Immunotherapy in Ovarian Cancer—Where Are We Going?

Maurie Markman, MD

Abstract

Over the past decade there have been major advances in the use of several innovative immunotherapeutic strategies in the management of a number of malignancies. Unfortunately, to date, despite considerable efforts in ovarian cancer in this therapeutic domain there has been limited evidence of clinical utility. Provocative research in vaccine-based treatments and early signs of efficacy for checkpoint inhibitors hold the potential promise that this situation will change in the not-so-distant future.

Introduction

It is increasingly clear that the multi-decade effort to attempt to manipulate an individual cancer patient's immune system to favorably impact the natural history of the malignancy in that individual is finally moving from the realm of theory and rare anecdotal activity to objective reality in an ever-increasing number of clinical settings. While highly provocative experiences documented the potential utility of infusing activated autologous T-cells in several situations, most notably metastatic melanoma, only a small minority of patients achieved major sustained clinical benefit. However, many of these responses have been documented to persist for as long as 30 years.[1] And of considerable interest, published data in the gastrointestinal cancer arena suggest the majority of such cancers possess potentially immunogenic mutations that might be exploited to develop an individual tumor-specific immune attack against these malignancies.[2]

More recently a focus on immune checkpoint inhibition has renewed major interest in a variety of strategies to manipulate the patient's own immune system to eliminate the cancer, or at least control its clinical manifestations for extended periods of time.[3,4] These clinical efforts are rapidly progressing in multiple areas, including in tumor types that were not traditionally believed to be targets for immune manipulation, such as cancers of the colon[5] and lung.[6]

Finally, it is increasingly clear that our overall knowledge of optimal strategies to effectively manipulate the immune system, either through infusion of immune-reactive T-cells, vaccination strategies, or inhibitors of immune blockage remain in their infancy. Consider, for example, recent reports suggesting the greatest benefit from inhibitors of immune blockage appears to occur in cancers that possess the largest number of individual mutations within the tumor,[7] the observation that the composition of an individual patient's gastrointestinal microbiology may substantially impact the effectiveness of this therapeutic strategy,[8] and the potential for local radiation therapy to potentiate the favorable influence of a systemic immune approach.[9]

Rationale

For several reasons ovarian cancer is an ideal tumor type for which to consider an immune-modulatory management approach. First, the cancer itself does not substantially negatively impact immune-regulatory cells that may be present within the bone marrow or other body locations. Second, while standard cytotoxic therapy of ovarian cancer can result in a depression in the number of immune-regulatory cells, these effects are generally modest in extent and short in duration. Further, until late in the course of the natural history of the illness, it is common for patients with ovarian cancer to maintain a quite reasonable performance status and satisfactory nutrition (except in the presence of cancer-related bowel dysfunction).

In addition, the majority of patients with ovarian cancer (even those with stage 4 disease) initially respond to cytotoxic therapy and can reasonably be anticipated to experience a period away from active treatment measured in "many months" to "many years". This time interval would presumably be sufficient for the required "activation" of immune defense mechanisms, either from a successful vaccination strategy or other form of immune modulation.

Pre-Clinical Data

A rather substantial pre-clinical experience has supported the theoretical potential for a variety of immunotherapeutic approaches in the management of ovarian cancer, including vaccination and immune cell-based infusions.[10-12]

Perhaps the most provocative pre-clinical data in this arena was published more than a decade ago from a group of investigators who noted in a retrospective analysis that ovarian cancer patients whose tumors were shown to contain CD3+ T cells (54%

of samples) experienced a 5-year overall survival (OS) of 38% compared to only 4.5% among the population without evidence of these cells.[13] The authors further noted that the absence of intratumoral T cells was associated with a higher level of vascular endothelial growth factor (VEGF), a well-recognized growth stimulatory factor for ovarian cancer.

