Review Article

Immunotherapy: An Evolving Paradigm in the Treatment of Advanced Cervical Cancer

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ABSTRACT

Purpose: In 2014, the US Food and Drug Administration approved the first targeted agent, bevacizumab, in the treatment of advanced stage, persistent, or recurrent cervical cancer. This oncologic milestone has catalyzed interest in the investigation of alternate therapies, including immunotherapy, in an effort to extend life and possibly cure patients with advanced stage disease.

Methods: This review article focuses on the evolving paradigm of immunotherapy in the treatment of cervical cancer, describing the biologic basis of this treatment modality and discussing applicable Phase I to II clinical trials.

Findings: To date several trials have been conducted exploring vaccine-based therapies, adoptive T-cell therapy, and immune-modulating agents in patients with cervical cancer with promising results.

Implications: Immunotherapy represents a promising therapeutic paradigm in the treatment of advanced cervical cancer. Additional investigation is warranted to try and identify alternate immune targets and predictors of response, allowing for the selection of patients most likely to benefit from immune-based treatments. (*Clin Ther*. 2015;37:20–38)

Key words: Cervical cancer, Immunotherapy, Human papillomavirus, Therapeutic vaccine, Checkpoint inhibitor, Chimeric T cell receptor antigen.

INTRODUCTION

In 2011 an estimated 529,800 cases of cervical cancer were diagnosed worldwide, with 275,100 deaths.[1] This global burden is attributable to the disproportionately high incidence of cervical cancer in developing, resource-poor countries that lack adequate health care infrastructure and screening programs. In the United States, an estimated 12,360 cases of cervical cancer will be diagnosed in 2014, with 4020 deaths; it is anticipated that this number will continue to decrease as human papillomavirus (HPV) vaccination rates increase and the focus shifts to primary prevention.[2] Despite advances in screening, vaccination, and treatment of early-stage disease, a proportion of patients will be diagnosed as having advanced stage (stage IVB), recurrent, or persistent cervical cancer. For this subset of patients, systemic chemotherapy remains the cornerstone of treatment.[3,4]

Since the publication of the initial studies examining cisplatin in the treatment of cervical cancer, a number of effective single-agent and combination drug regimens have been identified that exhibited improved response rates, without a significant effect on overall survival.[5–21] The poor oncologic outcome in this patient population represents an unmet clinical need and has driven the exploration of new treatment paradigms.[3]

Most recently, the results of Gynecologic Oncology Group (GOG) protocol 240 were presented and

Accepted for publication November 14, 2014.
http://dx.doi.org/10.1016/j.clinthera.2014.11.010
0149-2918/$ - see front matter

published, illustrating a significant improvement in overall survival (17 vs 13.3 m) with the incorporation of the antiangiogenic agent bevacizumab to a chemotherapy backbone, without a significant deterioration in quality of life.[22–25] This oncologic milestone represents the first time a targeted agent has resulted in an overall survival advantage in the gynecologic cancer arena. Ultimately, on August 14, 2014, the US Food and Drug Administration (FDA), following priority review, expanded the indication of bevacizumab to include advanced cervical cancer based on the findings of GOG 240. These results have opened the door to the development and study of additional therapies, including immunotherapy, to be used solely or in conjunction with targeted agents and cytotoxic chemotherapy.[26]

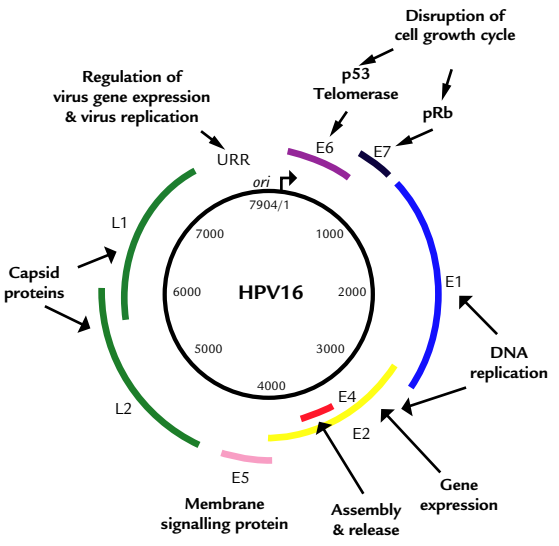

Figure 1. Schematic of human papillomavirus (HPV) genome. Adapted with permission from Elsevier.[76]

HPV PATHOGENICITY

Cervical cancer is unique among gynecologic malignant tumors because several risk factors have been well established and the causative agent, HPV, is known. HPV is a double-stranded, circular DNA virus (approximately 8 kilobase pairs) that exhibits unidirectional transcription. Approximately 170 HPV genotypes have been identified, with HPV-16 and HPV-18 accounting for >70% of invasive cervical cancer. The HPV genome is composed of 7 early proteins (E1, E2, E4, E5, E6, E7, and E8) and 2 late, structural proteins (L1 and L2) (Table I and Figure 1). Importantly, the complementary DNA for L1 represents the structural and immunogenic basis for the licensed prophylactic HPV vaccines currently available. To establish an infection, the HPV virus must infect the basal epithelial cells located in the cervical transformation zone, which are actively replicating and differentiating. In select cases, the viral DNA is incorporated into the host cell genome, resulting in interruption of several early genes, including E2, E4, and E5. Interruption of E2, which normally functions as a transcriptional regulator of E6 and E7, leads to up-regulation of E6 and E7, degradation of p53 and pRB, respectively, and ultimately malignant transformation.[27–29]

A BRIEF HISTORY OF CANCER IMMUNOTHERAPY

During the 1850s, noting that their patients' cancers would sometimes shrink when the tumor became

Table I. HPV genome.

E1	E2	E4	E5	E6	E7	L1	L2
ATPase	Regulator of E6 and E7	Disrupts cytokeratin matrix for release of virions	Potentiation of membrane bound EGF receptors	Bind and inacti-vate p53	Bind pRB leading to E2F activity	Major capsid (conserved)	Minor capsid (variable)

ATP = adenosine triphosphate; EGF = epidermal growth factor.