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Review Article

Immunotherapy in the Scenario of Cancer of the Penis an Update

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Abstract

Penile cancer or carcinoma of the penis is an uncommon malignant tumour of the penis which usually relates to penile squamous cell carcinoma (PSCC), that amounts to for more than 95% of all penile malignancies. Despite the fact that organ-sparing surgery is an effective treatment option for early-stage PSCC, surgical intervention alone is known often not to be curative for advanced PSCC with metastases to the inguinal and/or pelvic lymph nodes; in view of this systemic therapy is usually necessitated and this usually entails administration of platinum-based chemotherapy and surgery combined. Nevertheless, it has been realised that chemotherapy for PSCC had proven to be of limited efficacy and is often ensued by high toxicity, and patients with advanced PSCC usually portend poor prognosis. The limited treatment options and poor prognosis indicate the unmet need for advanced PSCC. Immune-based treatments had been approved for administration in various genitourinary and squamous cell carcinomas but they had been rarely reported in PSCC. Many studies had reported high expression of PDL1 in PSCC, which had been in the support of the potential application of immune checkpoint inhibitors in PSCC. In addition, human papillomavirus (HPV) infection is highly prevalent in PSCC and plays a pivotal role in the carcinogenesis of HPV-positive PSCC, indicating that therapeutic HPV vaccine might also be a potential treatment option. Furthermore, adoptive T cell therapy (ATC) had also demonstrated efficacy in treating advanced penile cancer in some early clinical trials. The development of new treatments relies upon the understanding of the underlying biological mechanisms and processes of tumour initiation, progression and metastasis. Immunotherapy has been reported in some scenarios to have improved the outcome of some reported cases of penile carcinoma. Immunotherapy is only available for the treatment of penile cancer in some developed countries and research centres but not in most developing country urology and oncology units. It would therefore be envisaged that majority of clinicians in the world would tend not to be familiar with utilisation of immunotherapy in the treatment of penile cancer. The ensuing article on immunotherapy in the scenario of penile cancer is divided into two parts: (A) Overview of immunotherapy, and (B) Miscellaneous narrations and discussions from some case reports, case series and studies related to penile cancer.

Key words: penile cancer; rare; immunotherapy; penectomy; biopsy; poor prognosis; radiotherapy; chemotherapy; research studies

Introduction

Penile cancer is a rare malignant neoplasm with about 26,000 new cases reported globally each year; despite the low overall incidence of about 1/100,000 within developed countries, the incidence is much higher within the developing countries [1] [2] [3] [4]. Penile cancer usually relates to penile squamous cell carcinoma (PSCC), which constitutes more than 95% of all penile malignancies; other penile malignancies, such as melanocytic lesions, mesenchymal tumours, lymphomas, and metastases, are less common malignant neoplasms of the penis. [1] [5] [6] It has been iterated that based upon the current knowledge, phimosis, chronic inflammation of the penis, smoking, lower socioeconomic status, ultraviolet exposure, and human papillomavirus (HPV) infection are regarded as risk factors for the development of penile cancer [1] [7] [8] [9] [10] [11] [12]. In addition, it has been iterated that about 30% of penile intraepithelial neoplasia (PeIN), which is an unfavourable histopathology examination feature associated with penile cancer, would progress to invasive penile cancer if the tumour is not treated. [1] [13]

With non-inferior 5-year survival in comparison with radical surgery, organ-sparing surgery alone has been recommended as the primary treatment curative intent for PeIN and localized invasive penile cancer by the guidelines of the European Association of Urology (EAU) and National Comprehensive Cancer Network (NCCN) [1] [6] [14]. Nevertheless, despite not affecting overall survival (OS), it has been pointed out that the probability of recurrence pursuant to organ-sparing surgery is high, and penectomy would then be inevitable for some patients. A retrospective study of 203 PSCC had revealed that 18% of patients had developed local recurrence pursuant to organ-sparing surgery, of whom about 17% required penectomy [15]. It has been pointed out that ensuing penectomy, patients' sexual life and overall well-being would be significantly affected. [1] [16].

The survival outcomes of patients who are diagnosed with advanced PSCC are stated to be affected by many factors including sub-types of pathology, perineural and lympho-vascular involvement, and extracapsular spread of lymph node metastasis), as well as surgery alone is usually not curative in this setting [1] [17] [18]. With curative intent, the NCCN guideline had recommended 4 cycles of neoadjuvant chemotherapy (NAC) with a combination of paclitaxel, ifosfamide, and cisplatin (TIP) for patients with inguinal lymph node(s) larger than 4 cm or patients who are at the N2/N3 stage, while adjuvant chemotherapy (AC) has recommended for patients whose tumours are associated with high-risk features including pelvic lymph node metastases, extra-nodal extension, bilateral inguinal lymph nodes involved, 4 cm tumour in lymph nodes) [1] [14]. It is worth noting that chemotherapy had been demonstrated to have limited benefits for PSCC patients, and the prognosis for advanced PSCC is stated to be not satisfactory with current treatment options. It had been pointed out that in a phase 2 trial which included 30 patients who were diagnosed with advanced N2/N3 stage PSCC without distant metastases, 4 cycles of NAC of TIP had been associated with a 50% objective response rate, 22 (73.3%) patients had undergone surgery pursuant to NAC, and the median progression months and median survival months were noted to be only 8.1 months (95% confidence interval [CI], 5.4 to 50 months) and 17.1 months (95% CI, 10.3 to 60 months), respectively. [19]. It had also been iterated that: other studies had reported many additional moderately efficacious and often highly toxic chemotherapy regimens for locally advanced or metastatic PSCC. [20] [21] [22] [23]. In addition, it has been pointed out that: the treatment options that available pursuant to chemotherapy failure are few and often have poor efficacy. Based on a retrospective study, patients with advanced PSCC had tended to be associated with a poor response to salvage therapy after first-line chemotherapy failure, with a median OS of less than six months. [15]. It has been clearly pointed out that the limited treatment options and poor prognosis do indicate an unmet need for systemic therapy for penile cancer. [1]

