Programmed death ligand 1 (PD-L1) as an immunotherapy target in patients with glioblastoma

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See the article by Berghoff et al., on pages 1064–1075.

In this issue of Neuro-Oncology, Berghoff et al present the results of their investigations into the expression of programmed death-ligand 1 (PD-L1) in human glioblastoma specimens and their relationship to other tissue-based and clinical parameters. In specimens from adults with newly diagnosed or recurrent glioblastoma, the investigators reported that diffuse/fibrillary PD-L1 expression of variable extent was found in more than 70% of glioblastoma specimens, with a higher proportion in newly diagnosed cases. Furthermore, more than 70% of cases showed evidence of high tumor-infiltrating lymphocyte (TIL) infiltration, although most were of sparse-to-moderate density. In glioblastoma samples from the Cancer Genome Atlas, the relationships between PD-L1 expression, molecular subtypes, and clinical outcomes were explored. Samples with known molecular subtypes were then classified according to their level of PD-L1 expression (high or low), and a significant difference in the distribution of PD-L1 high and low groups was found across molecular subtypes, with the mesenchymal subtype in particular having a high level of PD-L1 expression and the proneural and G-CIMP subtypes primarily having low expression of PD-L1. The anti-PD-L1 antibody, 5H1, used in this study is not commercially available, although its use has been confirmed in other experiments, whereas some commercially available antibodies have failed to show reliable PD-L1 labeling. The authors conclude that PD-L1 expression and TILs were found in most of the glioblastoma samples they evaluated, but a relationship between these parameters and outcome was not observed. Still, the high expression of PD-L1 in these glioblastoma samples suggests that it may be a valid target for further clinical investigation.

The complexity of the immune response has provided numerous potential therapeutic targets, in particular the ligand–receptor interactions or checkpoint pathways that provide signals to regulate T-cell activation or inhibition because these are thought to be exploited by tumor cells to evade immune detection. Three agents have demonstrated safety and efficacy and are now approved: ipilimumab (cytotoxic T-lymphocyte-associated antigen 4 [CTLA-4] inhibitor), pembrolizumab (PD-1 inhibitor) in metastatic melanoma, and nivolumab (PD-1 inhibitor) in metastatic melanoma and non–small cell lung cancer (NSCLC). Immune checkpoint inhibitors have also shown antitumor activity in certain poor-prognosis, advanced cancers. Given that overcoming the PD-1 pathway-mediated inhibition of the antitumor immune response has shown antitumor effect and that many tumor types exhibit enhanced expression of the PD-1/PD-L1/PD-L2 pathway, the PD-1 receptor ligands PD-L1 and PD-L2 have also been identified as possible targets to stimulate the immune response. Both PD-1 and PD-L1 inhibitors are being extensively studied in a range of solid tumor types and hematological malignancies (Table 1).

To develop effective immunotherapies, the importance of PD-L1 expression in cancer pathogenesis needs to be better understood, and the report here by Berghoff et al provides valuable new information in this area for glioblastoma. Earlier evidence suggested that PD-L1 expression may contribute to immunoresistance of human glioblastoma cells via activation of the PI3K/mTOR pathway and that loss of PTEN function appeared to change the level of PD-L1 expression. Glioblastomas may also upregulate PD-L1 expression in circulating monocytes and tumor-infiltrating macrophages, thereby causing immunosuppression. More research is needed to understand the significance of PD-L1 expression in glioblastoma.

Evidence from other tumor types such as melanoma, renal cell cancer, and NSCLC has demonstrated that PD-L1 expression is present in some patients with response to inhibitors of the PD-1/PD-L1 axis, although patients with PD-L1 negative tumors also had significant responses to treatment. In a recent report of the PD-L1 inhibitor MPDL3280A in a variety of solid tumors, responses were observed in patients whose tumor cells had high PD-L1 expression, and this relationship with clinical response was more robust for PD-L1 expression by TILs. The frequency of PD-L1 expression in glioblastoma, as demonstrated in the current study by Berghoff et al, is considerably higher than that observed in melanoma and NSCLC.
Table 1. Programmed death-ligand 1 and programmed cell death protein 1 inhibitors in development

