Penile cancer: current therapy and future directions

G. Sonpavde¹, L. C. Pagliaro², C. Buonerba³, T. B. Dorff⁴, R. J. Lee⁵ & G. Di Lorenzo³*¹

¹Department of Medicine, Section of Medical Oncology, UAB Comprehensive Cancer Center, Birmingham; ²Department of Genitourinary Medical Oncology, The University of Texas M.D. Anderson Cancer Center, Houston, USA; ³Genitourinary Cancer Section and Rare-Cancer Center, University Federico II, Naples, Italy; ⁴Department of Medicine, Section of Medical Oncology, University of Southern California, Los Angeles; ⁵Division of Hematology-Oncology, Department of Medicine, Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, USA

Received 1 August 2012; revised 23 October 2012; accepted 2 November 2012

Background: Penile cancer (PC) is a rare cancer in western countries, but is more common in parts of the developing world. Due to its rarity and the consequent lack of randomized trials, current therapy is based on retrospective studies and small prospective trials.

Design: Studies of PC therapy were searched in PubMed and abstracts at major conferences.

Results: PC is generally an aggressive malignancy characterized by early locoregional lymph node (LN) spread and later metastases in distant sites. Given the strong predictive value of LN involvement for overall survival, evaluating regional LNs is critical. Advanced LN involvement is increasingly being treated with multimodality therapy incorporating chemotherapy and/or radiation. A single superior cisplatin-based regimen has not been defined. Further advances may occur with a better collaboration on an international scale and comprehensive understanding of tumor biology. To this end, the preventive role of circumcision and understanding of the oncogenic roles of Human Papilloma Virus-16, and smoking may yield advances. Preliminary data suggest a role for agents targeting epidermal growth factor receptor and angiogenesis.

Conclusion: Advances in therapy for PC will require efficient trial designs, synergistic collaboration, incentives to industry and the efforts of patient advocacy groups and venture philanthropists.

Key words: biologic agents, chemotherapy, combined modality therapy, molecular targets, penile cancer, radiotherapy

introduction

Penile cancer (PC) is relatively rare in the developed countries, but higher incidences have been observed in the less developed countries. In 2012, 1570 new cases and 310 deaths from PC are predicted to occur in the USA, although the incidence declined from 1973 to 2002 (Table 1) [1, 2]. Conversely, the incidence climbs to 8.3 per 100 000 in parts of Asia, Africa and South America [3, 4].

In a study of registries including 6539 men with PC in the US during 1995–2003, Hispanic men had the highest incidence rates (6.58 per million) followed by black men (4.02 per million), white non-Hispanic men (3.90 per million), native American men (2.81 per million) and Asian-Pacific Islanders (2.40 per million) [5]. The median age of diagnosis was...
etiology, risk factors and prevention

Neonatal circumcision has been recognized to reduce the incidence of PC, possibly by inhibiting chronic inflammation [7, 8]. In fact, chronic inflammatory conditions such as balanopostitis and lichen sclerosis et atrophicus are among the strongest risk factors for PC [odds ratio (OR) >10], with 4%–8% of men with lichen sclerosis et atrophicus developing PC [9, 10]. PC virtually does not occur in the Jewish and Muslim populations, in which early circumcision is common. In a series of 458 cases in Ugandan Africans, the incidence was extremely low where circumcision was practiced [11]. Intriguingly, differences in incidence in the uncircumcised were observed over small distances, suggesting that unknown factors varying with geographical location may be operative. Moreover, early circumcision during infancy may be critical [12]. In a study including 110 men with PC and 355 matched controls, relative to men circumcised at birth, the risk for PC was 3.2 times greater among men who were never circumcised and 3.0 times greater among men who were circumcised after the neonatal period [12]. Those with a history of genital warts had 5.9 times the risk. Of 67 tumors tested for Human Papilloma Virus (HPV) DNA, 49% were positive, the majority of them being HPV-16 (70%). Among men uncircumcised at birth, the presence of smegma and difficulty in retracting the foreskin conferred a relative risk of 2.1 and 3.5, respectively. However, the role of smegma resulting from phimosis remains controversial [13, 14].

HPV, particularly HPV-16 and -18, appears to participate in pathogenesis, although HPV may only play a minor role in nonindemic areas [15–22]. Indeed, circumcision may exert its protective effect against the development of PC partly by preventing HPV infection [23, 24]. In a case–control study, penile HPV-DNA was detected in 166 of 847 uncircumcised men (19.6%) and in 16 of 292 circumcised men (5.5%) [23]. Monogamous women whose male partners had ≥6 sexual partners and were circumcised had a lower risk of cervical cancer than women whose partners had similar sexual history and were uncircumcised (OR 0.42). Studies of vaccination in men to prevent HPV-associated morbidities are ongoing [16, 25]. The increased risk of PC in patients with human immunodeficiency virus (HIV) infection may be mediated by coinfection with HPV, although the role of HIV in directly causing the malignancy is unclear [26].