It has been pointed out that immune-based treatment had been approved for the treatment of many genitourinary carcinomas. [24] [25] [26] [27] [28] [29] [30] [31]. Pembrolizumab, which is a type of immune checkpoint inhibitor (ICI), has been recommended by the NCCN guidelines as the second-line treatment for unresectable or metastatic PSCC with high tumour mutational burden (TMB-H) or deficient mismatch repair (dMMR). Nevertheless, the few and mainly case reports and basket trial data related to the effect of pembrolizumab on clinical outcomes had limited its widespread utilization in lethal advanced PSCC. [1] [32] [33] [34] [35] It had also been pointed out that just as higher expression of PDL1 correlates with improved response to ICI in other tumours, [36] the high PDL1 expression rate in PSCC tissue indicates that ICI might be a potentially effective therapy for PSCC. [37] Furthermore, it has been iterated that the distinct molecular mechanisms and prognosis between HPV-positive and HPV-negative PSCC make HPV-related therapies, such as therapeutic HPV vaccines, a potential focus for penile cancer treatment. [38] [39]. It had also been iterated that: adoptive T cells therapy (ATC) had also demonstrated efficacy in treating advanced penile cancer in some early clinical trials, also it has emerged as a potential treatment for penile cancer. [37]

The development of new therapy options relies upon the understanding of the underlying biological mechanisms and processes of tumour progression and metastasis. Considering the fact that some cases of penile cancer have been reported sporadically in different areas of the well with immunotherapy, it is important for all clinicians all over the world to be up to date with immunotherapy in the scenario of penile cancer. The ensuing article on immunotherapy in penile cancer is divided into two parts: (A) Overview of immunotherapy, and (B) Miscellaneous narrations and discussions from some case reports, case series and studies related to penile cancer.

Aim

To provide an update on immunotherapy in the scenario of penile cancer.

Methods

Internet databases were searched including: Google; Google Scholar; Yahoo; and PUBMED. The search words that were used included: Immunotherapy in penile cancer; immunotherapy in cancer of the penis and immunotherapy in malignant neoplasm of penis. Eighty-three (83) references were identified which were used to write the article which has been divided into two parts: (A) Overview of immunotherapy, and (B) Miscellaneous narrations and discussions from some case reports, case series and studies related to penile cancer.

Results

[A] OVERVIEW

Definition / general statements

- Immunotherapy is a terminology that is used for treatment that harnesses the body's immune system to fight disease, particularly cancer.
- There are several types of immunotherapy treatments, such as immune checkpoint inhibitor (ICI).
    - An example of ICI is pembrolizumab, which has been FDA approved for triple negative breast cancer (TNBC).
- Immunotherapy is a treatment of malignant neoplasm which leverages the body's own immune system to combat cancer.
- Immunotherapy entails stimulation of the immune system to identify and attack cancer cells.
- Immunotherapy can be administered alone or contemporaneously with other treatment options including chemotherapy, and radiotherapy.
- Immunotherapy could help the immune system recognize and attack cancer cells by increasing its activity or modifying how it functions.
- Some types of immunotherapy-treatments, like checkpoint inhibitors, specifically target the immune system's "checkpoints" to release the brakes and enable T cells to more effectively kill cancer cells.
- Other approaches include utilising cytokines, which are proteins that regulate immune responses, or even transplanting patient's own T cells which have been modified to target cancer cells (CAR T-cell therapy).
- Some of the immunotherapy types include the ensuing:
  Immune Checkpoint Inhibitors: These block proteins that prevent T cells from attacking cancer cells.
  Cytokines: These are proteins that stimulate immune cells to attack cancer cells.
  Vaccines: These train the immune system to recognize and attack cancer cells.
  CAR T-Cell Therapy: This entails modifying a patient's T cells to target and destroy cancer cells.
- Immunotherapy has demonstrated promising results in treating some cancers, including melanoma, kidney cancer, and leukaemia.
- Whilst generally immunotherapy is well-tolerated, some side effects of immunotherapy could include fatigue: rash, diarrhoea, nausea, and in rare cases, more serious issues like inflammation of the heart, lungs, or liver.
- Immunotherapy might not be effective for all types of cancer, and the effectiveness of immunotherapy could vary from individual to individual.
- Generally, therapeutic plans in immunotherapy are tailored to each individual's needs and the specific type of cancer that afflicts the individual.

Essential features of Immunotherapy.

