Recommendations for managing PD-1 blockade in the context of allogeneic HCT in Hodgkin lymphoma: taming a necessary evil

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PD-1 blockade is an effective therapy in relapsed/refractory (R/R) classical Hodgkin Lymphoma (cHL) who have relapsed after or are ineligible for autologous hematopoietic cell transplantation (HCT). Although single-agent anti-PD-1 monoclonal antibodies (mAb’s) are associated with high response rates and durable remissions, available results to date suggest that a large majority of patients will eventually progress on therapy. Many of these patients are potential candidates for allogeneic HCT (allo-HCT) after receiving anti-PD-1 mAb’s, and allo-HCT remains for now the only treatment with demonstrated curative potential in this setting. However, initial reports suggested that allo-HCT in this setting may be associated with increased risk of early transplant-related toxicity, likely driven by lingering effects of PD-1 blockade. Furthermore, many patients with R/R cHL who undergo allo-HCT will relapse after transplantation, most often with limited treatment options. Here again, PD-1 blockade appears to yield high response rates, but with an increased risk of attendant immune toxicity. Many questions remain regarding the use of PD-1 blockade before or after allo-HCT, especially in relation to the feasibility, outcome, optimal timing, and method of allo-HCT after PD-1 blockade. Despite the scarcity of prospective data, these questions are unavoidable and must be tackled by clinicians in the routine care of patients with advanced cHL. We provide consensus recommendations of a working group based on available data and experience, in an effort to help guide treatment decisions until more definitive data are obtained. (Blood. 2018;132(1):9-16)

Introduction

PD-1 blockade is associated with high response rates and durable benefit in patients with relapsed/refractory (R/R) classical Hodgkin lymphoma (cHL) who have relapsed after or are ineligible for autologous hematopoietic cell transplantation (auto-HCT).¹–⁵ Despite this, a majority of patients treated with PD-1-blocking antibodies (nivolumab and pembrolizumab) will eventually progress on these therapies. For patients with highly chemorefractory disease or those who relapse after auto-HCT, allogeneic HCT (allo-HCT) offers a potentially curative treatment option.⁶–⁸ Therefore, allo-HCT is a consideration for selected patients with R/R cHL who achieve a remission (partial remission [PR] or complete remission [CR]) with PD-1 blockade, or for those who progress on those agents and subsequently are able to achieve remission. However, prior immune modulation with PD-1 blockade could significantly alter allo-HCT outcomes, with the theoretical potential for both increased immune toxicity and increased graft-versus-tumor (GVT) efficacy, raising many questions about the appropriate use of allo-HCT in those patients.⁹ Moreover, relapse remains a problem after allo-HCT, with reported progression-free survival (PFS) ranging from 20% to 60% at 3 years.¹⁰¹¹ For post-allo-HCT relapses, treatment options are very limited,¹²–¹⁵ and the use of PD-1 blockade in this setting is attractive given the activity of the drugs in the pre-allo-HCT R/R setting and the theoretical enhancement of the graft-versus-lymphoma effect. Here again, there is significant concern about the risk of attendant immune toxicity.³ Given the complex and dynamic nature of these questions, specifically the use of allo-HCT after PD-1 blockade and that of PD-1 blockade for post-allo-HCT relapse, the authors of this review convened to form a working group of transplanters and nontransplanters with published experience in the treatment of patients receiving both PD-1 blockade and allogeneic hematopoietic stem cell transplantation. As there is currently a dearth of prospective data in this field, the aim of this working group was to provide a set of consensus recommendations to inform clinical practice until more definitive data are obtained.

Fundamental considerations

The PD-1 pathway serves as a checkpoint to limit T-cell-mediated immune responses.¹⁶ Both PD-1 ligands, PD-L1 and PD-L2, engage the PD-1 receptor, induce PD-1 signaling and associated T-cell tolerance.¹⁶ Weak cytotoxic T lymphocyte (CTL) activity in lymph nodes promotes local tumor escape.¹⁷ PD-1 blockade reverses this inhibition of T-cell activation and
perecising use of BV in earlier lines of therapy,30 many patients (estimated 5-year PFS 52%).29 Even so, a large majority of pa-
achieve a CR with BV (response rates (75%) in this setting, and a subset of patients who
change with continued PR. How should this patient be managed?

nivolumab and achieves PR after 4 doses of therapy. Repeat im-
with nodal and bony disease. She is treated with single-agent
consolidation, which is stopped after 6 months because of grade 3
expression permitted GVT activity without severe GVHD.17,23,24
The use of PD-1 blockade before or after allo-HCT may therefore
be associated with increased toxicity and/or increased efficacy, and the balance of those 2 effects is likely to significantly affect
patient outcomes.

