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Urologic Oncology: Seminars and Original Investigations 37 (2019) 403–408

UROLOGIC ONCOLOGY

Literature Review

Updates in the molecular epidemiology and systemic approaches to penile cancer

Jacob J. Adashek, D.O.[a], Andrea Necchi, M.D.[b], Philippe E. Spiess, M.D., M.S., F.R.C.S.(C), F.A.C.S.[c,*]

[a] *Department of Internal Medicine, University of South Florida, Moffitt Cancer Center, Tampa, FL*
[b] *Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy*
[c] *H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL*

Received 11 February 2019; received in revised form 10 April 2019; accepted 14 April 2019

Abstract

Penile cancer is a rare, but increasingly more common diagnosis. Although more there are more cases of penile cancer being diagnosed (the incidence is increasing), mortality (or conversely overall survival) has not changed. A detailed discussion of current treatments, along with potential therapeutic targets, and ongoing clinical trials is presented. This review gives insight to treatment strategies and novel modalities to combat a disease with sparse therapeutic options.

Keywords: Human papilloma virus; Penile cancer; Novel therapy

1. Introduction

Over the past 60 years, the incidence and overall number of men dying from penile squamous cell carcinoma (SCC) have both increased steadily; however, the overall survival (OS) of these men has not changed. The greatest increase in incidence has been in a younger cohort of patients mainly younger than or 64 years old with men >75 years old account for roughly a third of all cases [1]. Penile cancer is still considered a rare disease; factors impacting prognosis include: older age, tumor grade and stage, and regional lymph node (LN) invasion at diagnosis. The most well-defined risk factor for developing penile cancer is the association with human papillomavirus (HPV) infection and specifically with oncogenic strains such as: 16, 18, and 6/11 [2,3].

The majority of penile cancer diagnoses, 29% to 40%, are localized or stage I disease involving only the glans, prepuce, or both. The prognosis in these patients is excellent with 5-year OS of roughly 90% [4,5]. Although the trends of OS seem to be constant, there has been an increase in the use of treatment modalities utilizing cisplatin-based chemotherapy regimens and consolidation surgeries, implying that the survival impact of multimodality therapy options in locally-advanced disease remains unknown.

Although penile cancer is a rare diagnosis with increasing incidence, there lacks a consensus in management strategies and strong evidence to support specific guideline recommendations. The European Association of Urology (EAU) and the National Comprehensive Cancer Network (NCCN) guidelines recommend a LN dissection with judicious use of perioperative systemic chemotherapy for all patients with LN-positive nonmetastatic penile cancer [6]. Despite this recommendation, large retrospective studies have found that of patients with LN-positive disease only 66.8% of patients receive a LN dissection [7]. Perhaps understanding the molecular biology of penile SCC and clear effectiveness of such treatment modalities will increase guideline adherence and increase the understanding and role of various therapies in the therapeutic arsenal.

*Corresponding author. Tel.: (813) 745-2484; fax: (813) 745-8494.
E-mail addresses: philippe.spiess@moffitt.org, philippe.spiess72@gmail.com (P.E. Spiess).

https://doi.org/10.1016/j.urolonc.2019.04.012
1078-1439/

2. Understanding molecular pathways in penile cancer

One of the most well described mechanisms for the development of penile cancer is the state of chronic inflammation. The tumor suppressor (TP) gene, *p16,* is believed to play a key role in the pathogenesis of penile cancer via loss of the ability to induce apoptosis in cells with deleterious DNA damage [8].

Another set of modulators of inflammation and contributor to penile carcinogenesis is cyclooxygenase-2 (COX-2) and prostaglandin E2 (PGE2). The up-regulation of COX-2 causes a downstream cascade of up-regulation of PGE2 which in turn leads to a multitude of events such as: angiogenesis, cell division, epidermal growth factor receptor (EGFR) activation, and additionally activating the PI3K pathway; where the PI3K pathway was shown to be altered in 29% of patients' sampled tumors (Fig. 1) [9–12].

