Perspective

Programmed death ligand 1 expression and human papillomavirus status: penile cancer prognostic factors and new therapeutic opportunities

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Abstract: Penile cancer is a rare malignancy with limited treatment options beyond local resection and lymph node dissection. Risk factors for penile cancer development include phimosis, smoking, lack of circumcision, and human papillomavirus (HPV) infection. Based on cancer incidence and histologic subtyping, penile cancer is often stratified by HPV status. Cohort studies have found that HPV positive tumors have better prognosis. The success of HPV vaccination for the prevention of cervical cancer and genital warts has resulted in new recommendations for vaccination of men. However, these efforts would not be expected to improve outcomes in men with HPV negative tumors. New therapeutic strategies are needed to improve outcomes in men with advanced penile cancer. Programmed death ligand 1 (PD-L1) targeted treatments have been successful in other malignancies including melanoma and non-small cell lung cancer. Determining the frequency of PD-L1 positive tumor cells in penile cancer is needed to establish the potential benefit of using these targeted therapies in penile cancer patients. Evaluating the relationship between PD-L1 expression and HPV status may provide support for the proposed dual pathway to malignant transformation. Comparing PD-L1 status to HPV status should add another prognostic factor while expanding the therapeutic options for this malignancy.

Keywords: Penile cancer; programmed death ligand 1 (PD-L1); human papillomavirus (HPV); survival; squamous cell carcinoma (SCC)

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Penile cancer is a relatively rare malignancy with approximately 2,000 men diagnosed in the Unites States annually and approximately 300 deaths (1). Penile cancer stage and nodal status are strong prognostic factors with patients who have advanced disease having poor cancer specific survival (2). Risk factors for penile cancer development include poor hygiene, phimosis, smoking, lack of circumcision, increased number of sexual partners, and balanitis (3). In addition to these factors, nearly half of all penile cancers are found to be associated with human papillomavirus (HPV) infections (4). Taken together, two pathways for penile cancer development have been proposed, one resulting from HPV infection with high risk genotypes such as HPV 16 or HPV 18 and another resulting from chronic inflammation. Histologically, HPV infection has been shown to occur more frequently with warty and basaloid squamous cell carcinoma (SCC) as opposed to usual type and verrucous SCC (4). HPV-related penile cancer has also been evaluated as a prognostic marker for survival. In other HPV-associated tumors, such as oropharyngeal SCC and anal cancer, HPV positivity was associated with improved survival (5,6). Early studies found that HPV associated penile cancers were associated with an independent and significantly better disease-specific survival (7). These studies were confirmed in a similar study of a more contemporary cohort (8).

Unlike penile cancer, nearly all invasive cervical cancers

are associated with infection by oncogenic HPV (9). Without an available cure for HPV infection, preventing infection through vaccination has been a major focus of women's preventative health measures. The success of female vaccination and the resulting reduction in HPV-associated lesions led to studies of HPV vaccination in men. Early vaccination studies showed a significant reduction in HPV-associated genital lesions (10). Over time, the Centers for Disease Control and Prevention altered its stance on vaccination from an option to vaccinate to a recommendation for vaccination in all men beginning at the age of 11 with either the quadrivalent or 9-valent vaccine (11).

While the success of HPV vaccination should reduce HPV-associated penile cancer occurrences, clinicians must still manage the cancers that are found to be HPV negative. Unfortunately, these are the same cancers that have been shown to have worse survival. Surgical advances in the treatment of penile cancer have resulted in potential decreases in morbidity, but remain centered on early intervention with local resection, preservation of function when possible, and lymphadenectomy based on pathologic features and risk of metastases. For patients with locally advanced disease or metastases, obtaining long-term survival remains a challenge. Traditional chemotherapy regimens can be effective, but often there is eventually cancer progression. For some cancers, it is felt that immune system evasion may be one factor resulting in cancer progression. Recently, immune checkpoint inhibition has been proposed as a new treatment paradigm. In particular, new agents targeting programmed death ligand 1 (PD-L1) have been proposed. In cancers such as melanoma and non-small cell lung cancer, PD-L1 inhibition has been shown to be an effective treatment (12,13). Recently, the PD-L1 targeted agent atezolizumab, was found to be active in patients with metastatic urothelial carcinoma who had progressed following treatment with chemotherapy (14). This resulted in a new second line agent for bladder cancer.

Prior to evaluating the efficacy of PD-L1 targeted treatments in patients with advanced penile cancer, it is important to understand if PD-L1 expression occurs in penile SCC and if this expression may reflect the underlying aggressiveness of the tumor. An initial study was recently conducted to evaluate PD-L1 expression in a series of 37 patients with penile cancer. It was found that PD-L1 expression occurred in 62.2% of primary tumors and that expression was associated with worse survival (15). However, this study was limited to a small number of patients with relatively low incidence of HPV-associated penile cancer (15.2%). In the current study, Ottenhof *et al*. evaluate a larger cohort of patients with a higher proportion of patients having HPV-associated cancers (16). From 200 tumors, they found that 75% of tumors were negative for high risk HPV genotypes. Previous studies in this cohort of patients had shown that presence of high risk HPV genotypes provided a survival benefit (8). PD-L1 expression was detected in 48% of tumors. Tumors negative for high risk HPV had a significantly increased frequency of PD-L1 expression. Diffuse PD-L1 expression was associated with a significant increase in lymph node positive disease and PD-L1 was prognostic of lymph node involvement on multivariable analysis. For PD-L1 positive tumors, diffuse PD-L1 expression was associated with worse disease-specific survival. This was even more pronounced in cases without high risk HPV. In a multivariable analysis of survival, PD-L1 expression pattern was a significant predictor of survival. Once again, this was even more pronounced in tumors negative for high risk HPV.

For the past decade, the most important advances in penile cancer therapy had been the development of a vaccine that could prevent HPV-associated genital lesions and tumors. Increasingly both men and women are receiving this vaccine and this will remain a cornerstone of cancer prevention. However, there was growing evidence that tumors arising from an alternative pathway may be even more lethal than cancers that are HPV positive. A gap developed between our understanding of this more challenging prognosis and treatments that may prevent poor outcomes. The significance of this new study is that it identifies a group of patients (PD-L1 positive), occurring more frequently in HPV negative tumors that may be susceptible to novel checkpoint inhibiting therapies. New strategies for penile cancer therapy may include testing for PD-L1 expression in addition to HPV status. Before we get to this point, it will require that clinical trials evaluating the efficacy of PD-L1 treatments in penile cancer be conducted. Although tumor cell expression brings hope for activity, differing expression between tumor and immune cells may be more predictive of treatment response. Further, studies have found that some targetable genetic alterations may occur at a high enough frequency that additional drug options may be available. It is our hope that over time, with growing utilization of HPV vaccines, that HPV associated cancers will decline and that simultaneously, we can exploit vulnerabilities inherent to the remaining tumors using a combination of judicious surgical resection and targeted chemotherapy treatments. We await the results of clinical trials that are currently under consideration or about to open for enrollment.

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Footnote

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