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PHAST PHACT

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TODAY'S QUESTION:

What is the Interaction Between PD-1 and PD-L1 Inhibitors and Steroids? Should I worry?

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If you have a topic you would like the pharmacy team to answer, please send your suggestions to: pruskowskija@upmc.edu

Background:

Programmed cell death protein 1 (PD-1) and programmed death-ligand 1 (PD-L1) checkpoint inhibitors are revolutionizing treatment paradigms for a wide variety of cancer types. The PD-1 pathway is an important immune checkpoint which has the normal function of curbing T-cell responses to prevent complications of autoimmunity and overzealous immune activation. Cancer cells harboring somatic mutations can lead to presentation of neoantigens which can be recognized as "non-self" by T-cells. To evade this T-cell response, many cancers have been found to overexpress PD-L1, which attenuates the T-cell response and allows for immune system evasion. This recurring "hijacking" of the PD-1 pathway by cancer cells can be reversed by treatment with checkpoint inhibitors, which rearm T-cells to attack cancer cells by preventing the binding of PD-1 expressed on activated T-cells, to its ligand PD-L-1, overexpressed on cancer cells.

Table 1: FDA Approved Checkpoint Inhibitors

Generic Name (Trade Name)	Sub-Classification	Approved
Nivolumab (Opdivo®)	PD-1 Inhibitor	2014
Pembrolizumab (Keytruda®)	PD-1 Inhibitor	2014
Atezolizumab (Tecentriq®)	PDL-1 Inhibitor	2016
Avelumab (Bavencio®)	PDL-1 Inhibitor	2017
Durvalumab (Imfinzi®)	PDL-1 Inhibitor	2017

Clinical trials of PD-1 and PD-L1 inhibitors generally have excluded patients receiving baseline corticosteroids because of a potential adverse drug reaction. Given the immunosuppressive properties of corticosteroids and the potential effect on T-cell function, there is understandable concern that the use of these agents could decrease the efficacy of immune checkpoint blockade.

Importance:

Palliative care providers often care for patients receiving PD-1 and PD-L1 therapies. Corticosteroids are a cornerstone for the management of pain and other

symptoms. Palliative care providers should be aware of this potential interaction, so they can best relief symptoms without negatively affecting the efficacy of these agents.

The Literature:

- BMC Immunol. 2015 Jun 26;16:39.
  Dexamethasone enhances programmed cell death 1 (PD-1) expression during T cell activation: an insight into the optimum application of glucocorticoids in anti-cancer therapy.
  - Results: In our study, we used dexamethasone (DEX) as a model glucocorticoid and demonstrated that DEX could enhance PD-1 expression in a dose-dependent manner. The effects were completely inhibited by the glucocorticoid receptor (GR) antagonist mifepristone (RU486), indicating that the effect of DEX on PD-1 is mediated through GR. We further found the sensitivity to DEX-induced upregulation of PD-1 expression had a significant difference between different T cell subsets, with memory T cells more susceptible to this effect. We also showed that DEX could suppress T cell functions via inhibition of cytokines production such as IL-2, IFN-γ, TNF-α and induction of apoptosis of T cells.
  - Conclusion: "Our findings suggest a novel way by which DEX suppress the function of activated T lymphocytes by enhancing expression of PD-1 and provide an insight into the optimum clinical application of GCs."
  - *Discussion:* Interesting… so steroids might actually help?

- J Clin Oncol. 2018 Oct 1;36(28):2872-2878.
  Impact of Baseline Steroids on Efficacy of Programmed Cell Death-1 and Programmed Death-Ligand 1 Blockade in Patients With Non-Small-Cell Lung Cancer.
  - Methods: We identified patients who were PD-(L)1-naïve with advanced non-small-cell lung cancer from two institutions-Memorial Sloan Kettering Cancer Center and Gustave Roussy Cancer Center-who were treated with single-agent PD-(L)1 blockade. Clinical and pharmacy records were reviewed to identify corticosteroid use at the time of beginning anti-PD-(L)1therapy. We performed multivariable analyses using Cox proportional hazards regression model and logistic regression.
  - Results: Ninety (14%) of 640 patients treated with single-agent PD-(L)1 blockade received corticosteroids of ≥ 10 mg of prednisone equivalent daily at the start of the PD-(L)1 blockade
    - Common indications for corticosteroids were dyspnea (33%), fatigue (21%), and brain metastases (19%)
    - In both independent cohorts, Memorial Sloan Kettering Cancer Center (n = 455) and Gustave Roussy Cancer Center (n = 185), baseline corticosteroids were associated with decreased overall response rate, progression-free survival, and overall survival with PD-(L)1 blockade
    - In a multivariable analysis of the pooled population, adjusting for smoking history, performance status, and history of brain metastases, baseline corticosteroids remained significantly associated

with decreased progression-free survival (hazard ratio, 1.3; P = .03), and overall survival (hazard ratio, 1.7; P < .001)

- Conclusion: "Baseline corticosteroid use of ≥ 10 mg of prednisone equivalent was associated with poorer outcome in patients with non-small-cell lung cancer who were treated with PD-(L)1 blockade. Prudent use of corticosteroids at the time of initiating PD-(L)1 blockade is recommended."
- *Discussion:* Although this study was retrospective, this does raise some eyebrows

So… What does this all mean Jenn?

- Overall, I would say this is something to worry about
- Per the original inclusion/exclusion criteria of the original studies (and now per the package inserts), patients who must remain on steroids should have their dose reduced to ≤10 mg per day of prednisone (or equivalent) prior to initiating treatment with PD-1 or PD-L1 inhibitors
- The current literature suggests that if patients are receiving steroids prior to PD-1 or PD-L1 therapies, they have poor outcomes – so again try to reduce
- And although we cannot fully differentiate the predictive versus prognostic effects of steroids, steroids should be used with caution at treatment initiation and should probably be avoided unless medically necessary

Geriatric Considerations:

- Currently no pharmacokinetic or pharmacodynamic differences appears to exist between older adults and their younger counterparts regarding PD-1 and PD-L1 inhibitors. Older adults however are at a higher risk of steroid induced effects
- Of course and as always, start low and go slow with any medication, including steroids

Stay tuned for future PCP Phast Phacts on PD-1 and PD-L1 inhibitors!

CLINICAL PEARL:
Patients who must remain on steroids should have their dose reduced to ≤10 mg per day of prednisone (or equivalent) prior to initiating treatment with PD-1 or PD-L1 inhibitors.