Gynecologic Oncology xxx (2013) xxx–xxx

Contents lists available at SciVerse ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Review

Therapeutic vaccines for ovarian cancer

John B. Liao [a,b], Mary L. Disis [b,*]

[a] Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, University of Washington, 1959 NE Pacific St., Seattle, WA 98195, USA
[b] Tumor Vaccine Group, Center for Translational Medicine in Women's Health, University of Washington, 850 Republican St., Seattle, WA 98109, USA

HIGHLIGHTS

- Completed phase 2 and 3 trials with clinical endpoints have demonstrated modest responses.
- Targeting the immunosuppressive tumor microenvironment may augment the effectiveness of the next generation of vaccines.

ARTICLE INFO

Article history:
Received 17 May 2013
Accepted 17 June 2013
Available online xxxx

Keywords:
Ovarian cancer
Vaccines
Immune therapies

ABSTRACT

While therapeutic vaccines for ovarian cancer represent only a small fraction of active clinical trials, growing interest in this area and the accumulated data supporting the use of vaccines in cancer treatment portend further expansion of trials incorporating these strategies. This review explores the rationale for the use of vaccines for the treatment of ovarian cancer. It examines vaccine platforms that have been investigated and reviews the data from these studies. We also highlight recently reported phase 2 and 3 clinical trials with clinical outcomes as endpoints. Finally, we consider directions for the next generation of vaccines in light of these findings and our emerging understanding of agents that may augment vaccine responses by targeting the immunosuppressive impact of the tumor microenvironment.

Contents

Introduction

A survey of clinicaltrials.gov in March 2013 reveals that of all currently open and recruiting clinical trials for ovarian cancer patients, between 5 and 10% of studies evaluate approaches using immune based therapies. Approximately 40% of clinical trials involving modulation of the immune system employ a vaccine alone or in combination with other agents. While immuno-oncology represents but a small fraction of all open clinical trials for ovarian cancer, growing interest in this area and the accumulated data supporting the use of vaccines in cancer treatment, portends further expansion of trials incorporating these strategies. This article will review the rationale for the use of vaccine therapy in ovarian cancer, outline vaccine design considerations as we survey a sample of current and recent applications under investigation, and consider future directions for the field.

What is the rationale for vaccine therapy in ovarian cancer?

Ovarian cancer is immunogenic. The ability of the immune system to recognize ovarian cancer is associated with improved prognosis. The form of immunity associated with this improved prognosis is known; T cell infiltrates in ovarian cancers are shown to be associated

* Corresponding author. Fax: +1 206 685 3128.
E-mail address: ndisis@u.washington.edu (M.L. Disis).

0090-8258/$ – see front matter © 2013 Published by Elsevier Inc.
http://dx.doi.org/10.1016/j.ygyno.2013.06.023

with improved prognosis in a number of studies. The infiltration of T cells has been observed in ovarian cancers since 1982 [1]. The full prognostic significance of T-cell infiltration in ovarian cancers, that it rivaled optimal surgical cytoreduction, was subsequently reported by Zhang et al in 2003 [2]. The presence of intratumoral T cells was an independent prognostic factor for PFS and OS by multivariate analysis. These findings have been validated in several subsequent studies, and point to the specific importance of cytotoxic CD8 + T-cells [3–9]. Regulatory T cells, another subset of T cells that can modulate immune responses and maintain tolerance to self-antigen, have been shown to predict poor patient survival in ovarian cancer [6,10].

The natural pathobiology of ovarian cancer also allows opportunities for therapeutic vaccines to be applied. Although over 60% of women diagnosed with ovarian cancer will have distant metastases according to the most recent NCI SEER data, and response rates to initial chemotherapy and cytoreductive surgery can be as high as 85% [11]. Unfortunately, despite these initial responses, over two thirds of patients will recur and even in patients who achieve complete remissions, maintaining these has proven elusive [12]. Despite advances in therapies, cure rates have changed little and most patients can expect a relapsing and remitting clinical course of progressive resistance to chemotherapies. However, periods of remission could allow vaccines the necessary time in patients with low disease burdens to induce an effective antitumor response to prolong remissions and prevent recurrences.

Finally, we have already seen the ability of novel therapies, modulating T-cells, demonstrate responses in ovarian cancer patients. Cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) engagement of costimulatory molecules can result in the arrest of T cell responses and impaired antitumor response. When antibody blockage of CTLA-4 was used in heavily pretreated ovarian cancer patients, who had received multiple lines of chemotherapy, four of nine patients were able to achieve stable disease, by CA-125 and radiographic criteria, without significant toxicities [13,14]. Programmed death 1 (PD-1) is another T-cell coinhibitory receptor. Antibody blockage of its ligand, PD-L1, has been studied in patients with selected advanced cancers, including ovarian cancer. Patients with advanced or metastatic disease having failed at least one line of chemotherapy were treated with anti-PD-L1 antibody in an effort to block inhibitory signals on effector T cells. 18% of ovarian cancer patients (n = 17) were able to achieve stable disease for at least 6 months [15]. The success of these recent methods of T cell modulation in an antigen non-specific fashion, in pretreated patients, suggests that vaccines capable of generating more focused immune responses specifically targeting tumor antigens may be even more effective.