Allogenic HCT after PD-1 blockade
Case presentation 1
A 28-year-old woman with primary refractory cHL after doxorubicin,
bleomycin, vinblastine, and dacarbazine frontline chemotherapy has
a complete response with ifosfamide, carboplatin, and etoposide
and undergoes auto-HCT. She receives brentuximab vedotin (BV)
consolidation, which is stopped after 6 months because of grade 3
peripheral neuropathy. Three months later, her lymphoma relapses
with nodal and bony disease. She is treated with single-agent
nivolumab and achieves PR after 4 doses of therapy. Repeat im-
aging after 4 additional doses of nivolumab shows no significant
change with continued PR. How should this patient be managed?

Review of the existing data
Patients with chL who are ineligible for auto-HCT or relapse after
auto-HCT have historically had a poor prognosis with a median
survival of 2 years or less.25-28 Brentuximab achieves high re-
sponse rates (75%) in this setting, and a subset of patients who
achieve a CR with BV (~33%) will experience lengthy remissions
(estimated 5-year PFS 52%).29 Even so, a large majority of pa-
ients treated with BV will relapse; moreover, given the in-
creasing use of BV in earlier lines of therapy,30 many patients
with post-auto-HCT relapse will have already received BV. The
anti-PD-1 monoclonal antibodies nivolumab and pembrolizumab
are both approved in this setting and are associated with overall
response rates (ORRs) of ~70%.1,5 Here too a subset of patients
can achieve durable remissions.1,4,31,32 However, based on the
phase 1/2 data available to date, it appears that a majority of
patients will relapse within 1 to 2 years of starting PD-1 blockade,
and it is not clear yet what proportion of patients, if any, can
attain long-term remission. Thus, for patients responding to
anti-PD-1 mAb’s, allo-HCT represents the only modality with
known curative potential; indeed, allo-HCT with reduced intensity
conditioning (RIC) is associated with long-term disease-free
survival in 25% to 40% of patients.8,33,34 This raises the chal-
lenging question of how to optimally manage patients who
achieve a response to PD-1 blockade. One option is to proceed
to allo-HCT to capitalize on the response. Alternatively, patients
may remain on PD-1 therapy, in the hope of maintaining a
durable remission without incurring the risks of allo-HCT. This
approach would also allow patients to undergo other novel or
experimental therapies following PD-1 blockade, which could
themselves possibly serve as a bridge to allo-HCT. Remission
quality with PD-1 blockade is not as clear a predictor of outcome
as it is with BV, and patients with PRs can still have durable
remissions. Further complicating matters, initial reports suggest
that patients undergoing allo-HCT following PD-1 blockade may
be at increased risk for severe immune-related complications
early after transplantation. The largest series of chL patients
who received anti-PD-1 mAb’s prior to allo-HCT included 39 pa-
ients and reported higher than expected rates of grade 4 aGVHD
and veno-occlusive disease (VOD), as well as a noninfectious
febrile syndrome requiring prolonged steroid treatment. Com-
pared with matched controls, patients treated with anti-PD-1
mAb’s had a prolonged and severe reduction in circulating PD-1
positive T cells and a relative reduction in T regulatory cells after
transplantation, which could underlie the observed early im-
une complications.35 Despite this, the relapse rate appears
low (16% at 1 year), lower than historical series of chL patients
who underwent allo-HCT without prior anti-PD-1 therapy, and
PFS was encouraging in this cohort (74% at 1 year). Subsequent
accumulated experience seemed to support these results.2,34,38
However, larger studies are warranted to determine whether the
efficacy of allo-HCT is enhanced following anti-PD-1 therapy.