The human papillomavirus (HPV) and specifically oncogenic strains (16, 18, 31, 33) have been thought to account for 30% to 50% of penile SCC [13–15]. The HPV oncogenes encode for E5, E6, E7 of which E6 and E7 inactivate the p53 and p21/Retinoblastoma (Rb) pathways. By inactivating this pathway at multiple points in the cycle, this leads to an unregulated cell cycle and uncontrolled proliferation [16]. It has also been shown that HPV DNA can also be inserted within nonmalignant cells and cause up-regulation and amplification of the *MYC* gene leading to uncontrolled proliferation and progression of disease [17,18]. The HPV-E5 protein is responsible for the activation of EGFR, which subsequently leads to increase in uncontrolled cell growth and cell migration [19,20].

3. Current systemic therapies

Historically, we can acknowledge 2 periods of induction chemotherapy use for penile cancer, represented by the pretaxane and the posttaxane era (Table 1).

The mainstay of treatment for clinically-LN positive disease is the use of cisplatin- and taxane-based triple combination chemotherapy, which is the modern standard of care provided that patients are fit for an aggressive cytoreductive approach. Among these regimens there is the combination of paclitaxel, ifosfamide, and cisplatin (TIP) and the combination of docetaxel, cisplatin, and 5-FU (TPF) [22].

The landmark phase II trial in 2010 by Pagliaro et al. reported activity and efficacy data for patients with stage III or IV penile cancer treated with neoadjuvant TIP [23]. This study showed that of the patients who received this regimen, 50% had an objective response and 73% were down-staged and subsequently underwent surgery; where response to chemotherapy was significantly associated with both increased time to progression and overall survival ($P < 0.001$ and $P = 0.001$, respectively) [23]. This study is the reason TIP is the preferred combination regimen for systemic treatment in the NCCN guidelines.

Additional studies have been done that analyzed the use of 5-fluorouracil (5-FU) in combination with cisplatin; however the partial response (PR) rate was 32% and grade 3 or 4 neutropenia occurred in 20% of patients [24]. With a modest partial RR and significant toxicity, this regimen is reserved for patients who cannot tolerate TIP and generally not recommended in the neoadjuvant setting.

The overall outcomes achievable with neoadjuvant chemotherapy studies have been reported from an analysis of a

