study, response rates were low, at 11% (2 responders, patients with diffuse large B-cell [DLBCL] and follicular [FL] lymphomas). However, akin to outcomes in patients with melanomas, responders attained long-term CRs. As the activity of ipilimumab as a single agent was low in lymphoma, it currently is being tested in phase 2 studies as combination therapy with PD-1 inhibitors or conventional chemotherapy.

**PD-1/PD-L1 and PD-L2 blockade**

Pidelizumab is a humanized antibody that at the time it was tested was thought to be the first anti-PD-1 agent tested in patients with lymphomas. As a single agent, it had modest activity, inducing 1 CR in a patient with FL of 17 patients with a spectrum of hematological malignancies treated. In a larger phase 2 study, pidilizumab was administered in combination with rituximab to 29 patients with PL. All patients had relapsed after previous treatment with an anti-CD20 agent. Sixty-six percent of patients responded (52% CR and 14% PR) to the combination, which compared favorably with the expected 40% response rates seen with rituximab retreatment alone. Responses were long-lived, and the median progression-free survival has not yet been reached. On further examination of the biology of these responses, it was shown that FL cells express only limited amounts of PD-L1, and it was also subsequently shown that pidilizumab does not inhibit PD-1. It has been postulated that reversal of tumor stroma inhibition may be the mechanism of action of PD-1 inhibitors. In contrast, a multitude of preclinical studies have systematically documented an overexpression of PD-L1 and PD-L2 genes (amplifications, translocations, or copy number gains) present on chromosome 9q24 in the Reed-Sternberg (RS) cells of classical HL. The abundance of PD-L1 indicates RS cells are genetically dependent on the PD-1 pathway to evade T-cell attacks. In a seminal article, of 23 patients who were heavily pretreated (>4 lines of therapy, more than 70% had failed an autologous HSCT) and who received the PD-1 monoclonal antibody nivolumab, 87% (20/23) had an objective response, of which 11% were complete responses. The most common drug-related events were rash (22%) and thrombocytopenia, for which 2 patients needed drug discontinuation. Expected autoimmune toxicities such as pneumonitis and colitis were seen in a minority of patients, and none required treatment discontinuation. Results of the KEYNOTE-013 trial were presented at the 2015 ASH annual meeting. Similar to results with nivolumab, pembrolizumab induced responses in 65% of patients who were brentuximab refractory with an acceptable safety profile. The median progression-free survival for both trials has not yet been reached. On available tumor samples, the RS cells in both trials showed upregulated expression of PD-L1 and PD-L2 as potential biomarkers of response. On examining the PD-L1/PD-L2 expression on other lymphoma subtypes, primary mediastinal B-cell lymphoma, EBV-associated DLBCL, and T-cell-rich B-cell lymphomas express the highest levels of PD-L1. Indeed, all 3 of 11 patients with DLBCL who responded to nivolumab therapy in another trial had tumors that overexpressed PD-L1. Larger and confirmatory studies of safety and efficacy are underway to confirm the role of PD-1 inhibition in NHLs. The success of strategies targeting the CTLA4 and PD-1 pathways has also led to interest in the inhibition of a number of other negative regulators such as TIM-3, LAG-3, and VISTA, which are currently being evaluated in preclinical and early-phase studies.

**Cellular immunotherapy**

The potential for targeted cellular therapy of lymphoma was initially demonstrated by graft vs lymphoma activity seen after allogeneic HSCT. The posttransplant setting also provided the first venue in which the curative effect of T-cell immunotherapy on viral lymphoma was demonstrated more than 2 decades ago, when patients with posttransplant...
lymphoproliferative disorder (PTLD) were successfully treated with infusions of unmanipulated donor lymphocytes or donor-derived EBV-specific T cells. Aside from the oncogenic virus EBV, which is a natural target for immunotherapy present in a subset of B-cell neoplasms, lymphomas also express a number of antigens in the context of major histocompatibility complex (MHC) antigens that can be targeted by antigen-specific T cells or T cells genetically modified to express native T-cell receptors. In addition, T cells can be genetically engineered with CARs that will recognize surface antigens such as CD19 in an MHC-independent fashion.

