Diagnosis and Management of Immune Checkpoint Inhibitor–related Toxicities in Ovarian Cancer: A Series of Case Vignettes

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ABSTRACT

Use of immune checkpoint inhibitors targeting cytotoxic T-lymphocyte-associated antigen 4 and programmed cell death protein 1 have led to improved survival outcomes for advanced solid-tumor malignancies. This report helps the reader gain a better understanding of adverse events in patients with ovarian cancer on checkpoint inhibitor therapy. We describe 3 hypothetical case vignettes of patients with gynecologic cancer on checkpoint inhibitor immunotherapy and discuss common immune-related adverse events. The typical presentation and onset of immune-related events are different from those associated with conventional chemotherapy. This report highlights the importance of early recognition and management of these events. (*Clin Ther*. ▮▮▮▮;▮:▮▮▮–▮▮▮) © 2018 Elsevier HS Journals, Inc. All rights reserved.

Key words: immune checkpoint inhibitors, pneumonitis, thyroiditis, hypophysitis, anti-PD1, anti-CTLA-4.

INTRODUCTION

Immunotherapy has proven to be an exciting treatment modality in cancer care. For over a century, researchers have been investigating ways to activate one's own immune system to attack and destroy tumor cells using immunotherapy drugs alone or in combination with other immunotherapy agents and conventional chemotherapy. Advances in the management of melanoma and non–small cell lung cancer with immunotherapy antitumor agents have helped pave the way for the treatment of other solid tumors, including those of the head and neck, renal, and bladder. More recently, programmed cell death protein 1 (PD-1) receptor inhibitors were approved by the US Food and Drug Administration for use in high-instability microsatellite tumors, particularly gynecologic endometrial cancers.

The US Food and Drug Administration has approved 6 immune checkpoint inhibitors for the treatment of advanced malignancies, including gynecologic cancers. Ipilimumab targets cytotoxic T lymphocyte–associated antigen 4; nivolumab and pembrolizumab both target PD-1; and atezolizumab, durvalumab, and avelumab target PD-1 ligand. These monoclonal antibodies act as immune checkpoint inhibitors, removing the "breaks from the immune system" to activate T cells to fight cancer. However, T-cell activation can lead to attacks on normal tissues, causing immune-related adverse events such as colitis, hepatitis, pneumonitis, skin rash, thyroiditis, and hematologic toxicity.[1,2]

The therapeutic benefit of these immunotherapeutic agents in gynecologic cancers is currently being evaluated with clinical trials. Examples of clinical trials include GOG 3015 (ClinicalTrials.gov identifier: NCT03038100), a study of atezolizumab versus placebo in combination with paclitaxel, carboplatin, and bevacizumab in participants with newly diagnosed Stage III ovarian, fallopian tube, or primary peritoneal cancer; and Javelin Ovarian 200 (ClinicalTrials.gov identifier: NCT02580058), a study of avelumab alone or in combination with pegylated liposomal doxorubicin versus pegylated liposomal doxorubicin alone in patients with platinum-resistant/refractory ovarian cancer. This report uses 3 hypothetical cases of toxicity based on frequently encountered immune-related adverse events in patients with gynecologic cancer receiving immune checkpoint inhibitors.

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CASE VIGNETTES

Case 1: Thyroiditis

Patient 1 was a 45-year-old woman with a medical history notable for type 2 diabetes mellitus and *BRCA1* mutation. She was diagnosed with Stage IIIC high-grade serous carcinoma of the right ovary during an emergent exploratory laparotomy and right salpingo-oophorectomy for adnexal torsion by her general gynecologist. She was referred to a gynecologic oncologist and was dispositioned to receive neoadjuvant chemotherapy due to the unresectable nature of her disease. She elected to enroll in a clinical trial in which pembrolizumab was administered in combination with standard chemotherapy. She received 3 cycles of neoadjuvant dose-dense paclitaxel and carboplatin with pembrolizumab, followed by interval tumor-reductive surgery.

She resumed adjuvant chemotherapy on protocol with paclitaxel, carboplatin, and pembrolizumab. Routine laboratory values were obtained, including baseline thyroid function test levels, which were normal (Figure 1). Approximately 2 weeks after initiating pembrolizumab therapy, she presented to clinic with tachycardia (heart rate, 128 bpm). Physical examination revealed thyromegaly with pain on palpation, and tremor. Thyroid-stimulating hormone was 0.02 mIU/L. Metoprolol 25 mg PO once daily was started for tachycardia, and thyroid function studies were ordered to further investigate her examination findings. Thyroid ultrasound revealed a mildly enlarged thyroid gland, measuring 6.4 × 2.5 × 1.8 cm, compatible with thyroiditis. The thyroid-uptake scan showed poor visualization and below-normal ranges of radioiodine uptake by the thyroid, also compatible with thyroiditis. She was managed with metoprolol therapy for approximately 4 weeks. The patient went on to complete the remaining 2 cycles of adjuvant chemotherapy without consequence.

The patient presented to clinic to begin maintenance pembrolizumab (week 12 overall) with reports of swelling around her eyes for 10 days, increased fatigue, cold intolerance, and weight gain. She denied any visual changes or disturbance. On examination, she was noted to have a normal thyroid gland by palpation. Her thyroid-stimulating hormone results revealed that the patient was transitioning to the hypothyroid state (Figure 1). She was started on levothyroxine 50 μg/d. Following 3 weeks of therapy, the patient had subjectively improved; however, thyroid function testing showed persistent hypothyroid state (Figure 1). Levothyroxine dose was increased to 100 μg/d. After 8 weeks of hormone therapy, the associated symptoms of fatigue and weight gain continued to improve. She was continued on maintenance pembrolizumab and levothyroxine therapy at 112 μg/d, and was comanaged by the endocrinology service.

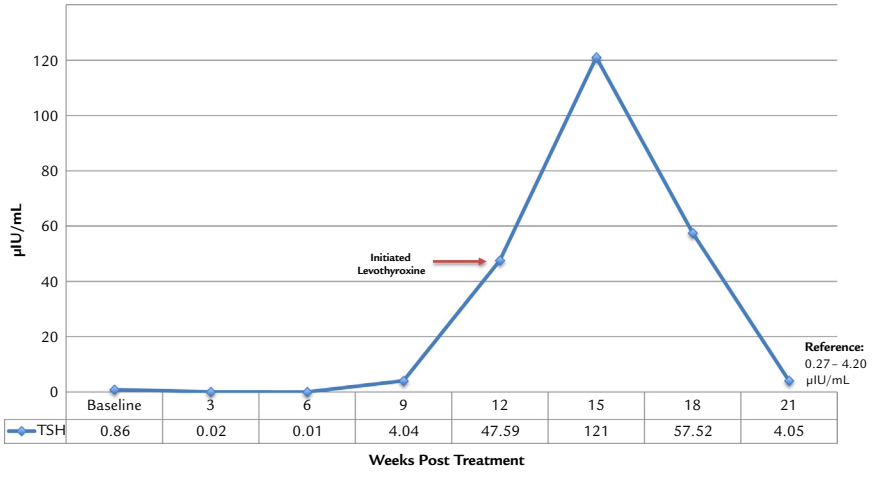

Figure 1. Trend of thyroid-stimulating hormone (TSH) values from baseline through the course of pembrolizumab therapy.

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