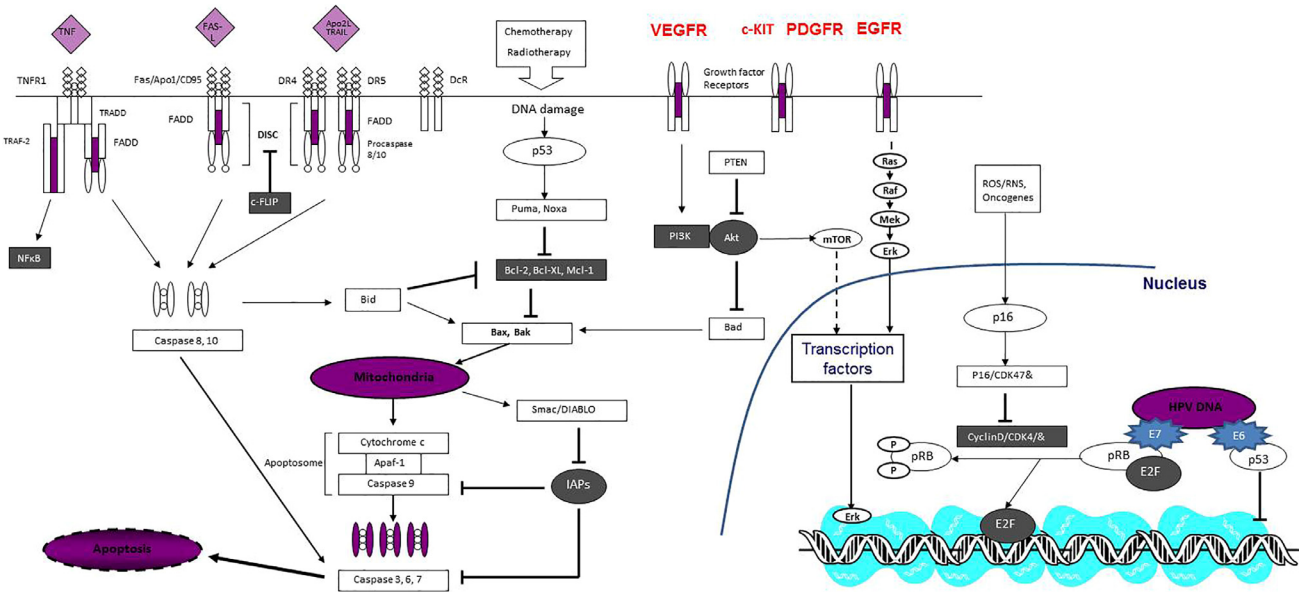

Fig. 1. Schematic diagram illustrating molecular pathway implicated in penile cancer
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Table 1.
Recent studies evaluating various systemic regimens for advanced penile cancer.

Series	Number of Pts treated	Mechanism of target	Intervention	ORR	Median PFS	Median OS (months)	Median TTP (months)	Follow-up (months)	pCR
Necchi A et al. (2018) [30]	28	Irreversible pan-EGFR inhibitor	Dacomitinib	32.1% (80% CI 21.0–43.0)	26.2% (95% CI 13.2–51.9) (12-month)	54.9% (95% CI 36.4-82.8) (12-month)	NR	Median 19.8 (IQR 6.3–25.7)	NR
Massarelli E et al. (2018) [37]	24	PD-1 inhibitor + HPV-16 vaccine	Nivolumab + ISA 101	NR	2.7 months (95% CI 2.5 -9.4)	17.5 months (95% CI 17.5 -inestimable)	NR	12.2	NR
Strauss J et al. (2018) [39]	16	PD-L1 and TGF-b inhibitors	Bifunctional fusion protein	45.5%	NR	NR	NR	NR	NR
Pagliaro LC et al. (2010) [23]	30	Taxane, alkylator, platinum	Paclitaxel, ifosfamide, cisplatin	NR	NR	17.1 (95% CI 10.3-60+)	8.1 (95% CI 5.4-50+)	Median 34 (IQR 14–59)	NR
Di Lorenzo G et al. (2012) [24]	25	Platinum, antimetabolite	Cisplatin, 5-FU	NR	20 weeks (IQR 11–20)	8 months (IQR 7 -12)	NR	NR	NR
Necchi A et al. (2017) [25]	94	Various Agents	Various Regimens	53.2%	23.2% (95% CI 14.8–32.6) (2-year RFS*)	35.8% (95% CI 25.1–46.6) (2-year)	NR	NR	13.8%
Pickering LM et al. (2018) [26]	22	Vinca alkaloid	Vinflunine (not FDA-approved)	27.3% (95% CI 10.7–50.2)	2.9 (95% CI 1.4–6.4)	8.4 (95% CI 3.2–14.1)	NR	NR	NR
Necchi A et al. (2016) [29]	28	Taxane, platinum, antimetabolite	Paclitaxel, 5-FU, cisplatin	NR	7.1% (95% CI 0–16.7) (2-year DFS**)	NR	NR	NR	14%
Haas GP et al. (1999) [21]	40	Platinum, antimetabolite, DNA synthesis inhibition	Cisplatin, methotrexate, bleomycin	32.5% (95% CI 19–49)	14 weeks (95% CI 10–21)	28 weeks (95% CI 25-35)	16 weeks (maximum 67)	9–57	12.5%

5-FU = 5-fluorouracil; DFS = disease-free survival; IQR = interquartile range; NR = not reported; ORR = objective response rate; OS = overall survival; pCR = pathologic complete response; PFS = progression-free survival; RFS = recurrence-free survival; TTP = time to progression.

large retrospective multicenter dataset that included several different regimens. The pathologic CR rate approximated 13%, the clinical objective response rate (ORR) was about 50%, although the 2-year OS estimate remained suboptimal (35.8%) [25].

In the attempt to improve the outcomes of these patients by providing a more tolerable chemotherapy regimen, UK authors have reported the results of a phase II trial of neoadjuvant/first-line vinflunine in penile cancer (VinCaP study): in 25 patients, the objective response rate was 27.3% (10.7–50.2) and the clinical benefit rate 45.5% (95% confidence interval [CI], 24.4–67.8) [26].