**EBV-specific T cells for PTLD**

We have recently reviewed our single-center experience treating PTLD, using EBV-specific T cells in a series of trials using different manufacturing techniques. Of 36 patients who received donor-derived EBV-specific T cells to treat PTLD during the last 2 decades, 31 (86%) achieved complete and durable remissions. An additional 162 high-risk patients received infusions as prophylaxis, and only 1 patient, who received steroids soon after the T-cell infusion, developed PTLD. This patient was salvaged with a second dose of cells. Quelling early concerns, infusions of allogeneic T cells enriched for EBV antigens showed minimal evidence of exacerbating GVHD (8 of 162 patients had reactivation of acute and another 2 had extensive chronic GVHD) compared with a more than 30% GVHD risk with unseparated donor lymphocyte infusions. The most serious adverse events were the consequence of inflammation within bulky PTLD tumors surrounding the airway, seen in 2 patients. An additional patient with bulky disease developed a cytokine release syndrome (CRS) 2 weeks after T-cell infusion, necessitating corticosteroids and tumor necrosis factor α blocking agents. These safety and efficacy outcomes are comparable to studies done at the Memorial Sloan-Kettering Cancer Center, where 23 patients with active PTLD were treated with EBV-specific T cells derived from their stem cell donors, and more than 70% responded with no increase in GVHD.

The limitations of the original donor-derived EBV-specific T-cell protocol were that manufacturing the cells took up to 3 months, using lymphoblastoid cell lines (LCLs), and access to these specialized products was limited to specific centers. A number of groups have therefore evaluated more rapid selection methodologies. Given that EBV-seropositive donors have detectable frequencies of circulating EBV-specific T cells, Moosmann et al captured cells from peripheral blood that secreted interferon γ in response to stimulation with select EBV epitopes and showed that infusions of even small doses (0.4 to 9.7 × 10^6 cells/kg) of enriched EBV-specific T cells were capable of inducing CR in 3 of 6 patients infused.

Building on the successes of γ-capture, Icheva et al isolated T cells specific for EBNA1, an antigen expressed by most EBV lymphomas, in follow-up studies, characterizing the mechanisms of resistance among nonresponders will be critical. According to preliminary preclinical studies, it is plausible that combination therapy with checkpoint inhibitors could have strong synergistic effects and greatly broaden the applicability of both strategies.

**EBV-specific T cells for type 2 latency lymphomas**

PTLD is a highly immunogenic tumor expressing the full gamut of all 11 EBV latent cycle antigens, including the highly immunogenic EBNA 3 antigens, and thus is an optimal target for T-cell immunotherapy strategies. Approximately 40% of lymphomas that express the type I and II latency EBV antigens express only 1 to 3 poorly immunogenic antigens, such as latent membrane protein 1 (LMP-1), LMP-2, and EBNA1, which is the only antigen expressed by endemic Burkitt lymphomas. In addition, unlike the patients with PTLD, in which cells are manufactured from the normal stem cell donor, strategies in type II latency lymphomas require autologous cell manufacture from patients who have received multiple rounds of chemotherapy that negatively affect the function of their EBV-specific T cells. To reconstitute and expand autologous LMP-1/LMP-2-specific T cells, investigators in our group developed a platform using genetically modified dendritic cells to express target antigens as powerful stimulators for patient T cells in vitro. The resulting T-cell lines enriched for clones recognizing LMP-1 and LMP-2 were then infused as prophylaxis to 29 patients in remission and 21 patients with active disease. Adverse events were limited to 1 patient with active disease, who developed a self-limited CRS 4 weeks postinfusion. There were no relapses in the prophylaxis group, and 13 of 21 patients with chemo- and radiotherapy refractory disease developed clinical responses, of which 11 were CRs. In stark contrast to nonresponders, most responders had impressive in vivo expansion of T cells targeting not only the target antigens LMP-1 and/or LMP-2 but also nontargeted lymphoma-associated antigens such as MAGE-a4, PRAME, and Survivin. Although EBV-specific T cells are highly effective in a significant number of relapsed EBV lymphomas, in follow-up studies, characterizing the mechanisms of resistance among nonresponders will be critical. According to preliminary preclinical studies, it is plausible that combination therapy with checkpoint inhibitors could have strong synergistic effects and greatly broaden the applicability of both strategies.