Recommendations
Patient selection The following discussion only applies to
patients who would otherwise be good candidates for allo-HCT
based on age, comorbidities, and donor availability (recognizing
that haploidentical donors can be successfully used in older
patients with chL39 and that therefore most patients will have an
available donor). In the absence of a clearly documented large
difference in outcome between patients in PR and CR after PD-1
blockade, we do not recommend using depth of remission as the
sole criterion for determining which patient should go to allo-
HCT after PD-1 blockade. In general, given the favorable safety
profile of these agents and the toxicity of allo-HCT in this setting,
we favor keeping responders on therapy instead of stopping
this therapy to proceed to allo-HCT. In our experience, it is
frequently possible to reinstate remission after PD-1 blockade
failure. Supporting this approach, a recent retrospective analy-
sis showed that initial salvage chemotherapy following PD-1
blockade resulted in an overall response in 10/19 (53%) of
patients.40 Nevertheless, we strongly recommend a referral to
transplant center to discuss considerations around allo-HCT, and
to at least prepare for a potential transplant at time of PD-1
blockade failure. We would consider early allo-HCT for patients
in remission after PD-1 blockade with heavily pretreated re-
fractory disease and no viable post-
allo-HCT setting, donor CTLs may be activated by
T cells and a relative reduction in T regulatory cells after
transplantation, which could underlie the observed early im-
une complications.35 Despite this, the relapse rate appears
low (16% at 1 year), lower than historical series of chL patients
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PFS was encouraging in this cohort (74% at 1 year). Subsequent
accumulated experience seemed to support these results.2,34,38
However, larger studies are warranted to determine whether the
efficacy of allo-HCT is enhanced following anti-PD-1 therapy.

Transplant strategy At present, there is no consensus re-
garding the optimal transplant strategy for patients previously
treated with immune checkpoint blockade. Given the biological
mechanism of immune checkpoint blockade and observed early

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posttransplant immune toxicity, we favor using a transplant strategy that minimizes GVHD and VOD risk. Given the absence of data suggesting a benefit to myeloablative conditioning, the frequent heavy pretreatment (including auto-HCT) in these patients, and the increased risk of VOD and GVHD with ablative conditioning, we favor RIC irrespective of depth of response. Graft source, HLA match, and GVHD prophylaxis are the additional key considerations for reducing GVHD risk. In the largest published series of allo-HCT after PD-1 blockade, aGVHD risk was significantly lower among 11 patients receiving a bone marrow graft compared with 28 patients receiving peripheral blood graft (0% vs 32%, *P* = .04). Based on this preliminary data, we prefer to use bone marrow grafts in this setting. GVHD prophylaxis with posttransplant cyclophosphamide (PtCy) has been a very effective strategy to reduce GVHD in other transplant settings associated with an elevated risk of GVHD.[41-43] Merryman et al found no association between GVHD prophylaxis regimen and GVHD rates in their study of 39 patients including the 14 patients who received PtCy. However, a recent retrospective analysis of 11 patients who underwent allogeneic allogeneic hematopoietic stem cell transplantation with PtCy GVHD prophylaxis after treatment with a checkpoint inhibitor demonstrated low rates of both aGVHD and cGVHD.[44] Based on these results and the favorable anecdotal experience using this strategy at our centers, we consider transplantation using a bone marrow graft followed by a PtCy-based GVHD prophylactic regimen (eg, PtCy/tacrolimus/mycophenolate mofetil) for patients with previous exposure to immune checkpoint agents. We also use ursodiol for VOD prophylaxis in all patients.[45] We encourage clinicians to have heightened awareness of early transplant complications (early severe GVHD, VOD, noninfectious febrile syndrome), which are likely more common in this population and may require early immunosuppressive treatments. If GVHD occurs, we recommend treating as outlined in the management of treatment emergent GVHD (teGVHD) section. In our experience, early intervention may be critical and second-line treatments of GVHD could be considered earlier than in a context without PD-1 blockade.

**PD-1 blockade after allogenic HCT**

**Case presentation 2**

A 27-year-old female with relapsed cHL post-auto-HCT achieved a partial response to brentuximab and underwent a matched sibling allo-HCT, receiving fludarabine and melphalan RIC and posttransplant methotrexate with tacrolimus for GVHD prophylaxis. She tapered off immunosuppression at day 180 without evidence of GVHD but relapsed at day 220. Is treatment with single-agent PD-1 blockade a good treatment option? After weighing the risks and benefits, the physician decides to treat this relapse with nivolumab 3 mg/kg. Within 14 days of her first dose, she develops stage IV hepatic aGVHD (peak bilirubin 20.4 mg/dL). How should this GVHD be managed?

