The Use of Granulocyte-Macrophage Colony-Stimulating Factor in Melanoma Treatment

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H&O What are the limitations of checkpoint blockade alone for patients with metastatic melanoma?

SH Ipilimumab (Yervoy, Bristol-Myers Squibb) is an agent that blocks cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), which is an immune checkpoint molecule that inhibits the activity of T cells. Approximately 10% to 15% of patients with metastatic melanoma have a complete or partial response to ipilimumab, and approximately 22% of patients are alive after 3 years, according to a pooled analysis of 1861 patients that was presented at the 2013 European Cancer Congress by Schadendorf.

H&O What gave you the idea to study sargramostim in combination with ipilimumab for metastatic melanoma?

SH The original description of CTLA-4 blockade was based on combination studies and mouse models that employed the use of a cell vaccine that was engineered to express granulocyte-macrophage colony-stimulating factor (GM-CSF). The GM-CSF was secreted in the microenvironment, which likely attracted immune cells there. These studies suggested some synergy between CTLA-4 blockade and GM-CSFs. In addition, we had studied some patients with autologous tumors that expressed GM-CSF and found that the addition of ipilimumab seemed to have some clinical efficacy; this work was published in the Proceedings of the National Academy of Sciences in 2003 and 2008.

Given the effects of localized expression of GM-CSF, we wanted to look at the impact of systemic GM-CSF using sargramostim in combination with checkpoint blockade using ipilimumab. Systemic GM-CSF has been studied as a single agent in several cancers, including ovarian cancer and prostate cancer, and in combination with peptide vaccines in the adjuvant setting in melanoma.

H&O What was the first study to look at the combination of systemic GM-CSF and ipilimumab for metastatic cancer?

SH The first was a phase 1 study by Fong and colleagues, which looked at the combination of systemic GM-CSF and ipilimumab in prostate cancer. For this study, which was published in Cancer Research in 2009, the researchers treated 24 patients with metastatic castration-resistant prostate cancer with increasing doses of ipilimumab plus subcutaneous injections of fixed-dose GM-CSF. The researchers found that of the 6 patients treated at the highest dose level, 3 had decreases in prostate-specific antigen level of more than 50%, and 1 patient had a partial response in visceral metastases.

H&O Could you please discuss the design and results of your recent study on sargramostim and ipilimumab?

SH As part of the Eastern Cooperative Oncology Group (ECOG), we conducted a randomized study from December 2010 until July 2011 of 245 patients with unresectable stage...
III or IV melanoma. Patients needed to have received at least 1 prior therapy, have an ECOG performance status of 0 or 1, and not have any central nervous system metastases.

We randomly assigned the patients to receive either intravenous ipilimumab (10 mg/kg), or ipilimumab plus subcutaneous sargramostim (250 μg). What the study showed is that after 13.3 months of follow-up, patients who received the combination had longer overall survival and 1-year survival than those who received ipilimumab alone. In addition, people who received the combination were less likely to experience high-grade adverse events. There was no difference in progression-free survival (see the Table).

**Table**. Summary of Efficacy End Points and Incidence of Toxicities

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Ipilimumab Plus Sargramostim (n=123)</th>
<th>Ipilimumab Only (n=122)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of deaths</td>
<td>44</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>OS, median (95% CI), mo</td>
<td>17.5 (14.9-Not reached)</td>
<td>12.7 (10.0-Not reached)</td>
<td>.01 (1 Sided)</td>
</tr>
<tr>
<td>1-Year survival rate (95% CI), %</td>
<td>68.9 (60.6-85.5)</td>
<td>52.9 (43.6-62.2)</td>
<td>.01 (1 Sided)</td>
</tr>
<tr>
<td>Mortality HR (1-sided 90% repeated CI)</td>
<td>0.64 (Not applicable-0.90)</td>
<td>1 [Reference]</td>
<td></td>
</tr>
<tr>
<td>PFS, median (95% CI), mo</td>
<td>3.1 (2.9-4.6)</td>
<td>3.1 (2.9-4.0)</td>
<td>.37 (2 Sided)</td>
</tr>
<tr>
<td>Grade 3-5 adverse events (95% CI), %</td>
<td>44.9 (35.8-54.4)</td>
<td>58.3 (49.0-67.2)</td>
<td>.04 (2 Sided)</td>
</tr>
</tbody>
</table>

HR, hazard ratio; mo, months; no., number; OS, overall survival; PFS, progression-free survival.