- Immune checkpoint inhibitors (ICI) include the ensuing:
- PD-1 (programmed cell death-1) inhibitor (e.g., pembrolizumab)
- Application: adjuvant therapy for PDL1 positive locally advanced or metastatic TNBC
- Companion diagnostic: PDL1 IHC 22C3 pharmDx (combined positive score [CPS] ≥ 10)
- Neoadjuvant therapy for high risk, early-stage TNBC
- PDL1 (programmed death ligand 1) inhibitor (e.g., atezolizumab)
- Application (FDA approval withdrawn): adjuvant therapy for PDL1 positive locally advanced or metastatic TNBC.
- Companion diagnostic: VENTANA PDL1 (SP142) Assay (≥ 1% IC)

Terminologies

The ensuing terminologies tend to be used for immunotherapy:

- Immune checkpoint inhibitors (ICI)
- Programmed death ligand 1 (PDL1)
- PD-1 inhibitor (e.g., pembrolizumab)
- PDL1 inhibitor (e.g., atezolizumab, durvalumab)

Pathophysiology of immunotherapy

The pathophysiology of immunotherapy had been summated as follows:

- Mechanism of action for immune checkpoint inhibitors (ICI), such as PD-1 inhibitor (e.g., pembrolizumab) and PDL1 inhibitor (e.g., atezolizumab) include the ensuing:
- Binding of PDL1 to PD-1 does inhibit T cell activity, known as immune checkpoint regulation, which prevents excessive immune activities and protects normal cells.
- PDL1 is expressed in various cancer cells, allowing cancer cells to evade immune surveillance.
- ICI blocks the interaction between PDL1 and PD-1, and hence enhances antitumor immune response.
- PDL2 is an alternative ligand and might have a complementary role to PDL1.

Clinical features of immunotherapy

- It has been iterated that the FDA had approved application of ICIs for breast cancer, mainly for TNBC.
- Pembrolizumab
- Mechanism: PD-1 inhibitor.
- Application: pembrolizumab in adjuvant systemic therapy for PDL1 positive locally advanced or metastatic TNBC.
- Landmark clinical trial: KEYNOTE-355.
- Companion diagnostic assay: PDL1 IHC 22C3 pharmDx
- PDL1 positive definition: CPS ≥ 10
- CPS: number of PDL1 staining cells (tumour cells, lymphocytes, macrophages) divided by the total number of viable tumour cells, multiplied by 100
- Pembrolizumab in neoadjuvant setting for high risk, early-stage TNBC regardless of PDL1 expression.
- Landmark clinical trial: KEYNOTE-522.
- Other biomarkers include:
- Tumour mutational burden (TMB) high (≥ 10 mutations/megabase).
- The FDA had approved pembrolizumab for the treatment of adult and paediatric patients with unresectable or metastatic tumour mutational burden high (TMB H) (≥ 10 mutations/megabase [mut/Mb]) solid tumours, as determined by an FDA approved test.
- Clinical trial: KEYNOTE-158. MSI H
- The FDA had approved pembrolizumab for select patients with MSI H or dMMR solid tumours
- Clinical trials: KN-012, 016, 028, 158 and 164
- Atezolizumab
- Mechanism: PDL1 inhibitor. Application: the FDA approved atezolizumab as adjuvant systemic therapy for PDL1 positive locally advanced or metastatic TNBC.
- Landmark clinical trial: IMpassion130.
- Companion diagnostic assay: VENTANA PDL1 (SP142) Assay.
- PDL1 positivity definition: ≥ 1% IC
- % IC: proportion of tumour area occupied by PDL1 expressing tumour infiltrating immune cells of any intensity
- The application was withdrawn based on IMpassion131.
- Ongoing trials exploring additional applications.
- Pembrolizumab combined with poly ADP ribose polymerase (PARP) inhibitor.
- Durvalumab (PDL1 inhibitor) combined with stereotactic body radiation therapy (SBRT) or oleclumab (anti-CD73 mAb).

Prognostic factors

- Presence of tumour infiltrating lymphocytes (TILs) in the tumour microenvironment indicates an existing antitumor immune response and is both prognostic and predictive.

Microscopic (histologic) description

- PDL1 expression is assessed using the combined positive score (CPS), a companion diagnostic assay with PDL1 IHC 22C3 pharmDx, for identifying patients with TNBC for treatment with pembrolizumab.
    - CPS = # PDL1 staining cells (tumour cells, lymphocytes, macrophages) / total # of viable tumour cells x 100. [
    - PDL1 staining should be included in the scoring (numerator) and is defined as follows:
        - Any noticeable and distinct linear membrane staining (≥ 1+) of viable tumour

cells, clearly distinguishable from cytoplasmic staining.

- Any membrane or cytoplasmic staining (≥ 1+) of lymphocytes and macrophages (mononuclear inflammatory cells, MICs) within tumour nests or the surrounding stroma.