**Third-party T cells**

The remarkable safety profile of EBV-specific T cells has allowed investigators to explore the possibilities of using “third-party” products derived from healthy donors to treat PTLD and other EBV-positive diseases in the posttransplant setting. The convenience of “off-the-shelf” access and the ability to select donors on the basis of preexisting responses to EBV are the main advantages of this approach. These strategies have been clinically tested in patients with EBV reactivation or PTLD and are summarized in Table 2. The use of a third-party product was first described by Haque et al, who infused banked EBV-specific virus-specific T cells to treat PTLD after solid organ or HSCT transplantation, and reported response rates of 64% and 52% at 5 weeks and 6 months, with no GVHD.

In a follow-up study with a new Good Manufacturing Practice compliant bank, this group reported very encouraging results, with 8 of 10 patients infused to treat EBV lymphoproliferative diseases obtaining complete responses. Similar efficacy has been seen at Sloan Kettering, where 4 of 5 patients attained CRs after receiving third-party EBV-specific virus-specific T cells for PTLD.

In a much larger series of 57 patients that has so far been reported only in abstract form, the Sloan Kettering group reports 36 PRs or CRs, for an overall response rate of 63%. Overall, at our center, we have treated 11 patients with EBV PTLD with third-party EBV- or multivirus-specific T cells, and 73% of patients experienced a CR. Although response rates are lower than seen with transplant donor-EBV-specific T cells, they are nevertheless encouraging, and it will be important to identify beneficial characteristics of the banked T cells so that this approach may have wider application.
Table 2. Published trials using third-party virus-specific T cells to treat EBV lymphoma

<table>
<thead>
<tr>
<th>Activation method</th>
<th>Patients</th>
<th>CR or PR</th>
<th>Failure</th>
<th>GVHD</th>
<th>ORR</th>
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<td>LCL-induced</td>
<td>33 (includes SOT)</td>
<td>17</td>
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<td>52%</td>
<td>Haque et al, 200741</td>
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<td></td>
<td>57</td>
<td>36</td>
<td>18</td>
<td>None</td>
<td>63%</td>
<td>Prokop et al, 201542</td>
</tr>
<tr>
<td>10 (includes SOT)</td>
<td>8</td>
<td>6</td>
<td>3</td>
<td>2</td>
<td>67%</td>
<td>Leen et al, 201543</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>25%</td>
<td>Naik et al, 201644</td>
</tr>
<tr>
<td>Pepmix-induced</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>None</td>
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<td>Naik et al, 201644</td>
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<td>0</td>
<td>0</td>
<td>None</td>
<td>100%</td>
<td>Uhlin et al, 201045</td>
</tr>
</tbody>
</table>

LCL, lymphoblastoid cell lines; SOT, post-solid organ transplantation.

Tumor-associated antigen–specific T cells

More than 60% of all lymphomas are EBV negative. To successfully apply cellular therapies to these patients, several groups have devised strategies to harness the potential of T cells to target these tumors. A number of self-antigens classically silenced in normal tissues are selectively overexpressed by malignant lymphoma cells. These antigens represent suitable targets for T-cell immunotherapy because of their tumor-restricted expression. To target a range of tumor-associated antigens (PRAME, MAGE-A4, NY-ESO1, Survivin, and SSX2) expressed by lymphoma cells in the context of MH molecules, our center and others have implemented clinical trials to test ex vivo expanded autologous multimmunotargeted antigen-specific T cells. In early reports, this therapy is safe, with responses seen in patients with active HL or NHL.26