What is the track record of ovarian cancer vaccine therapy?

An ideal antigen for an ovarian cancer therapeutic vaccine would be solely expressed on ovarian cancer cells, be highly immunogenic with a bias toward a cytotoxic antitumor response, and be able to be carried or expressed using the chosen vaccine platform. Additionally, the target should be biologically necessary in maintaining the malignant phenotype so that tumor cells cannot escape immune targeting through loss of expression. These would be considered tumor specific antigens. Few, if any, candidate antigens will meet all these criteria. HPV oncoproteins E6 and E7 in cervical cancer are one of the few examples of this, viral proteins that are also required for the malignant phenotype. For most malignancies, vaccine targets represent tumor-associated antigens, which are over expressed in tumor cells, but also are present in lower quantities in normal cells [16]. Because they are self-antigens, they are inherently less immunogenic. Candidate antigens being evaluated in ovarian cancer generally fall into this classification. A number of candidate antigens including HER2/neu, p53, CA125, MUC1, CEA, folate receptor alpha, cancer testis antigens like NY-ESO-1 and insulin growth factor binding proteins have all been proposed as potential vaccine targets in ovarian cancer due to their reported immunogenicity [17–27].

Therapeutic cancer vaccines have been evaluated using a number of platforms including peptides/protein or DNA in combination with adjuvant, anti-idiotype vaccines, recombinant viruses or other microbes, tumor cells or tumor cell lysates, or the delivery of activated dendritic cells to patients. A number of these strategies are currently being studied for ovarian cancer and their advantages and limitations can be influenced by factors inherent to the specific platform (Table 1).

Peptide strategies are attractive because they allow the direct translation of an identified tumor associated antigen into a vaccine and precise measurement of immune responses. Peptides of a specific length and sequence can represent epitopes that may be presented on MHC molecules to effector T cells. However, peptides and proteins have limited ability to elicit balanced and durable CD4 and CD8 responses alone. Peptide and protein based vaccine platforms are usually administered with an immune modulator or adjuvant because they are only weakly immunogenic. These vaccines may only represent a portion of a tumor-associated antigen and selection of epitopes may be limited by the diversity of HLA alleles in patients that are able to recognize these epitopes. Long peptides incorporating both CD8 + and CD4 + epitopes have the potential to be more efficiently presented to T cells and have been demonstrated in vaccination targeting HPV E6 and E7 in cervical cancer [28]. This strategy has been reported in a phase 1 trial of 28 ovarian cancer patients using overlapping long peptides from a human tumor self-antigen, NY-ESO-1 with adjuvant. The vaccine was well tolerated and able to induce both cellular, CD4 + and CD8 +, and antibody responses in nearly all vaccinated patients when given with a Poly-ICLC adjuvant [29].

While a peptide or protein strategy may be limited by the knowledge of and ability of a specific patient's MHC molecules to present the selected amino acids sequences, it has the potential to target multiple antigens. Additionally, downregulation of surface MHC class I is hypothesized to be a strategy of immune evasion in a number of malignancies. A look at the feasibility of selected peptides from candidate antigens: p53, SP17, survivin, WT1, and NY-ESO-1 to be incorporated in a multiantigen vaccine was undertaken by Vermeij and colleagues. In tumor samples from 270 primary ovarian cancer patients, 93.2% overexpressed at least one of the candidate antigens. Over 70% of patients overexpressed 2 or more of the candidate antigens. The authors also found that expression of MHC class I was present in over 78% of ovarian cancer tested. This combination of findings suggests that a vaccine directing a cellular immune response against multiple target antigens may find some success in ovarian cancer [30].

Table 1
Vaccine platforms used for ovarian cancer.

Platform	Advantages	Limitations
Peptide/protein [19,29,68–70]	Specific epitopes can be targeted Immune responses can be defined	Cost HLA restriction Weak immunogenicity, requires adjuvant
DNA	Ease of production Able to accommodate multiple antigens	Weak immunogenicity, requires adjuvant Less experience in ovarian cancer
Virus/bacteria [22,31,71]	Ease of production Immunogenicity of vector	Antigen competition with vector Need to attenuate pathogen
Anti-idiotype [34–36]	Can target carbohydrate antigens	Labor intensive production Phase III trials targeting CA125 do not show clinical response
Dendritic cell [67]	Antigen presentation controlled and efficient	Cost Restricted to individual patient Requires leukapheresis Labor intensive production
Whole tumor [41]	Defined and undefined antigens targeted	Cost Restricted to individual patient Require availability of tumor Potential for autoimmunity

Please cite this article as: Liao JB, Disis ML, Therapeutic vaccines for ovarian cancer, Gynecol Oncol (2013), http://dx.doi.org/10.1016/j.ygyno.2013.06.023