- The scored area should be defined to include only the tumour and associated stroma.
- In situ components should be excluded from the CPS scoring.
  - Inflammatory cells associated with the in-situ components should also be excluded from the numerator
- CPS score result.
  - CPS < 10: negative
  - CPS ≥ 10: positive
- Minimum of 100 viable tumour cells must be present in the PDL1 stained slide (biopsy and resection) for the specimen to be considered adequate for evaluation.
  - Cytology and decalcified bone specimens are not suitable for PDL1 testing

[B] Miscellaneous Narrations And Discussions From Some Case Reports, Case Series, And Studies Related To Immunotherapy In The Scenario Of Penile Cancer

Taghizadeh **et al.** made the ensuing preamble simple summary

- Penile cancer is an uncommon and challenging disease, particularly in its advanced stages where its treatment options are limited.
- Recent advances in immunotherapy, especially immune checkpoint inhibitors (ICIs), have offer new hope by enhancing the body's immune response against cancer cells.
- These therapies have demonstrated promise in improving survival rates, particularly in patients with specific biomarkers such as PD-L1 expression and HPV positivity.
- Combining ICIs with chemotherapy or radiation therapy might further increase their effectiveness.
- Nevertheless, in view of the rarity of penile cancer, international collaboration is essential to undertake large-scale trials and optimize treatments.
- Penile squamous cell carcinoma (PSCC) is an uncommon and challenging malignancy with limited options of treatment for advanced disease stages.
- Immune checkpoint inhibitors (ICIs) have emerged as a promising treatment strategy, leveraging the immune system's ability to counteract tumour-induced immune evasion.
- They had synthesized the current evidence on the efficacy of ICIs in PSCC, with a focus on their application in advanced and refractory settings.

Taghizadeh et al. undertook a comprehensive literature search across PubMed, Web of Science, Embase, and ClinicalTrials.gov so as to identify studies investigating ICIs in the treatment of PSCC. Taghizadeh et al. [] selected and analysed studies based upon pre-defined inclusion and exclusion criteria, and data related to treatment efficacy, biomarker relevance, and safety were extracted. Taghizadeh et al. summated the results as follows:

- Clinical trials and real-world data had suggested that ICIs could provide durable responses in a subset of patients who are afflicted by advanced PSCC, particularly those with biomarkers such as PD-L1 expression and HPV positivity.
- Combination approaches, including ICIs with chemotherapy or radiotherapy, as well as neoadjuvant or adjuvant utilisation had demonstrated the potential for expanding treatment paradigms.
- Nevertheless, in view of the rarity of PSCC, robust evidence has remained limited, necessitating further research and international collaboration.

Taghizadeh et al**.** made the ensuing conclusions:

- ICIs represent a promising treatment avenue for PSCC, with the potential to improve patient outcomes and quality of life.
- Nevertheless, optimizing therapeutic strategies necessitates enhanced patient stratification, exploration of earlier incorporation of ICIs, and investigation of novel combination therapies.
- Centralized care and collaborative research efforts are pivotal to the advancement of the role of immunotherapy in PSCC management.

Joshi et al. [37] made the ensuing iterations:

- Penile cancer is an uncommon genitourinary malignancy that is associated with poor outcomes and severely limited therapeutic options which are generally non-curative when used to treat localized disease with high-risk features or advanced disease.
- In order to address the unmet need for treatment modalities with increased effectiveness, immune-based therapies such as immune-checkpoint blockade, human papilloma virus (HPV)-directed vaccines and adoptive T cell therapies had emerged as potential treatment options for advanced penile cancer.
- A diverse array of immune cells such as cytotoxic T lymphocytes (CTLs), tumour-associated macrophages and myeloid-derived suppressor cells have been demonstrated to infiltrate penile cancer tumours, with distinct immune landscapes being demonstrated in HPV-positive compared with HPV-negative tumours.
- Study results have also illustrated the prognostic value of immune cells such as tumour-associated macrophages, immune markers such as programmed death ligand-1, and HPV-status in penile cancer.
- Taken altogether, the aforementioned findings do underscore the clinical relevance of the tumour immune microenvironment as a source of both prognostic indicators and potential treatment targets for immune-based treatments.
- Current evidence related to the safety and efficacy of immune-based therapies is limited in penile cancer; nevertheless, a number of clinical and preclinical studies have been ongoing to assess these treatments in this disease based upon promising results from studies in other malignancies, including other squamous cell carcinomas.
- Furthermore, an opportunity does exist to combine immune-based therapies with existing lines of systemic therapy to offer the most benefit to patients who are afflicted by advanced penile cancer.

- Future work should focus upon expansion of pre-clinical models for immune-based drug discovery.

Joshi et al. [37] made the ensuing salient and key points:

- The immune landscape of penile cancer is defined by unique patterns of immune cell infiltration that also serve as prognostic indicators of metastasis and survival.
- Human papilloma virus (HPV) infection status could be utilised to stratify patients into two groups with differing tumour immune microenvironments (TIMEs) based upon key markers such as programmed death-ligand 1.
- Immune-based therapies including immune-checkpoint blockade, adoptive T cell therapies, and HPV-targeting therapeutic vaccines are each promising candidate therapies, even though these treatments have been largely unexplored in penile cancer; nevertheless, they are currently being assessed prospectively.
- The optimal management of locally advanced penile cancer might entail a multi-modal approach which combines immune-based treatments with chemotherapeutic and/or targeted agents early in the disease course followed by surgery.
- Pre-clinical models which will improve upon the understanding of the TIME and the mechanisms that underly responses to immune-based therapies are required.
- In this rare disease context, future pre-clinical and clinical work on immune-based therapies would benefit from the centralization of care and the pooling of collaborative scientific knowledge and resources.

