



Contents lists available at ScienceDirect

AAACE Clinical Case Reports

journal homepage: www.aaaceclinicalcasereports.com

Commentary

Immunotherapy in Anaplastic Thyroid Cancer: Much Yet to Be Learned

Keith C. Bible, MD, PhD *

Division of Medical Oncology, Mayo Clinic, Rochester, Minnesota



ARTICLE INFO

Article history:

Available online 20 March 2021

Harnessing the immune system to eradicate cancer has been a quest of oncologists and cancer immunologists since at least the 1970s. The intravesical instillation of *Mycobacterium bovis* bacillus Calmette-Guérin was among the first immunomodulating therapies demonstrated useful as a proof of principle. Although this approach improves the management of noninvasive bladder cancer, it is ineffective in bladder invasive disease and is a relatively nonspecific "brute force" strategy. With the advent of bone marrow transplantation, it was later realized that the transplanted marrow-resident immune components of related donors (allogeneic transplantation) are more effective in eradicating hematologic cancers than a patient's own immune components (autologous transplantation), suggesting factors effective in cancer patients that might constrain their own immune system's ability to recognize and attack cancer.

These early approaches, however, were seriously limited by side effects, including autoimmune damage, and were critically impaired owing to the lack of sufficiently robust knowledge to fully exploit involved immune mechanisms. Nonetheless, early experiences led us toward breakthrough discoveries, including the identification of immune checkpoints constituting receptor-ligand immunoregulatory complexes, which are specifically circumvented by some cancers to evade immune responses. Accordingly, the crux of engineered, current, clinically effective immunotherapy is in disrupting the binding of the immune checkpoint protein receptor programmed cell death protein 1 (PD-1), which resides on lymphocytes, to its corresponding immune inhibitory ligand programmed death ligand-1 (PD-L1; overexpressed in some cancers to block immune response) using therapeutic antibodies, such as

pembrolizumab, an antibody in particular directed to bind to PD-1. In addition to pembrolizumab, there are a collection of similarly checkpoint-targeted and effective antibodies binding to either PD-1 or PD-L1, including spartalizumab, as recently tested in anaplastic thyroid cancer (ATC).

Interest in using immunotherapeutic approaches for treating thyroid cancers was in part stimulated by our realization that the thyroid gland is among the most immunogenic tissues in the human body. This has been postulated owing to the high occurrence of autoimmune thyroid disease, and provocatively because autoimmune thyroid disease is possibly the most common immunologic toxicity of checkpoint inhibitors. In this context, the case report of Yang et al¹ details a patient with stage IVB ATC who attained durable disease control (a historically and remarkably favorable outcome) in response to a high-dose neck or nodal basin radiation therapy (7500 cGy) concomitantly administered with pembrolizumab immunotherapy. The patient's ATC progressed in the setting of an underlying papillary thyroid cancer previously treated with surgery and radioactive iodine therapy. Upon detection, the ATC PD-L1 staining was 95%, as assessed by immunohistochemistry (IHC), intimating a potential tethering of the immune system by overexpression of this checkpoint ligand and raising the potential of therapeutic benefit from PD-1/PD-L1 inhibition therapy. The anecdotally yet highly favorable outcome of this patient in response to checkpoint inhibition, along with additional parallel as well as preclinical and clinical data, raise the significant and provocative clinical issues of how and under what conditions checkpoint inhibitor immunotherapy, such as pembrolizumab, can be most productively used in ATC.

One question that arises in this context is that of patient selection and whether candidate biomarkers of immunotherapeutic response might practically predict favorable responses to PD-1/PD-L1 inhibitors, such as pembrolizumab, in ATC. Specifically, some biomarkers have been found in other cancers to correlate in response to checkpoint inhibitors, prompting the tumor agnostic regulatory approval of pembrolizumab in all cancers with positive PD-L1 IHC staining. Therefore, by analogy, one objective in ATC is to analyze which patients might best respond or alternatively not respond at all to checkpoint inhibitor therapy. Significantly, ATC has been reported in some studies to almost universally express PD-L1,² raising the prospect of substantial therapeutic benefit from immunotherapy in ATC. Unfortunately, such is not the case. To date,

See related Case Report by Yang et al in this issue (<https://doi.org/10.1016/j.aaace.2021.03.003>).