**Review of the existing data**

**Response rate**

Many case reports and case series have been published regarding PD-1 blockade therapy in cHL patients with relapsed disease after allo-HCT.[37,38,46-54] All 12 patients reported in these publications experienced at least a partial response, and 4 developed GVHD. In our 2 retrospective studies,[55,56] we observed an ORR of 85% (N = 41 of 48 assessable patients) to anti-PD-1 mAb’s in a heavily pretreated cHL cohort relapsing after allo-HCT, including 48% complete responses (N = 23). In the phase 2 studies using nivolumab and pembrolizumab for R/R cHL, ORR was 69% and 73% (CR rate of 29% and 28%), respectively.[1,4] Although lacking the rigor of a clinical trial, we observed an unexpectedly high response rate in our post-allo-HCT cohort at least comparable to that observed in previous anti-PD-1 cHL trials, despite the advanced stage of disease and short duration of therapy in many patients. Median PFSs in our retrospective studies were 20 months in the US cohort and not reached (at a median follow up 12 months) in the French cohort, which also compares favorably with the experience in the phase 2 studies on nonallografted patients.

**Risk factors and types of teGVHD**

The table below highlights the baseline patient characteristics of the 2 largest retrospective studies using anti-PD-1 mAb’s after allo-HCT post-PD-1 blockade has been reported in a variety of clinical scenarios including various graft sources, conditioning intensity, and prophylactic GVHD strategies.[46,50,55] Several trends are emerging from the current body of published cases that may be associated with risk of teGVHD. Table 1 highlights the baseline patient characteristics and frequency of teGVHD from the 2 largest retrospective studies.

**Table 1. Baseline patient characteristics of the 2 largest retrospective studies using anti-PD-1 mAb’s after allo-HCT**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All patients</th>
<th>No GVHD</th>
<th>Developed GVHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>51</td>
<td>28</td>
<td>23*</td>
</tr>
<tr>
<td>Average age</td>
<td>36</td>
<td>36</td>
<td>37</td>
</tr>
<tr>
<td>Disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hodgkin</td>
<td>49</td>
<td>28</td>
<td>21</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Donor type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Matched sibling</td>
<td>27</td>
<td>13</td>
<td>14</td>
</tr>
<tr>
<td>Matched unrelated</td>
<td>14</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Mismatch unrelated</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Haploidentical related</td>
<td>5</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Umbilical cord blood</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Peripheral blood graft source, n</td>
<td>39</td>
<td>18</td>
<td>21</td>
</tr>
<tr>
<td>RIC, n</td>
<td>38</td>
<td>20</td>
<td>18</td>
</tr>
<tr>
<td>Calcineurin inhibitor-based GVHD prophylaxis, n</td>
<td>51</td>
<td>28</td>
<td>23</td>
</tr>
<tr>
<td>Prior history of GVHD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>aGVHD</td>
<td>16</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>cGVHD</td>
<td>16</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>No prior GVHD</td>
<td>19</td>
<td>14</td>
<td>5</td>
</tr>
<tr>
<td>Average time from allo-HCT to anti-PD-1 initiation (days)</td>
<td>994</td>
<td>1210</td>
<td>731</td>
</tr>
<tr>
<td>Receiving systemic immunosuppressive therapy at time of anti-PD-1, n</td>
<td>8</td>
<td>5</td>
<td>3</td>
</tr>
</tbody>
</table>

*Including 10 deaths related to GVHD.*
series of patients from the United States and France receiving anti-PD-1 post-allo-HCT. Of the 23 patients who developed GVHD after anti-PD-1 in the 2 largest series,55,56 16 were classified as developing aGVHD (or overlap), occurring after 1 to 2 doses of anti-PD-1, and in 11 it was severe (grade 3 or 4). Eleven of 16 experienced hepatic GVHD. Severe hepatic aGVHD is a rare occurrence in allo-HCT, yet we observed 8 patients with stage III aGVHD (ie, bilirubin $>6). Moreover, grade 3 to 5 hepatic (>$3 x upper limit of normal) toxicity from anti-PD-1 mAb’s was observed in $<5\%$ of patients in phase 1 and 2 trials.14,57 In a separate retrospective series, Schoch et al reported no evidence of teGVHD in 7 patients treated with anti-PD-1 mAb’s after allo-HCT.44