Tang et al. made the ensuing iterations:

- Penile cancer is an uncommon malignant neoplasm which usually refers to penile squamous cell carcinoma (PSCC), that accounts for more than 95% of all penile malignancies.
- Even though organ-sparing surgery is an effective treatment for early-stage PSCC, surgical intervention alone is often not curative for advanced PSCC with metastases to the inguinal and/or pelvic lymph nodes; hence, systemic therapy is required (usually platinum-based chemotherapy and surgery combined).
- Nevertheless, chemotherapy for PSCC had proven to be of limited efficacy and it is often ensued by high toxicity, and patients with advanced PSCC usually do portend a poor prognosis.
- The limited therapeutic options and poor prognosis do indicate the unmet need for advanced PSCC.
- Immune-based treatments have been approved for various genitourinary and squamous cell carcinomas but are rarely reported in PSCC.
- Up to 2022, many studies had reported high expression of PDL1 in PSCC, supporting the potential application of immune checkpoint inhibitors in PSCC.
- Additionally, human papillomavirus (HPV) infection is highly prevalent in PSCC and plays a key role in the carcinogenesis of HPV-positive PSCC, indicating that therapeutic HPV vaccine might also be a potential treatment modality.
- Moreover, adoptive T cell therapy (ATC) had also demonstrated efficacy in treating advanced penile cancer in some early clinical trials.
- The development of new treatments relies upon the understanding of the underlying biological mechanisms and processes of tumour initiation, progression and metastasis.
- Hence, based upon the interest, they had reviewed the tumour immune microenvironment and the emerging immunotherapy for penile cancer.

Buonerba et al. made the ensuing educative iterations:

- Penile carcinoma is a rare disease, with incidence rates varying in the range of 1 to 10 cases per 100,000 men depending upon ethnicity, geographic area, cultural background and social habits.
- Tumorigenesis of penile carcinoma is governed by a complex interplay of many causative factors. These include initiating agents, such as tobacco toxins, UV radiation and, possibly, household contaminants from solid fuel combustion, which have been implicated in carcinoma of the cervix, as well as promoting agents, such as cytokines related to chronic inflammation and high-risk HPV, mainly HPV-16 and HPV-18, which are well known for their major etiopathogenetic role in cervix carcinomas.
- With regard to patients who are afflicted by carcinoma of the penis, keratinizing squamous cell and verrucous lesions harbour high-risk HPV only in 30% of cases and co-exist with squamous cell hyperplasia and/or lichen sclerosus, while basaloid and warty carcinomas, which are composed of small, undifferentiated basaloid cells with koilocytic changes, harbour HPV in 80–100% of cases.
- Positivity to high-risk HPV has tended to be associated with both prognostic and biological implications in penile cancer.
- In fact, HPV infection might be associated with better outcomes in penile cancer men, as had been reported in a retrospective study of 171 patients demonstrating a 5-year cancer-specific survival rate of 78 and 93%, respectively, in the high-risk HPV-negative subgroup versus the high-risk HPV-positive sub-group (log rank test $p = 0.03$).
- In addition, while HPV-positive tumours do express more frequently HER3 and cytoplasmic Akt1, HPV-negative tumours do express more frequently phosphorylated EGFR, which is consistent with the negative prognostic effect associated with presence of phosphorylated EGFR.

Buonerba et al. also summated the role of HPV as a potential target for immunotherapy in an educative manner as follows:

- The HPV proteins E6 and E7 play a pivotal role in HPV-mediated carcinogenesis.
- Further to inactivating p53, E6 could bind to transcription factors (myc), autocrine motility factors which regulate cell adhesion and polarity (paxillin), apoptosis-inducing factors (Bcl2) and replication and DNA repair factors (mcm7), while the E7 protein inactivates the retinoblastoma tumour-suppressor protein via proteasome-dependent degradation and causes p16INK4a overexpression, that could be identified upon immunohistochemistry and could be employed as a reliable diagnostic marker of high-risk HPV infection.
- The p16INK4a protein is overexpressed both in intraepithelial and invasive lesions, and could serve as a reliable diagnostic histologic biomarker of HPV infection in penile cancers.
- Upon the basis of the established etiopathogenetic role of HPV in a sub-group of penile cancer patients, they had wished to

postulate that HPV-associated antigens have the potential to provide specific targets for an immunotherapy approach in men with penile cancer.

- At the time of publication of their article in 2017, two vaccines based upon HPV L1 virus-like particles were commercially available and had been approved in young women in order to prevent HPV infection, that is Gardasil ®(Merck & Co., NJ, USA) and Cervarix® (GlaxoSmithKline, England, UK).
- While Gardasil contains virus-like particles from HPV-16 and HPV-18, but also from low-risk carcinogenic genotypes 6 and 11, that cause benign genital warts, Cervarix contains virus-like particles from HPV-16 and HPV-18 only.
- Spontaneous clearance of high-risk HPV does occur in about one third of women after 6 months and in about half of the women after 12 months.
- Even though available preventive anti-HPV vaccines are able to induce both antibody and cellular responses, they are not able to improve spontaneous HPV clearance rate, so they could not be considered as candidates for an immunotherapy approach in HPV-mediated tumours.
- While HPV L1 protein is predominantly expressed in terminally differentiated keratinocytes, expression of the E6 and E7 proteins is retained through all of the epithelial layers and through multiple stages of infection. As a result, an immune response against E6 and E7 antigens might be effective to clear E6- and E7-expressing neoplastic cells.