There is a paucity of data regarding the administration of adjuvant chemotherapy in penile cancer. Some oncologists feel comfortable with extrapolating the neoadjuvant data to this setting; however, no studies to date have tested this. There have been 2 historic control trials that showed some benefit with adjuvant vincristine, bleomycin, and methotrexate, but the toxicities were debilitating and subsequent studies abandoned [27,28].

In another study looking at a taxane, cisplatin, and 5-FU (T-PF) in both the adjuvant and neoadjuvant settings, the authors reported a 2-year disease-free survival (DFS) of 36.8% versus 7.1%, respectively; and subsequently concluded that although uncertain in the neoadjuvant setting, T-PF in the adjuvant setting now represents a therapeutic option as reported by the updated EAU penile cancer guidelines [22].

Interestingly in this study, p53 immunohistochemical expression was significantly associated with a poorer outcome with adjuvant TPF and this biomarker warrants further studies to enable a more rational patient selection for systemic therapy postoperatively [29].

The current treatment landscape of advanced penile cancer is dearth, with marginal data for options after first-line therapy after progression on TIP. The adjuvant space is an area of uncharted exploration in large randomized controlled trials and could offer new insights in to the management of these patients.

4. Promising targeted therapies

With the advent of next generation sequencing (NGS) for solid tumors, new targets are being identified that have potential therapeutic value. By analyzing large cohorts of patients' tumor signatures, various genes are found to more often play specific roles in specific tumors' pathogenesis more so than in other tumor types.

In patients with penile SCC who were stage II-III or M1, a phase II study of 28 patients treated with dacomitinib in the first-line setting reported an ORR of 32.1% (80% CI 21.0–43.0%), with a 12-month PFS of 26.2% (95% CI, 13.2–51.9), and a 12-month OS of 54.9% (95% CI, 36.4–82.8). This irreversible, pan-epidermal growth factor receptor (HER) inhibitor was found to be both efficacious as well as tolerable in the first-line setting in patients with penile SCC regardless of HPV and EGFR status. Interestingly, mutations in the PI3K/Akt/mTOR pathway were found in 42.9% of responders compared to only 8.3% of nonresponders [30].

Additional work has been done to investigate the role of the PI3K/Akt/mTOR in the pathogenesis and prognostication of penile SCC as well as serving as potential therapeutic targets. In an archival tissue-based study of 57 samples, 47% of samples showed up-regulation of Akt and additionally that Akt expression was inversely related to risk of recurrence (Hazard ratio [HR] 3.95; 95% CI, 1.47–10.59; $P = 0.02$) [31]. This study lays the groundwork and proof of concept for trials assessing the efficacy of various PI3K/Akt/mTOR pathway inhibitors in the treatment of penile SCC.

In another study that included 11 patients with unresectable or metastatic disease who had previously progressed on at least one cisplatin-containing regimen, panitumumab, an EGFR monoclonal antibody, was tested for efficacy and safety. This study reported a median PFS of 1.9 months (Interquartile range [IQR], 0.9–3.0 months) and a median OS of 9.5 months (IQR, 4.9–12.6) [32]. In this study, KRAS mutations were not analyzed prior or preceding treatment; however, this study provided more insight in the potential benefit of targeting the EGFR and HER families and adds to the growing evidence of the role EGFR signaling plays in the pathogenesis and progression of penile SCC.

In another archival-tissue based study of 78 cases of metastatic penile SCC, mTOR pathway alterations were identified in 11% of cases (7% PTEN, 4% NF1), DNA repair mutations in 14% of cases (7% BRCA2, 7% ATM), and tyrosine kinase alterations in 14% of cases (6% EGFR, 4% FGFR, 4% ERBB2). In this study microsatellite instability-high (MSI-high) status was found to be 0%; however, the tumor mutational burden (TMB) was found to be ≥20 mutations/Mb in 8% of patients [33]. The 2 best predictors to response to immunotherapy (IO) are MSI and TMB; from this dataset, there is some level of evidence that a select subset of patients could potentially derive benefit from treatment with IO.