Clinical Experience

Based on the observation of potentially highly clinically relevant ovarian cancer tumor-associated antigens, investigators have initiated multiple clinical trials, including a number of phase III randomized efforts, to examine a vaccine-based strategy in the malignancy.[10-12] Unfortunately, to date, even though it has been shown to be possible to successfully "immunize" patients (eg, positive antibody response to the vaccine-based antigen), all such reported vaccination efforts have failed to demonstrate an improvement in a clinically relevant outcome (eg, progression-free survival [PFS] or OS). However, active research efforts in this important arena (both pre-clinical and clinical) appropriately continue.[10,11]

It should be noted here that one form of "antibody-based" therapy of ovarian cancer has been shown to be clinically effective, and this is the administration of the monoclonal antibody (bevacizumab) directed against VEGF.[14,15] In phase III randomized trials in several clinical settings (newly diagnosed, recurrent potentially-platinum-sensitive, platinum-resistant disease) the administration of this agent has been shown to improve PFS compared to cytotoxic chemotherapy alone. In contrast, several other "antibody-based" therapies widely employed in other tumor types, including trastuzumab in breast cancer,16 and cetuximab in colon cancer,[11] have been shown in phase II studies to have limited activity in ovarian cancer.

Despite the pre-clinical suggestion that ovarian cancer may be an excellent model with which to explore a variety of immunomodulatory strategies, there has been quite modest reported clinical trial activity in this arena. To date, most of the studies have been small phase II efforts or only a few ovarian cancer patients have been included among a much larger group of patients with other cancer types undergoing therapy with a particular strategy. The unfortunate result is that only anecdotal evidence of therapeutic efficacy exists, including the unique approach of direct intraperitoneal delivery of a potent immunostimulatory agent, IL-2.[17]

Similar statements can also be made for the extent of current published evidence for a potential clinical role for immune-checkpoint blockade as a therapeutic strategy in ovarian cancer. A company-sponsored phase II trial of single agent ipilimumab in ovarian cancer is scheduled for completion in approximately 1 year (ClinicalTrials.gov identifier: NCT01611558). An NRG study (NRG-GY003) is comparing single agent nivolumab with or without ipilimumab in a similar setting. The results of both trials are awaited with considerable interest.

TABLE 1. Potential Immune-Based Approaches In The Management Of Ovarian Cancer

1. Monoclonal antibodies (eg, anti-angiogenic agents)
2. Vaccines (eg, anti-CA125)
3. Immune cellular therapy (eg, autologous modified T-cells)
4. Immune checkpoint blockade (eg, ipilimumab; anti PD-1 agents)

There have been several reports noting objective, but to-date limited, clinical activity associated with an anti-PD-1 approach in previously treated ovarian cancer. In one report involving multiple tumor types, only one of 17 ovarian cancer patients treated with one such agent (BMS-936559) achieved an objective response.[4] In the single phase II study published to date in the peer-reviewed literature and focused solely on ovarian cancer patients, an overall response rate of 15% (3 of 20 patients) was reported following treatment with the anti-PD-1 antibody nivolumab, with a median PFS of 3.5 months being observed in the trial.[18] Similar response data have been noted in a preliminary report of pembrolizumab administered in a phase IB study to patients with PD-L1 positive ovarian cancer (3 of 20 patients; 15%), including two responses at up to about one year.[19]

While the objective response rate reported in these small trials was certainly not overly impressive, complete and durable remissions were observed in these study populations. It is reasonable to anticipate that detailed analysis of the responding patient population will provide highly relevant insight into their unique molecular and immunological characteristic that will assist in the future selection of patients most likely to benefit from this particular therapeutic strategy.

Follow-up of these reported trials, as well as additional experience with checkpoint inhibitors will absolutely be required before any definitive statements can be made regarding the potential utility of this class of agents in the routine management of advanced ovarian cancer.

Conclusion

While the theoretical potential of a role for immune modulation in the treatment of ovarian cancer remains very much alive, the promise has yet to be fulfilled. It is hoped that ongoing and planned studies exploring a variety of strategies to manipulate the immune system in women with ovarian cancer will ultimately demonstrate the unequivocal clinical utility of this therapeutic strategy.

Affiliation: Maurie Markman, MD, is from Cancer Treatment Centers of America, Philadelphia, PA; and Drexel University

College of Medicine, Philadelphia, PA.

Disclosures: None

Address Correspondence to: Maurie Markman, MD, 1331 E Wyoming Ave, Philadelphia, PA 19124, phone: 215-537-7400; fax: 215-537-7139; email: maurie.markman@ctca-hope.com

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