Buonerba et al. also made the ensuing educative summations related to future perspective: VGX-3100 & anti-PD1/PD-L1 agents:

- The novel immunotherapy agent VGX-3100 (Inovio Pharmaceuticals, PA, USA), that is delivered through electroporation, is based upon two property DNA synthetic plasmids that encode the E6 and E7 genes of HPV-16 and HPV-18.
- Electroporation utilises brief electric pulses to cause transient and reversible permeabilization of the cell membrane, that optimizes transfection of nucleic acids, with a 100–1000-fold enhancement of plasmid delivery and gene expression.
- VGX-3100 was tested in a pivotal Phase I study in 18 women who had recurrent cervical intraepithelial neoplasia (CIN) grade 2 or 3, demonstrating encouraging results in terms of HPV-specific $CD8^{(+)}$ and $CD4^{+}$ T-cell response.
- In a subsequent double-blind, placebo-controlled Phase IIb study, 167 patients who had CIN2/3 associated with HPV-16 and HPV-18 were randomly assigned in a 3:1 ratio to receive 6 mg VGX-3100 (n = 125) or 1 ml placebo solution (n = 42), both given intramuscularly at 0, 4 and 12 weeks. The primary objective of the study, which was improvement of histopathology regression rate of CIN 2/3 lesions, was met in the modified intention-to-treat analysis, with 55 (48·2%) of the 114 patients receiving VGX-3100 and 12 (30·0%) of the 40 placebo recipients showing regression to CIN 1 or no disease. The safety profile of VGX-3100 was found to be excellent, with the majority of patients demonstrating injection-site reactions, and erythema being significantly more frequent in the VGX-3100 group (98/125, 78·4%) with respect to the placebo group (24/42, 57·1%; p = 0·007).
- Whilst VGX-3100 might be useful for the avoidance of morbidity of surgical treatment in women with CIN2/3 cancers, this agent might provide survival benefits in patients who have limited treatment options such as those with penile carcinoma.
- As they had reported previously, prognosis of penile cancer is excellent in patients who have non-invasive disease, whilst in patients who are afflicted by invasive tumours, 5-year cancer-specific survival rates vary in the ranges of 75% to 93%, 40% to 70%, 33% to 50% and 20% to 34% in men with cN0, cN1, cN2 and cN3 disease.
- Prognosis of patients requiring systemic chemotherapy for advanced disease is poor which has tended to be associated with about 6 months to 12 months survival. [21]
- They had speculated that a potential setting of experimental use of VGX 3100 in a clinical trial might include men with p16INK4a-positive penile cancer who have undergone complete surgical resection, but are at significant risk of disease recurrence.
- Conversely, they had also speculated that in men with metastatic penile cancer that tested positive for HPV 16/18, given the high burden of the disease, combination of an active, antigen-specific immunotherapy treatment such as VGX 3100 with an anti-PD (Programmed Death)-1/PD-L1 (Programmed Death-Ligand 1) agent might be beneficial.
- In a recently published retrospective study, 23 (62.2%) of 37 primary tumours were positive for PD-L1 expression, with a strong positive correlation of PD-L1 expression in primary and metastatic samples.
- Anti PD-1 agent nivolumab has demonstrated efficacy in head and neck cancers, which share histologic (squamous histology) and pathogenic (HPV infection) characteristics with penile cancer.

Buonerba et al. concluded that:

Even though the industry may show little interest in rare diseases such as penile cancer, a continued effort should be made by independent investigators to contribute to advances in the treatment of such a devastating disease, given its high morbidity and mortality.

Hui et al. reported two cases of penile cancer as follows:

Case One

A 64-year-old male, manifested with a two-month history of difficulty urinating and he was found to have a fungating penile mass which had involved 50% of his penis. The mass was noted to be hard and fixed and had extended from the glans proximally up the shaft of his penis. He also had bilateral palpable inguinal lymphadenopathy. He did not have any associated constitutional symptoms. Given there was a high suspicion for malignancy, the patient underwent partial penectomy within a month of his presentation. Pathology examination of biopsy specimens of the lesion confirmed a pT2 tumour with invasive keratinizing squamous cell carcinoma, poorly differentiated, and tumour size of 5 cm × 4 cm × 2.5 cm, with corpus spongiosum and lympho-vascular involvements. Pursuant to the procedure, the patient had PET-CT scan for staging, and the imaging demonstrated enlarged hypermetabolic bilateral axillary lymph nodes concerning for metastatic disease. Furthermore, there was a large centrally necrotic lymph node conglomerate within his left groin which had increased FDG avidity. He had left inguinal and bilateral pelvic lymph node dissections pathology examination of which demonstrated features of metastatic squamous cell carcinoma in multiple lymph nodes. The left inguinal mass was also found to be metastatic well-differentiated SCC. His diagnosis was staged at T2N3M0. Pursuant to his surgical procedures, he was commenced on adjuvant chemotherapy. He began first line chemotherapy with paclitaxel, ifosfamide, and cisplatin (TIP). He underwent 4 cycles of TIP but he eventually developed disease progression upon evidence of his repeat radiology-imaging. At that point, he was commenced on cetuximab given EGFR amplification on tumour analysis with the Foundation One testing platform. Nevertheless, he had an allergic reaction to cetuximab, so his treatment was changed to panitumumab. He had stable disease and a progression-free survival of 6 months with anti-EGFR treatment, which is clinically significant given that this treatment was given in the second-line setting for an aggressive tumour type that other than chemotherapy there was no other approved drug at the time of his treatment. He was ultimately started

on the PD-1 inhibitor nivolumab. He had initial response to immunotherapy followed by stable disease, so he had a disease control rate of an additional 6 months with this investigational agent at that time. Ultimately, he was placed on hospice and he died two years from the time of diagnosis.