T cells genetically modified to express native or artificial receptors

An alternative approach is to introduce a new receptor into T cells to target antigens expressed by lymphoma cells. One strategy is to introduce an optimized native receptor for a target such as survivin,26 but this strategy is restricted by HLA type. A much more widely used strategy to target lymphoma has been to transfer a CAR, which confers antigen specificity, to T cells for antigens expressed by lymphoma cells in a non-MHC-restricted fashion. The common CAR constructs in clinical practice contain the antigen-binding pocket or a single chain variable fragment (scFv) derived from an immunoglobulin molecule, a spacer or hinge region, and finally, a range of different endodomains (ζ, CD28, 4-1BB, OX40, etc.). In sharp contrast with T-cell-receptor activation, activation of CAR-modified T cells has the advantage of not being HLA restricted but, rather, dependent on the binding of the scFv with its cognate antigen, typically on the surface of tumor cells. In landmark studies, extraordinary clinical responses have been seen in patients with B-cell acute lymphoblastic leukemia (ALL), when CAR-modified T cells bearing an scFv specific for the B-cell antigen CD19 induced long-term remissions in more than 90% of treated patients.27,28 Although B-cell ALL remains the poster child for this treatment, success in treating the closely related CD19+ B-cell lymphoma has not yet been as paradigm shifting. However, some promising responses have been observed, and results from published or presented trials using T cells genetically modified with CARs to treat lymphoma patients are summarized in Table 3.

CD19

CD19 is an attractive target for cellular immunotherapy because of its expression during all stages of B-cell differentiation and malignant transformation and its absence on any other cell types. The first- and early second-generation studies with CD19 CAR T cells, regardless of the scFv used, had minimal antilymphoma effects.29,30 Among the plausible explanations were lack of persistence beyond 1 week (compared with >9 years seen with gene-marked EBV-specific T cells) and poor T-cell expansion. There is now robust evidence that “lymphodepletion,” or pretreating patients with lymphotoxic agents such as fludarabine (25 mg/m2 for 5 days) and cyclophosphamide (60 mg/kg for 2 days), is a crucial step that produces an environment in which the infused T cells can thrive. The necessity of lymphodepletion was first reported by Kochenderfer’s group as a case report of 1 patient with chemorefractory FL treated with this conditioning before infusion of second-generation (CD28 endodomain) CD19-CAR T cells and systemic IL-2.31 The patient went on to develop a partial response lasting 32 weeks. This PR coincided with B-cell aplasia, a characteristic “on-target, off-tumor” toxicity of targeting CD19 and a surrogate marker of efficacy lasting 39 weeks after treatment.31 Since then, the same group has reported a larger series of 15 patients: 9 with DLBCL, 2 with indolent lymphomas, and 4 with CLL.32 All patients received 1 dose of CD19 CAR-T cells after lymphodepleting conditioning; however, IL-2 was omitted for toxicity concerns. Of 13 evaluable patients, impressively, 12 achieved a clinical response (8 CRs, 4 PRs, and 1 SD), including the first durable CRs in 4 of 7 patients with chemorefractory DLBCL. CD19 CAR transgenes peaked between days 7 and 17, which coincided with the peak incidence for adverse events of grade 2-3 CRS and self-limited neurological toxicities that have been associated with T-cell therapies. The rationale for combining lymphodepletion with CAR T-cell therapy was solidified further when Turtle et al elegantly demonstrated that the elimination of CD19 CAR T cells in some patients was possibly a result of host T-cell responses to the CD19 transgene.33 When cyclophosphamide alone was used for lymphodepletion in 12 patients with NHL, the overall response rate after infusion of a CD19 CAR with a 4-1BB costimulatory endodomain was 50%, with only 1 CR and a high incidence of murine scFv rejection by endogenous T cells. The addition of fludarabine in 16 additional patients improved the overall response rate to 67%, with a remarkable improvement in CRs (42%).

The University of Pennsylvania is also undertaking studies with a CD19 CAR with 4-1BB in patients with NHL, and results in refractory DLBCL and FL were presented at the 2015 ASH meeting, with promising response rates in excess of 70% for both tumor types in a total of 26 adult patients.34 Unlike the rapid responses seen in patients with CLL, CRs took more than 3 months for patients with DLBCL and FL, in some cases mirroring the response patterns of solid tumors to other forms of immunotherapy, such as checkpoint inhibition. The clinical outcomes of published CD19 CAR-T cell lymphoma trials are summarized in Table 3. In summary, complex mechanisms govern the responses of lymphomas to CD19 CAR T cells; among them, tumor characteristics, type of conditioning therapy, and the
CAR constructs used are current topics being investigated in multiple trials. Characteristic findings in responders have been the development of clinical CRS at the time of peak CAR expansion and B-cell aplasia necessitating immunoglobulin replacement therapy.