5. Potential utility of checkpoint inhibition

The first tissue/site-agnostic approval of a checkpoint inhibitor, pembrolizumab, paved the way for testing the utility of IO in penile SCC. In a retrospective study of 213 patients, researchers analyzed various immune mediators with the goal of being able to prognosticate penile SCC better. It was reported that diffuse PD-L1 tumor expression was associated and a significant predictor for LN metastases (odds ratio [OR] 2.8; $P = 0.05$). In addition, diffuse PD-L1 expression was also significantly associated with worse disease-specific survival (DSS) (HR 2.8; $P = 0.03$) and that PD-L1 expression was significantly higher in HPV-negative samples ($P = 0.03$) [34].

Another archival-tissue study of 53 invasive penile SCC cases were analyzed and found that 40% of all cases expressed PD-L1. With subgroup analysis showing, 44% of stage pT2 or higher expressed PD-L1 and 38% of samples with concurrent LN metastases also stained positive for PD-L1 [35]. This study is a great example of the potential benefit of using IO in penile SCC and especially in patients with more aggressive disease biology.

In efforts to validate PD-L1 as a potential target for therapeutics, tissue from 37 patients was analyzed with anti-PD-L1 primary antibody immunohistochemistry and considered positive is ≥ 5% staining. Of the 37 samples, 62.2% of samples stained positive for PD-L1. The study also looked at primary tumor compared to LN metastases samples and found that primary tumor PD-L1 expression was significantly associated with expression in LN metastases ($P = 0.024$) and inversely related to cancer-specific survival (CSS) ($P = 0.011$) [36].

6. Evolving role of immunotherapeutic approaches

Another interesting approach was taken in a phase II trial of the combination of nivolumab with an HPV-16 vaccine, ISA 101. In this trial of 24 patients, although no patients had penile cancer, they all had an incurable HPV-16-positive cancer. This novel combination led to a median PFS of 2.7 months (95% CI, 2.5−9.4) and a median OS of 17.5 months (95% CI, 17.5 to inestimable) [37]. This trial can be thought of as a proof-of-concept for future trials in patients with HPV-16-positive penile cancer. It is estimated that 14%to 100% of penile cancers are caused by HPV DNA and of them, HPV-16 is the most common strain detected [38]. The approach of combining an HPV-16 specific vaccine with IO is a logical future direction in the treatment of penile cancer.

In a phase I study of 16 patients with HPV-positive cancers, albeit none with penile cancer, patients were treated with a bifunctional fusion protein, which targeted both PD-L1 and TGF-b with the basis that HPV-positive cancers have been shown to significantly overexpress TGF-b. An updated release regarding the safety and efficacy, showed that 56% of patients had disease reduction where 1 patient had a durable complete remission (CR), 4 patients had durable PRs, and an ORR of 45.5% [39].

In addition to the previously described potential immunotherapeutic options, there is ongoing research into the validity of chimeric antigen receptors (CAR) T cells in solid tumors, namely melanoma where durable CRs have been described [40]. This approach of using CAR T cells in HPV-positive tumors by targeting HPV-16 E6 has been shown to provide increasing intervals of DFS between metastasectomies. In addition, resected tumor samples were found to contain a set of T cells with high affinity for HPV-16 E6 [41].

7. Conclusions

The current systemic treatment landscape for penile cancer only includes combination chemotherapy. Historically, patients with metastatic disease have had a grim prognosis with unfortunately treatment outcomes not significantly improved over the past two decades. With this review outlining the forecast of multiple treatment strategies, hopefully penile cancer will become a disease exhibiting a more favorable outlook.

The understanding of the role of HPV in the pathogenesis of penile cancer will surely pioneer the future directions of immunotherapeutics and genomic-driven treatment options for those afflicted with this heinous malignancy. There is a promising platform of therapies emerging particularly in the realm of immunotherapy. As therapies continue to emerge and become more personalized to patients' tumor genomics and biomarker expressions, the goal is to assuage the burden of this diagnosis.

Disclosures

JJA has no disclosures. AN discloses institutional research grants by Pfizer and Ipsen. PES has no disclosures.

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