Cancer Vaccines and Immunomodulatory Therapy

David E. Avigan, MD
Beth Israel Deaconess Medical Center, Harvard Medical School

Patients with hematological malignancies exhibit a range of immunosuppressive mechanisms that lead to tumor immunity. These include impairments in the antigen-presentation machinery, defects in T-cell receptor signaling, secretion of immunosuppressive and proapoptotic factors, upregulation of inhibitory pathways, and recruitment of regulatory cells. Treatment advances in multiple myeloma demonstrate the challenges and opportunities of immunomodulatory therapy for patients with hematologic malignancies.

With the advent of novel biological therapies such as lenalidomide and bortezomib, first-line multiple myeloma therapy is associated with higher levels of cytoreduction. Autologous stem cell transplantation (ASCT) enhances consolidation and prolongs progression-free survival (PFS), while lenalidomide maintenance therapy further prolongs response duration. Allo-HSCT is curative for a subset of patients due to the graft-versus-disease (GVD) effect. Mediated by alloreactive lymphocytes, GVD highlights the potential for cellular immunotherapy in multiple myeloma. However, allo-HSCT is associated with significant morbidity and mortality due to the lack of specificity of the alloreactive response, leading to the development of graft-versus-host disease (GVHD). Therefore, one of the major goals of immunotherapy in multiple myeloma is to induce myeloma-specific immune responses that selectively target malignant cells that persist after standard treatment with biologic agents and ASCT.

Therapeutic cancer vaccines are designed to restore immune competence and stimulate tumor-specific immunity. One promising vaccine strategy involves the fusion of patient-derived tumor cells with autologous dendritic cells (DCs). The DC/tumor fusions present a broad array of patient-specific tumor antigens in the context of DC-mediated costimulation. Several studies have examined the safety, immunologic potency, and clinical efficacy of the DC/tumor fusion vaccine in patients with hematologic cancers. In a phase 1 trial of 17 patients with multiple myeloma, treatment with the DC/tumor fusion vaccine was associated with a 10-fold expansion of myeloma-reactive lymphocytes and disease stabilization in the majority of patients with advanced disease. Future directions in DC/tumor fusion cell vaccine research involve the use of combination regimens that promote T-cell proliferation and suppress inhibitor factors, thereby augmenting responses to myeloma-specific tumor vaccines. Lenalidomide maintenance therapy prolongs PFS and overall survival following ASCT in patients with multiple myeloma. Lenalidomide also appears to increase the T-cell mediated immune response to the DC/myeloma fusion cell vaccine. The phase II Blood and Marrow Transplant Clinical Trials Network (BMT CTN) 1401 trial will evaluate ASCT followed by lenalidomide maintenance therapy for patients with multiple myeloma with or without DC/myeloma fusion cell vaccination.

Another promising area of investigation involves the combined use of the DC/tumor fusion vaccine in conjunction with programmed cell death-1 (PD-1)/PD-1 ligand (PDL-1) blockade. The PD-1/PDL-1 pathway plays a key role in maintaining the balance between immune activation and immune tolerance. High levels of PDL-1 expression have been observed on myeloma cells, suggesting a role for the PD-1/PDL-1 checkpoint pathway in facilitating immune tolerance and supporting tumor growth. Tumor PDL-1 expression also appears to promote tolerance in potentially reactive T cells and interferes with cytotoxic T-cell (CTL)-mediated lysis, resulting in muted immunologic responses to vaccine therapy. In contrast, blocking the PD-1/PDL-1 pathway appears to restore the functionality of active T cells. In a recent phase 1 study, treatment with nivolumab, a monoclonal PD-1 receptor antibody, demonstrated promising but muted activity in patients with hematologic malignancies, including stable disease in 67% of patients with multiple myeloma (Table 2). In a preclinical study of myeloma cells, the presence of pidilizumab (CT-011), an anti-PD-1 antibody, enhanced activated T cell responses following treatment with the DC/tumor fusion vaccine.
Table 2. Nivolumab Therapy in Hematologic Malignancies

<table>
<thead>
<tr>
<th>Indication</th>
<th>ORR (%)</th>
<th>CR (%)</th>
<th>PR (%)</th>
<th>SD (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-cell lymphoma (n=29)</td>
<td>28%</td>
<td>7%</td>
<td>21%</td>
<td>48%</td>
</tr>
<tr>
<td>Follicular lymphoma (n=10)</td>
<td>40%</td>
<td>10%</td>
<td>30%</td>
<td>60%</td>
</tr>
<tr>
<td>Diffuse large B-cell lymphoma (n=11)</td>
<td>36%</td>
<td>9%</td>
<td>27%</td>
<td>27%</td>
</tr>
<tr>
<td>T-cell lymphoma (n=23)</td>
<td>17%</td>
<td>0%</td>
<td>17%</td>
<td>43%</td>
</tr>
<tr>
<td>Mycosis fungoides (n=13)</td>
<td>15%</td>
<td>0%</td>
<td>15%</td>
<td>69%</td>
</tr>
<tr>
<td>Peripheral T-cell lymphoma (n=5)</td>
<td>40%</td>
<td>0%</td>
<td>40%</td>
<td>0%</td>
</tr>
<tr>
<td>Multiple myeloma (n=27)</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>67%</td>
</tr>
<tr>
<td>Primary mediastinal B-cell lymphoma (n=2)</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>100%</td>
</tr>
</tbody>
</table>

CR = complete response; ORR = objective response rate; PR = partial response; SD = stable disease.

At the 2015 American Society of Hematology (ASH) annual meeting, researchers presented findings from an ongoing trial of pidilizumab in combination with the DC/myeloma fusion cell vaccine following ASCT in patients with multiple myeloma. To date, 22 patients have completed vaccination and treatment with pidilizumab. Results indicated a marked increase from baseline in circulating tumor-reactive lymphocytes following post-transplant immunotherapy, including CD4+ cells (p=0.06) and CD8+ cells (p<0.05). The most common adverse events included grade 1-2 diarrhea, arthralgias, myalgias, fatigue, headache, nausea, chills, transaminits, cytopenia, elevated thyroid-stimulating hormone (TSH), and vaccine-site reactions. Objective responses included a very good partial response (VGPR) in 6 patients, and a CR or near-CR in 6 patients, including 3 patients who converted following immunotherapy. These findings support the combined use of DC/myeloma fusion cell vaccination and PD-1 blockade following ASCT to induce antitumor immunity and eradicate post-transplant disease in patients with multiple myeloma.

Summary

Cellular immunotherapy harnesses the power and specificity of the immune system to target malignant cells, particularly residual cancer cells. Combining DC/tumor fusion cell vaccines with novel immunomodulating agents represents a new opportunity for improving and maintaining tumor-specific immune responses induced by vaccination. Additional promising adjuncts to vaccine therapy include agents targeting other immune pathways, including those governed by the oncocergic MUC1 protein.

Financial Disclosures

Dr. Avigan discloses no financial relationships relevant to the content of this presentation.

Acknowledgements

This summary was created from the proceedings of the 2015 Chabner Colloquium: Collaboration in Clinical Trials, which was held on Monday, October 26, 2015, in Boston, MA. The Society for Translational Oncology received educational grants in support of this activity from AbbVie Inc., Chugai Academy for Advanced Oncology (CHAAO), Epizyme, Inc., Incyte Corporation, Lilly USA, LLC, Merrimack Pharmaceuticals, Inc., Novartis Pharmaceuticals Corporation, Otsuka America Pharmaceutical, Inc., and Pfizer Inc.

References