Case Two

A 79-year-old man, who had a longstanding history of advanced prostate cancer on androgen deprivation therapy presented to his urologist after he had noticed a mass upon the tip of his urethral meatus. A subsequent biopsy of the mass was positive for SCC, and he underwent partial penectomy and lymph node dissection which showed positive right inguinal lymph nodes (three out of seven) revealing pathologic T2N2M0 disease. He received adjuvant chemotherapy by extrapolating data of its benefit when given in the neoadjuvant setting. He standard TIP regimen was not pursued given patient's concern for side effects. The patient proceeded with alternative plan of chemoradiation with 5 weeks of weekly low dose carboplatin and paclitaxel. In addition, he received radiotherapy with a total dose of 5000 cGy over 25 fractions to the right inguinal region. Nevertheless, the patient developed disease recurrence with nodal involvement nine months later. On re-staging CT imaging, he was found to have new involvement of the left pelvis. A nodal conglomerate measuring 31 mm ×58 mm with central necrotic change was identified in the left inguinal region. Given the patient's age, performance status, and local recurrence of disease, he was commenced on therapy with chemoradiation with curative intent one month subsequently. Treatment with an additional round of chemoradiation with low dose carboplatin and paclitaxel was given for 5 weeks. He had radiotherapy with a total dose of 5000 cGy over 25 fractions to the left pelvic region. He had stable disease with chemoradiation, but he eventually developed disease progression within a year from the end of chemotherapy. At that point, he was considered for second-line therapy with the PD-L1 inhibitor atezolizumab. After being on atezolizumab for about 2 years, he developed biopsy-proven bullous pemphigoid, an immune-mediated toxicity of the skin that has been described with those agents. A re-staging scan at about 2 years demonstrated near complete response, so he had been placed on treatment holiday at the time of the report. He was commenced on prednisone 1 mg/kg per immune-mediated management guidelines and had quick resolution of his blistering symptoms.

Hui et al. made the ensuing educative discussions:

- The standard neoadjuvant regimen of TIP, consisting of paclitaxel, ifosfamide, and cisplatin, had been found to be one of the most efficacious regimens for patients with penile cancer.
- In a study of 61 patients, 54 (90%) of them had received chemotherapy with TIP. 39 (65%) of these patients had either partial or complete response to the treatment. The study demonstrated that about 50% of patients with response to treatment who also had consolidative lymphadenectomy remained alive at 5 years.
- Nevertheless, there are very few standardized treatments for patients with continued disease progression after the standard neoadjuvant treatment. Therefore, there is an unmet need to identify other therapeutic options which could include either targeted therapies or immune checkpoint inhibitors like those that were offered to our patients.

Cheng et al. made the ensuing iterations:

- Metastatic penile squamous cell carcinoma (mPSCC) is an uncommon and aggressive malignancy with limited treatment options.
- Standard systemic treatments include paclitaxel, ifosfamide, cisplatin (TIP), fluorouracil and cisplatin (5-FU + cis), paclitaxel monotherapy and cetuximab.
- These regimens were evaluated as small single-arm studies.
- The HERCULES trial, a single-arm phase 2 clinical study, showed the safety and efficacy of combining immunotherapy with chemotherapy, signalling a potential benefit of immunotherapy.
- Their retrospective analysis evaluated the safety and efficacy of single-agent immunotherapy at the University of Kansas and Aurora St. Luke's Medical Center.

Cheng et al. undertook a multi-centre retrospective, IRB-approved study of mPSCC patients treated with single-agent immunotherapy from 2015 to 2023. Cheng et al. assessed the objective response rates per RECIST version 1.1, and progression-free survival (PFS) and overall survival (OS) were estimated utilising the Kaplan-Meier method. Adverse events were graded per CTCAE version 5.0, with only grade 3+ immune-related adverse events being recorded. Cheng et al. [80] summated the results as follows:

- Nine patients with mPSCC were included, with a median age of 75 years (range, 50-92).
- More than half (n=5) had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 2 or more, and most (n=8) had visceral metastasis.
- Single-agent immunotherapy was administered as first-line (n=3), second-line (n=4), and third-line or beyond (n=2). Pembrolizumab was used in six patients, with two receiving nivolumab and one cemiplimab.
- The objective response rate was 33.3% (n=3), including one complete response. Median PFS was 2.82 months (range, 1.0-14.3), and median OS was 4.3 months (range, 1.0-24.9).
- Patients who responded had PFS exceeding 12 months, with two still ongoing at data cutoff. No grade 3 or higher treatment-related adverse event has been observed during the treatment period.
- Additional analyses to correlate the response with HPV positivity were ongoing.