<table>
<thead>
<tr>
<th>Investigational Agent</th>
<th>Target</th>
<th>Tumor Type(s)</th>
<th>Highest Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMS936559</td>
<td>PD-L1</td>
<td>Advanced solid tumors, including melanoma, NSCLC, SCCHN, GBM, renal cell carcinoma, bladder cancer</td>
<td>1 (multiple)</td>
</tr>
<tr>
<td>MEDI4736</td>
<td>PD-L1</td>
<td>NSCLC, SCCHN, GBM, and other advanced solid tumors</td>
<td>3 (NSCLC)</td>
</tr>
<tr>
<td>MPDL3280A</td>
<td>PD-L1</td>
<td>Bladder cancer, NSCLC, renal cell carcinoma, and other advanced solid tumors</td>
<td>3 (NSCLC)</td>
</tr>
<tr>
<td>MSB0010718C AMP224</td>
<td>PD-L1</td>
<td>Advanced solid tumors</td>
<td>2 (Merkel cell)</td>
</tr>
<tr>
<td></td>
<td>PD-1</td>
<td>Advanced solid tumors, CRC</td>
<td>1 (advanced solid tumors, CRC)</td>
</tr>
<tr>
<td>AMP514/ MEDI0680</td>
<td>PD-1</td>
<td>Advanced malignancies, aggressive B-cell lymphomas</td>
<td>2 (aggressive B-cell lymphomas)</td>
</tr>
<tr>
<td>Pidilizumab</td>
<td>PD-1</td>
<td>Multiple myeloma, GBM, lymphoma</td>
<td>2 (lymphoma)</td>
</tr>
<tr>
<td>Pembroliozumab</td>
<td>PD-1</td>
<td>NSCLC, GBM, SCCHN, pancreatic cancer, renal cell cancer, other advanced solid tumors, lymphoma</td>
<td>Marketed (metastatic melanoma)</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>PD-1</td>
<td>CRC, GBM, HCC, NSCLC, SCCHN, SCLC, breast cancer, bladder cancer, gastric cancer, melanoma, multiple myeloma, ovarian cancer, pancreatic cancer, renal cancer, lymphoma (HL, NHL)</td>
<td>Marketed (metastatic melanoma, NSCLC)</td>
</tr>
</tbody>
</table>

Abbreviations: CRC, colorectal cancer; GBM, glioblastoma; HCC, hepatocellular cancer; HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma; NSCLC, non–small-cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; SCCHN, squamous cell cancer of the head and neck; SCLC, small-cell lung cancer.

(~30%),13 suggesting it may have a strategic role in immune suppression in various glioblastoma molecular subtypes, although, the potential therapeutic value of PD-L1 inhibitors in glioblastoma has yet to be confirmed in clinical trials.

One consideration in the development of antibody inhibitors of immune checkpoints in glioblastoma is the blood-brain barrier. The conventional belief that immune responses were limited in the brain because of the presence of this barrier has now been replaced by an understanding that there is 2-way communication between the immune system in the central nervous system and the systemic circulation. In actuality the blood-brain barrier has selective permeability and participates in regulating the movement of cells and molecules of the brain microenvironment.14 Glioblastoma cells are known to release factors that disrupt the endothelial tight junctions of the blood-brain barrier, and activation of the peripheral immune system can lead to leakiness of the blood-brain barrier, permitting the movement of activated macrophages and lymphocytes across the blood-brain barrier.15 and tumor cells have been located circulating in the peripheral blood of patients with glioblastoma.16 Because the PD-L1 ligand is located on the tumor cell, a PD-L1 inhibitor would have to penetrate both the blood-brain barrier and the blood-tumor barrier to be effective, and there is some evidence of tumor uptake of monoclonal antibodies in patients with glioblastoma.17 It remains to be seen if these early findings will be validated by clinical studies to show whether PD-L1 antibody can penetrate to glioblastoma cells in therapeutic concentrations.

In conclusion, the higher expression of PD-L1 in glioblastoma than in other cancer cells suggests that PD-L1 may have a key function in the immunomodulatory attributes of glioblastoma. Researchers have yet to show a definitive link between high expression and survival, and currently there is a paucity of information to permit therapeutic decision-making based on the presence or absence of PD-L1 expression. The true predictive and prognostic role of PD-L1 continues to be under intensive investigation, and the findings of Berghoff et al provide further insight into molecular differences between varying glioblastoma subtypes and support the need for clinical trials of PD-L1 inhibitors in glioblastoma.

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References