Table 2. Systemic treatments of patients developing teGVHD from the 2 largest series

<table>
<thead>
<tr>
<th>Treatments</th>
<th>N = 21*</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic steroids</td>
<td>20</td>
<td>95</td>
</tr>
<tr>
<td>Calcineurin inhibitors</td>
<td>10</td>
<td>48</td>
</tr>
<tr>
<td>Extracorporeal photopheresis (ECP)</td>
<td>6</td>
<td>29</td>
</tr>
<tr>
<td>Mycophenolate</td>
<td>6</td>
<td>29</td>
</tr>
<tr>
<td>Rituximab</td>
<td>3</td>
<td>14</td>
</tr>
<tr>
<td>ATG</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>Basiliximab</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>Sirolimus</td>
<td>1</td>
<td>5</td>
</tr>
</tbody>
</table>

*One patient in the US study was treated with topicals only and responded. One patient in the French study died abruptly from multiorgan failure and was not treated with any systemic therapies.

Table 3. Recommendations for patients receiving PD-1 blockade

<table>
<thead>
<tr>
<th>Recommendations</th>
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<tbody>
<tr>
<td><strong>Patient selection</strong></td>
</tr>
<tr>
<td>Early referral to transplant center for all patients who may be allo-HCT candidates*</td>
</tr>
<tr>
<td>Consider allo-HCT for patients in remission (PR or CR) after PD-1 blockade with very limited post-PD-1 salvage options (ie, low chance to reach a new objective response)*</td>
</tr>
<tr>
<td>Consider allo-HCT for any patient after failure of auto-HCT and PD-1 blockade who achieves subsequent remission</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Transplant strategy</th>
</tr>
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<tbody>
<tr>
<td>Hold PD-1 therapy for at least 6 wk before allo-HCT</td>
</tr>
<tr>
<td>Use VOD prophylaxis (ie, ursodiol) and monitor closely for VOD*</td>
</tr>
<tr>
<td>Reduce the risk of GVHD by favoring:</td>
</tr>
<tr>
<td>Bone marrow source</td>
</tr>
<tr>
<td>RIC</td>
</tr>
<tr>
<td>PtCy-based GVHD prophylactic regimen (eg, PtCy/tacrolimus/MMF)*</td>
</tr>
<tr>
<td>Perform close monitoring of early transplant complications (eg, noninfectious febrile syndrome)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Management of transplant complications</th>
</tr>
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<tbody>
<tr>
<td>In the case of noninfectious febrile syndrome:</td>
</tr>
<tr>
<td>Consider rapid initiation of IV methylprednisolone at 1 mg/kg per day*</td>
</tr>
<tr>
<td>In the case of GVHD:</td>
</tr>
<tr>
<td>Rapid initiation of IV methylprednisolone at 2 mg/kg per day</td>
</tr>
<tr>
<td>Early intervention with second-line immunosuppression if the patient does not respond rapidly to steroids: consider ATG for second line* or, alternatively, calcineurin inhibitor + ECP*</td>
</tr>
</tbody>
</table>

*Recommendation based on expert opinion and experience. The other recommendations are based on published data.
would trigger severe GVHD and lethality after conditioning-related inflammation of host tissues similar to that observed in murine models. So, although the definition of “earlier” remains ill-defined, we would encourage restraint in administering anti-PD-1 mAb’s within the first 180 days post-allo-HCT outside the context of a clinical trial. As shown in a recent study, PD-1-expressing T-cells were increased early after transplantation and this was associated with worse survival. We speculate that anti-PD-1 mAb’s upregulate major histocompatibility antigens via activation of the interferon-γ pathway, 2,21 decrease T regulatory cells, 65 and increase activated T and NK cells, thereby decreasing peripheral tolerance and increasing the incidence of GVHD. Well-designed correlative studies assessing T-cell subsets, PD-1/PD-L1 expression, and GVHD predictive markers before and after anti-PD-1 administration will be key to better understanding risks and identifying patients suitable to receive anti-PD-1 mAb’s post-allo-HCT.

