An Overview of Immune Checkpoint Inhibitors in Gynecologic Cancers

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ABSTRACT

Purpose: The goal of this study was to compile a review of topics pertinent to the use of immune checkpoint inhibitors in gynecologic malignancies, including foundation for use, current agents available and trials in gynecologic cancers, special populations of interest, identification and management of toxicities, and considerations in predictive biomarkers and response assessment.

Methods: A literature review of selected topics in reference to immune checkpoint inhibitors and gynecologic cancers was conducted on PubMed and the US Food and Drug Administration drug search application. A review of current and ongoing clinical trials was performed in clinicaltrials.gov, and selected preliminary results reported in PubMed abstracts and through the American Society of Clinical Oncologists were compiled.

Findings: Although immunotherapy in gynecologic malignancy is relatively new, 7 agents are currently approved for use in other oncologic indications, and a multitude of trials in gynecologic cancer are ongoing. Immunotherapy has a specific set of drug toxicities that manifest and are managed unlike traditional cytotoxic therapies.

Implications: Application of the knowledge of immune checkpoint inhibitor use in gynecologic cancers will improve care for women with cancers of the female reproductive tract. As more complex and newer immunotherapies evolve, it will be vital to accurately characterize each specific drug class and management thereof. (*Clin Ther*. ▮▮▮▮;▮:▮▮▮–▮▮▮) © 2018 Elsevier HS Journals, Inc. All rights reserved.

Key words: Immunotherapy, Gynecologic Cancers, CTLA-4 Inhibitors, PD1/PDL1 Inhibitors, Toxicity Management.

INTRODUCTION

Immune checkpoint inhibitors (ICPIs) are rapidly being trialed, tested, and approved for use in solid and hematologic malignancies, including gynecologic cancers. The present review provides an introduction to the current uses of immunotherapy in oncology, as well as specific applications to gynecologic malignancies. This review includes discussion of the role of the immune system and the tumor microenvironment as the basis for ICPI use in cancer. A review of approved and developing indications for ICPIs in the field of gynecologic oncology is provided via overview of relevant clinical trials and reported outcomes, when available. An overview of the unique immune-related adverse events (irAEs) associated with ICPIs and their appropriate management, as well as anticipated challenges associated with ICPI use, is discussed.

MATERIALS AND METHODS

A current review of the literature pertaining to IPCIs was performed. For current clinical and pharmacologic data relevant to each approved ICPI, the US Food and Drug Administration (FDA) website was searched at https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm for package inserts and references to clinical trials that were the basis for agent approval. For each of the gynecologic cancer types, a PubMed and ASCOpubs.org search was performed. Trials included were: (1) completed clinical trials in gynecologic oncology; or (2) published abstracts with preliminary results.

ClinicalTrials.gov was queried to outline a composite of ongoing ICPI-based clinical trials in gynecologic malignancies. To perform a review of irAEs, a PubMed search of the following terms was performed: *nivolumab, pembrolizumab, atezolizumab, avelumab, ipilimumab, durvalumab,* and *tremelimumab* in combination with *immune related adverse events/toxicity/management.*

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All literature searches and queries were performed in 2017 and articles published in English were evaluated. Relevant case reports, review articles, systematic reviews, and meta-analyses were included for review.

APPROVED ICPIS

The ICPIs in clinical practice fall into 2 broad classes: cytotoxic T lymphocyte antigen–4 (CTLA-4) inhibitors and the programmed death receptor–1 (PD1)/programmed death– ligand 1 (PDL1) inhibitors. CTLA-4 is a CD28-like molecule that is similarly upregulated upon T lymphocyte activation but works with opposite effect.[1] CTLA-4 has a higher affinity than CD28 to B7 and exerts its inhibitory function by blocking the promotion of interkeukin-2 and downregulation of cytotoxic T-cell proliferation. PD1 is expressed on all T cells, and PDL1 is expressed on antigen-presenting cells and some nonhematopoietic cell lines.[1–4] The production and expression of these inhibitory immune checkpoint molecules have been shown to be upregulated in tumors and in the tumor microenvironment.[5] PD1 is a central player in peripheral tolerance. Once activated, the PD1/PDL1 complex leads to upregulation of other inhibitor cells, such a T-regulatory (Treg) cells, CD25 lymphocytes, and myeloid-derived suppressor cells,[1,4,5] and decreases the cytotoxic efficacy of cytotoxic T lymphocytes (CTL) by disabling the apoptosis, or programmed cell death, pathway.[1,4] The inhibition of the pro-oncogenic immunosuppressive pathways is the foundation of the mechanism of action and efficacy of ICPIs.

In 2011, the US Food and Drug Administration (FDA) approved ipilimumab, an anti–CTLA-4 antibody for use in treating melanoma. This approval marked the beginning of a new era for cancer immunotherapy.[1,6] Ipilimumab's approval followed Phase III clinical trials showing improvement in overall survival among subjects with metastatic melanoma in both upfront and second-line treatment settings.[6,7] Ipilimumab remains the only FDA-approved CTLA-4 inhibitor, although others are in clinical trials.

Inhibition of PD1/PDL1 with monoclonal antibodies became an approved therapy with pembrolizumab in metastatic melanoma in 2014. Pembrolizumab is a fully humanized immunoglobulin monoclonal antibody against PD1. Additional FDA-approved indications for pembrolizumab include front-line use in non–small cell squamous cell carcinoma of the lung and recurrent head and neck squamous cell carcinomas.[8,9] Recently, pembrolizumab was also approved for use in solid tumors with high microsatellite instability (MSI-H) or mismatch repair (MMR) gene defects. Nivolumab, also a PD1 inhibitor, is currently approved for use in metastatic melanoma, non–small cell squamous cell carcinoma of the lung, renal cell carcinoma, classic Hodgkin lymphoma, head and neck squamous cell carcinomas, urothelial carcinoma, and hepatocellular carcinoma.[10] Atezolizumab, avelumab, and durvalumab are PDL inhibitors that are currently approved for uses outside of gynecologic cancers. Atezolizumab and durvalumab are approved for use in urothelial cancers. Avelumab is currently approved for use in metastatic Merkel cell carcinoma.[11–13] There are many ongoing clinical trials investigating the utility of these agents and other newer ICPIs in a variety of oncologic settings, including gynecologic cancers, both as single agents and in combination with cytotoxic chemotherapy, radiation, targeted therapies, and other immune modulators.

ICPIs IN ENDOMETRIAL CANCER

Endometrial cancer is the most common gynecologic malignancy in US women, with >61,000 projected new cases and >10,000 estimated cancer-related deaths in 2017.[14] Classically, endometrial cancer is divided into either type I or type II, based on histology findings and grade.[15,16] Although this classification system correlates to prognosis, contemporary research by The Cancer Genome Atlas has shown that endometrial cancer can be better classified into 4 distinct molecular subtypes: ultra-mutated, hypermutated, copy number high, and copy number low.[17–19] It is the hypermutated group that is of most interest in terms of immunotherapy because it carries a high number of MMR defects.[19] The MMR pathway functions to repair single-strand breaks, mispairings, and small insertions or deletions that occur during DNA replication. Germline MMR deficiencies of 1 of the 4 DNA MMR genes (*MLH1, MSH2, MSH6*, or *PMS2*) are associated with Lynch syndrome, which accounts for 2% to 6% of all cases of endometrial cancer.[20,21] However, the vast majority of MMR pathway deficiencies in endometrial cancers are secondary to somatic mutations.[22]

The importance of evaluating for mutational status in endometrial cancers has been emphasized in the