**κ-light chain CAR**
To avoid the indefinite B-cell aplasia induced by CD19 CAR T cells, Ramos et al have clinically tested a CAR construct targeting κ light chain. Because human B and plasma cells bear either α κ or λ light chain, targeting κ alone would spare λ− cells. Indeed, when 9 patients with κ+ NHLs were treated with second-generation κ CAR T cells bearing a CD28 endodomain, none of the patients developed B-cell aplasia; 3 patients had a response (2 CRs and 1 PR); and, similar to observations with CD19 CAR T cells, in all patients, the transgene signal in peripheral blood peaked by 2 weeks and persisted from 6 weeks to 9 months.35

**CD30**
CD30 is expressed by the malignant RS cells of HL and select T-cell lymphomas. Brentuximab vedotin, a chemotherapy-linked anti-CD30 antibody, has shown remarkable activity in CD30+ lymphomas with an acceptable safety profile. However, most patients eventually progress despite continued expression of CD30, possibly through resistance to the chemotherapy component. CD30 targeted CAR-T cells may overcome this limitation. In a trial at our institution, 9 patients (7 with HL and 2 with T-cell lymphoma), 8 of whom had previously failed brentuximab, were treated with CD30 CAR T cells without lymphodepleting therapy.36 The infusions were safe, without any instances of severe CRS; however, transgene levels returned to background levels by week 4 after peaking 7 days after infusion. So far, objective responses have been detected in 2 patients (1 CR and 1 PR), and 4 patients have had stable disease. We are currently exploring the addition of lymphodepleting chemotherapy before CD30 CAR T-cell infusions to enhance persistence.

### Other targets
Several other targets are under preclinical or early clinical evaluation. CARs specific for CD20 were tested in early studies,37 but this antigen has been supplanted by CD19 as a target. B-cell maturation antigen, which has shown promise as a target in myeloma, is also expressed in a portion of B-cell lymphomas. T-cell lymphomas are a more challenging target, as most targetable surface antigens are also expressed on normal T cells, and so could result in severe immune- nodedeficiency. However, a recent report suggested that T cells genetically modified to express a CAR targeting CD5 can effectively eliminate T-cell lymphoma lines in vitro and significantly inhibit disease progression in xenograft mouse models of T-ALL without significant fratricide.38

### Future directions
**Rationale for combinations**
The blockade of 2 immune checkpoints has been shown to have increased clinical benefit in patients with melanoma and currently is being evaluated in lymphoma. Combining tumor-specific T-cell therapy with checkpoint inhibition is another logical strategy. In EBV lymphoma, the virus can commande the PD-1 pathway to evade endogenous EBV-specific T-cell responses.38 Furthermore, infusions of tumor-targeted T cells often induce antigen/epitope spreading, which CPIs could potentially enhance. Finally, Kochenderfer et al have shown that among responders to CD19 CAR-T-cell therapy, the transgene-expressing CAR T cells tend to upregulate PD-1 expression.39

Another strategy to overcome immune inhibitory cytokine signals within the tumor milieu is to engineer adoptively transferred T cells with countermeasures. One such example is the use of a disabled TGFβ receptor or a “double-negative receptor” in EBV-specific T cells to overcome the inhibition induced by TGFβ at the tumor site.39 Finally, targeting single antigens carries the inherent risk for immune escape, which has been well documented in CD19 CAR studies in leukemia and can be reduced by targeting multiple antigens.
Appropriate timing and risk/benefits of immunotherapy

Current clinical trials are exploring the use of immunotherapeutic agents in multiply relapsed and chemorefractory disease. Thus, most patients come to clinical trials with significantly damaged endogenous immune systems, which could negatively affect novel immunotherapies such as checkpoint inhibition that rely heavily on endogenous immune responses. Thus, it will be interesting to see whether outcomes are better if checkpoint inhibitors are given earlier in the disease course. The need for effective lymphodepletion may make autologous H SCT an attractive platform for immunotherapies in the future. Finally, for T-cell immunotherapies to become broadly applicable, manufacturing will need to be optimized and the cost will need to be competitive with other therapies. Overall, the key attribute for broad implementation of CAR-T cells and CPs in lymphoma will be their success in producing long-term disease control. At present, the risk for adverse effects is higher with CAR-transduced T cells than with other modalities, and it will be important to ascertain whether they also produce more sustained disease control.

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References