Others have suggested that initial low doses of anti-PD-1 post-allograft or concomitant immunosuppression may be a safer approach. In a recently reported prospective study, 66 8 patients were treated with nivolumab after allograft (6 patients at 1 mg/kg and 2 patients at 0.5 mg/kg). In the 1 mg/kg cohort, there were 2 deaths (1 patient with sepsis and fatal acute respiratory distress syndrome, and 1 patient who developed fatal thrombotic cerebral vascular accidents) as well as a number of additional adverse events including cGVHD, grade 3 pneumonitis, and transaminitis (N = 1 each). Because of the toxicity observed at 1 mg/kg, a 0.5-mg/kg cohort recently opened, and no significant toxicities have been observed in the 2 patients accrued to date. Consequently, if anti-PD-1 mAb’s are given post-allo-HCT outside the context of a clinical trial, we would strongly consider starting at a low dose and consider escalating the dose if there is no apparent efficacy and no significant toxicity.

Management of teGVHD Table 2 highlights systemic treatments used for teGVHD in our 2 series. In the US study, 3 of 17 patients had complete responses to GVHD directed treatment. One patient received topical treatments only for mild skin cGVHD. One patient with stage I hepatic aGVHD had a complete response to high-dose steroids alone. The last patient, similar to the case presentation, failed to respond to high-dose steroids and mycophenolate...
moilet (MMF), but had a complete response to ATG. One additional patient in the US study received ATG and had a partial response to grade 3 aGVHD (stage III hepatic, stage II skin) and was alive at last follow-up. These anecdotal cases support the idea that significantly T-cell depleting or modulating strategies may be necessary to temper teGVHD. In the French cohort, 2 patients with teGVHD responded well to standard first-line treatment of aGVHD, 2 mg/kg of methylprednisolone alone (N = 2). Two patients did not respond to high-dose steroids but were controlled with cyclosporine and basiliximab/ECP, respectively. Thus, although the ideal treatment of GVHD post-anti-PD-1 remains far from clear, early intervention with significantly T-cell modulating or and/or depleting drugs may be useful to treat severe teGVHD. We recommend consideration of ATG, or alternatively calcineurin inhibitor + ECP, as second-line strategy if not responsive to high-dose steroids.

Recommendations

Today, the majority of patients with post–allo-HCT chL relapse will have received PD-1 blockade before allo-HCT. Given the expected response rates and the scarcity of other options in this setting, retreatment with PD-1 blockade could be chosen, especially if a patient has no history of GVHD, relapse > 180 days after transplant, and no reasonable alternative options. Nevertheless, in the 2 published retrospective series, teGVHD was common and often refractory to GVHD directed treatment. Currently, dose exploration of anti-PD-1 mAb’s is being explored in clinical trials for relapse after allo-HCT. Although these and other strategies to reduce the risk of teGVHD are being tested, we would strongly consider starting anti-PD-1 mAb’s at a low dose (eg, 0.5 mg/kg nivolumab) when given outside the context of a clinical trial. We recommend close monitoring for evidence of GVHD. In the event of teGVHD, we recommend immediate cessation of therapy and rapid initiation of high-dose corticosteroids (2 mg/kg per day). Further immunosuppression should be given promptly if the patient does not respond to steroids, with a preference for calcineurin inhibitor + ECP or ATG.

Conclusion

With the growing role of PD-1 blockade in chL, most patients who consider allo-HCT will have already received an anti-PD-1 mAb. Careful considerations of the risk and benefit of transplantation is important, and we propose recommendations for managing this decision (Table 3) and for choosing a transplant method that best accounts for downstream effects of prior PD-1 blockade. In addition, the efficacy of PD-1 blockade in post–allo-HCT relapse and the lack of good alternative options, anti-PD-1 therapy is likely to be a consideration for most if not all patients in this setting. Here again, we provide recommendations (Table 4) for the timing and dosing of those agents, as well as for the management of GVHD-related toxicity. We acknowledge the substantial gaps in our knowledge and look to future carefully designed retrospective and prospective studies (Table 5) to shed further light on the optimal handling of the PD-1/allo-HCT interface. We strongly advocate that patients be treated on a clinical trial whenever possible and encourage continued efforts to collect off-trial data through international collaborations and registries.

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Authorship


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Footnotes


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