Cheng et al. made the ensuing conclusions**:**

- Their findings had indicated that single-agent immunotherapy could yield favourable response rates and durations in older and/or frail mPSCC patients.
- While their sample size was small and retrospective, the response rates were comparable to those in the HERCULES trial (33.3% vs. 39.4% with chemoimmunotherapy). Notably, grade 3+ treatment-related adverse events were lower in our study compared to 51.4% of HERCULES patients.
- This underscored the potential of single-agent immunotherapy as a safe and effective option for this rare malignancy.
- Further prospective studies are required to optimize treatment strategies for mPSCC.

Huang et al. made the ensuing iterations:

- Penile squamous cell carcinoma (PSCC) accounts for over 95% of penile malignancies and causes significant mortality and morbidity in developing countries.
- Molecular mechanisms and treatments of PSCC had been understudied, owing to scarcity of laboratory models.

Huang et al. described a genetically engineered mouse model of PSCC, by co-deletion of Smad4 and Apc in the androgen-responsive epithelium of the penis. Huang et al. made the ensuing discussions:

- Mouse PSCC fosters an immunosuppressive microenvironment with myeloid-derived suppressor cells (MDSCs) as a dominant population.
- Pre-clinical trials in the model demonstrate synergistic efficacy of immune checkpoint blockade with the MDSC-diminishing drugs cabozantinib or celecoxib.
- A critical clinical problem of PSCC is chemoresistance to cisplatin, which is induced by Pten deficiency on the backdrop of Smad4/Apc co-deletion.
- Drug screen studies informed by targeted proteomics identify a few potential therapeutic strategies for PSCC.
- Their studies had established what they believed to be essential resources for studying PSCC biology and developing therapeutic strategies.

Li et al. made the ensuing iterations:

- Penile squamous cell carcinoma (SCC) is a rare malignant tumour in males with a poor prognosis.
- Currently, the primary treatment is surgery.
- Recurrent cases have limited treatment options after failed radiotherapy and chemotherapy.
- The treatment effect of immunotherapy in penile SCCs had not been reported.
- Tislelizumab, a new PD1 inhibitor, had demonstrated a satisfactory impact in treating head and neck SCC and lung SCC combined with chemotherapy.
- Nevertheless, there is currently no report on its efficacy in penile SCC.

Li et al. reported a 76-year-old man with multiple enlarged inguinal lymph nodes 11 months after radical surgery for penile SCC, who was administered immunotherapy (tislelizumab) combined with chemotherapy (albumin paclitaxel plus nedaplatin) for 2 cycles. He had pelvic magnetic resonance imaging (MRI) scan, which demonstrated that the multiple lymph nodes in his groin area had disappeared. Li et al. concluded that:

- To their knowledge, their reported case was the first case report of immunotherapy combined with chemotherapy demonstrating promising results in recurrent penile SCC.
- The reported case had provided a basis for developing a new treatment option combining immunotherapy and chemotherapy, whose efficacy needs to be further evaluated in penile SCC.

Fadigas et al. made the ensuing iterations:

- Penile cancer (PeCa) ranks as the 30th most prevalent cancer globally, predominantly affecting populations in developing countries.
- Phimosis and Human Papillomavirus (HPV) infection are recognized as the primary risk factors.
- Early-stage diagnosis typically warrants limited excision or non-invasive therapies.
- Nevertheless, recent research into the carcinogenesis, tumour microenvironment, and the role of the host immune system in its development suggests that immunotherapy could be a promising treatment for PeCa.
- The rarity of the disease, combined with the success of standard treatments and the fact that many patients in clinical trials lack alternative options, contributes to the challenges in patient recruitment for these studies.
- Furthermore, the psychological burden stemming from the stigma associated with such an aggressive genital disease and the preference for quicker treatment options, such as surgery with reconstructive procedures, exacerbates these recruitment difficulties.

Fadigas et al. undertook a systematic review to explore various immunotherapy approaches in treating PeCa to elucidate the potential role of immunotherapy in this context. They had sourced the literature from freely accessible, full-text randomized controlled trials, non-randomized controlled trials, and original articles published in English between 2017 and 2023. Eligible clinical trials were required to be in phase 2 and have published results. Even though only one study had met the inclusion criteria-a significant limitation-the objective response rate recorded was 6% across nineteen patients with different tumour histologies, of which only six had PeCa. Fadigas et al. concluded that:

- Currently, other studies are either recruiting or ongoing, necessitating further observation, as results from a single study cannot be generalized to the broader population.

Conclusions

- Penile cancer has remained a challenging malignant neoplasm to treat in men particularly in advanced disease.
- Chemotherapy has historically served as the primary treatment modality in recurrent, locally advanced or metastatic penile cancer.
- Even though many case reports had shown potential clinical efficacy in patients whose tumours harbour EGFR or BRCA2 mutations, prospective data lacks in oncogenic driver mutated penile cancer.
- Many recent phase II trials had shown clinical benefit in a subset of patients who receive treatment with immune checkpoint inhibitors; nevertheless, given the genomic profile of penile cancer, it has remained unclear if immunotherapy might benefit most patients with penile cancer.
- Nevertheless, given the paucity of data for currently employed chemotherapy regimens in these aforementioned settings, many ongoing studies have aimed to evaluate the safety and efficacy of immune checkpoint inhibitors as well as antibody drug conjugates as potential newer generation approaches in treating this uncommon cancer.

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