It is being expressed. GM-CSF is likely involved with inflammatory/immunological homeostasis of the lung and gut, and we have seen that knocking out the GM-CSF gene results in inflammation of the lung and gut. If a GM-CSF–knockout mouse develops colitis, giving back GM-CSF can reverse that colitis. GM-CSF even has been used to treat patients with idiopathic inflammatory bowel disease in clinical trials. These findings suggest that GM-CSF may play different roles in inflammation, depending on the organs of the body that they are being expressed in. The lung and gut, which help protect us from invading microorganisms, may be unique in terms of the role in inflammation that GM-CSF is playing there.

**H&O** How do you explain the finding that the drug combination increased overall survival but not progression-free survival?

**SH** We know that both agents induce an inflammatory microenvironment that could obscure decreases in tumor size, which might explain how an agent can have antitumor effects without giving that impression on an early scan. That discordance needs to be worked out.

Interestingly, if you look at the data on sipuleucel-T (Provenge, Dendreon)—the vaccine for prostate cancer—you will see that it was approved based on overall survival benefit and that there was no progression-free survival difference. That vaccine also has a GM-CSF component to it, which may be another clue about the unique biology of GM-CSF.

**H&O** Why would there be a lower incidence of toxicities with the combination than with ipilimumab alone?

**SH** That needs further investigation. One hint may come from what we have seen in some of the preclinical animal models. The action of GM-CSF may depend upon where it is being expressed. GM-CSF is likely involved with inflammatory/immunological homeostasis of the lung and gut, and we have seen that knocking out the GM-CSF gene results in inflammation of the lung and gut. If a GM-CSF–knockout mouse develops colitis, giving back GM-CSF can reverse that colitis. GM-CSF even has been used to treat patients with idiopathic inflammatory bowel disease in clinical trials. These findings suggest that GM-CSF may play different roles in inflammation, depending on the organs of the body that they are being expressed in. The lung and gut, which help protect us from invading microorganisms, may be unique in terms of the role in inflammation that GM-CSF is playing there.

**H&O** How are some of the limitations of your study?

**SH** First of all, this was a randomized phase 2 study, so the size was relatively small. Second, this study was conducted with a dose of ipilimumab that was higher than the dose that was approved by the US Food and Drug Administration. It also included maintenance treatment, because that was the regimen we thought was best at the time this study was developed.

**H&O** Is there a synergistic effect between the 2 agents?

**SH** That is what was suggested by our study, which needs to be confirmed. But in the animal models with the vaccine, there was a suggestion of synergy when GM-CSF was secreted into the microenvironment.

**H&O** What is the mechanism by which GM-CSF is believed to enhance the action of ipilimumab?

**SH** There are several possibilities. The likelihood is that GM-CSF promotes antigen presentation. If you increase
antigen presentation and then take the brakes off of the immune system using ipilimumab, that could create a synergistic effect. Ipilimumab also may deplete regulatory cells, which may be another benefit. Although we understand some of the mechanisms, much of what is occurring probably needs further investigation.

**H&O** What do you think the next steps should be in research?

**SH** The next step should be a confirmatory phase 3 trial that incorporates newer immunotherapy checkpoint agents, such as the programmed death 1 (PD-1) checkpoint inhibitors. Our group is currently pursuing such a trial to see whether sargramostim can boost the function of PD-1 inhibitors.

**Suggested Readings**