Abbreviation: ATC, anaplastic thyroid cancer.

* Address correspondence and reprint requests to Dr Keith C. Bible, Emeritus Professor of Oncology, Division of Medical Oncology, Mayo Clinic, Rochester, MN 55905.

E-mail address: keithcbible@gmail.com.

<https://doi.org/10.1016/j.aaace.2021.03.005>

2376-0605/© 2021 AAACE. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

the most favorable and promising response rates to such immunotherapeutic monotherapy in ATC was 19% overall and 35% among those patients with ATC with >50% PD-L1 IHC staining, as reported in a recent spartalizumab trial.³ Therefore, PD-L1 IHC staining alone may not be a robustly predictive biomarker of immunotherapeutic response in ATC. Whether other candidate predictive biomarkers, such as tumor mutational burden or mismatch repair deficiencies, perform better in robustly predicting response to immunotherapies in ATC remains uncertain; however, this arena is certainly worthy of further detailed study.

Besides the discovery of candidate biomarkers that may better predict the therapeutic response to PD-1/PD-L1 inhibitors in ATC is whether specific cotherapies might additionally have potential to confer enhanced and even synergistic therapeutic responses, such as radiation therapy, as possibly observed in this report. The rationale for applying this approach relates to the concept that enhanced tumor antigen release, termed as antigen presentation, resulting from cell death induced by radiation therapy that occurs in the setting of an upregulated immune system further heightened consequent to the checkpoint inhibitor therapy might prime or sensitize host immunity for enhanced therapeutic benefit. This intriguing question was preliminarily approached in a therapeutic phase 2 clinical trial, assessing responses to the co-administration of pembrolizumab and chemoimmunotherapy as initial therapy in patients with IVA and IVB ATC.⁴ Unfortunately, this trial was terminated due to concerns of inefficacy and toxicities on the basis of the death of the first treated patient from rapidly recurrent/progressive disease and due to the deaths of the next 2 sequentially treated patients associated with what seemed to be extreme

toxicities possibly incited by the addition of immunotherapy to large volume radiotherapy.⁴ Therefore, safely and effectively applying this cotherapeutic strategy in ATC may be very challenging. However, there are ongoing efforts to address this relevant question in a modified fashion intended to avert the previously observed toxicities and yet gain synergistic benefit from immunoradiotherapy in ATC, but whether this approach may prove successful remains to be conclusively demonstrated.

Although there remains optimism that checkpoint inhibitors, such as pembrolizumab, may significantly contribute to the therapeutic armamentarium for ATC, we have much to learn to optimize their best applications, although progress is being made.

Disclosure

The authors have no multiplicity of interest to disclose.

References

1. Yang S-R, Tsai M-H, Hung C-J, Peng S-L, Chiu N-T, Huang Y-H, Tsai H-J. Anaplastic thyroid cancer successfully treated with radiation and immunotherapy: a case report. *AACE Clin Case Rep.* 2021;7(5):299–302.
2. Chintakuntlawar AV, Rumilla KM, Smith CY, et al. Expression of PD-1 and PD-L1 in anaplastic thyroid cancer patients treated with multimodal therapy: results from a retrospective study. *J Clin Endocrinol Metab.* 2017;102(6):1943–1950.
3. Capdevila J, Wirth LJ, Ernst T, et al. PD-1 blockade in anaplastic thyroid carcinoma. *J Clin Oncol.* 2020;38(23):2620–2627.
4. Chintakuntlawar AV, Yin J, Foote RL, et al. A phase 2 study of pembrolizumab combined with chemoradiotherapy as initial treatment for anaplastic thyroid cancer. *Thyroid.* 2019;29(11):1615–1622.