Additional risk factors may include tobacco exposure as well as psoralens and ultraviolet A (PUVA) photochemotherapy; familial predisposition has not yet been identified. Current smoking conferred a higher risk compared with never smokers, albeit a causal link is unclear [27, 28]. In a prospective study of 892 men with psoriasis who had received PUVA, the standard morbidity ratio, which compares morbidity in the sample population with that expected on the basis of population incidence data, was 58.8 for invasive and in situ penile tumors [29]. Moreover, the incidence was dose dependent.

diagnosis and staging

The glans penis is the most common site of origin followed by the prepuce, coronal sulcus and shaft [2, 30]. Most patients present with localized disease as a mass, ulcer or inflammatory lesion (Table 1) [31]. Inguinal lymphadenopathy by physical examination exhibits low positive and negative predictive values. In one report of 100 men with PC treated according to the European Association of Urology (EAU) guidelines in a single institution, 72% of men with palpable lymph nodes (LN) and 18% with impalpable LNs had pathological LN involvement [32]. Hence, an inguinal fine needle aspiration (FNA) biopsy has been recommended by the National Comprehensive Cancer Network (NCCN, v. 1.2012) to guide therapy in patients with palpable inguinal nodes. Subsequent excisional biopsy has been recommended if the FNA is negative (to avoid sampling error), and proceeding with full inguinal LN dissection is recommended if the FNA is positive for tumor. In those with impalpable LNs, surveillance for low-risk patients (≤T1G1) and sentinel LN biopsy in high-risk patients has been recommended.

A fluorodeoxyglucose (FDG)-positron emission tomography (PET) scan may be useful in detecting LN metastasis, but more
data are needed [33–37]. Magnetic resonance imaging appeared highly accurate in locoregional staging according to one study (n = 55) [38]. For now, staging with computerized tomography imaging of the pelvis should be standard for all men presenting with T1 or greater disease, with abdomen and chest imaging added for poorly differentiated tumors or >N2 stage. The most common sites of distant metastases are lung, liver and bone.

pathology

The vast majority of malignancies of the penis are squamous cell cancers (SCCs), but other histologic types are observed in ~5% of cases, such as melanomas, basal cell carcinomas and sarcomas [39]. The World Health Organization (WHO) classifies penile SCC, or PC, as usual, basaloid, verrucous, warty (condylomatous), papillary, sarcomatoid, adenosquamous and mixed [40]. In a surgical series of 333 patients receiving homogeneous surgery, basaloid, sarcomatoid and adenosquamous carcinomas displayed the highest histological grade and deep tissue infiltration, while verrucous, papillary and condylomatous (warty) carcinomas were associated with low grade and superficial invasion. This relationship translated into distinct clinical behavior, with a higher 10-year survival rate for verrucous, adenosquamous, mixed, papillary and warty carcinoma (100%, 100%, 97%, 92% and 90%, respectively), while patients with the usual and basaloid types had 78% and 76% 10-year survival, respectively. Of note, 75% of patients with sarcomatoid carcinoma died, usually within a year of diagnosis [41]. Interestingly, verrucous carcinomas appear to exhibit low p16 and HPV expression [42]. Grading has established a prognostic role for PC with crucial clinical implications [43, 44]. Higher grade and basaloid and warty tumors are more consistently associated with HPV, suggesting that distinct pathogenic pathways may drive tumors [20, 45, 46].

molecular biology

Epidermal growth factor receptor (EGFR) overexpression appears to be almost universal and correlated with the grade, but not the stage [47–49]. In an American series, KRAS (Kirsten rat sarcoma) mutations and ERCC1 (excision repair cross-complementing group 1) amplification appeared rare or absent, which may portend responsiveness to EGFR inhibitors and platinum chemotherapy. EGFR had the highest relative expression followed by thymidylate synthetase. However, in a Spanish series (n = 28), 22% of evaluable tumors had mis-sense mutations in KRAS, suggesting that there may be regional differences in biology [50]. In another study, somatic mis-sense mutations in PIK3CA, HRAS and KRAS were found in 11 of 28 (39%) PC samples [51]. PIK3CA mutations were found in all grades and stages, whereas HRAS and KRAS mutations were found in more advanced tumors. The mutations were mutually exclusive, suggesting that dysregulation of either pathway is sufficient for tumor growth. A preliminary examination of the COSMIC dataset (n = 28) revealed p53 or PIK3CA mutations in 8 of the 28 (29%) tumors (http://www.sanger.ac.uk/cosmic, 18 June 2012, date last accessed) [52].

EGFR, HER3 and HER4 protein overexpression was found in one study of 148 cases, although no EGFR gene amplification was detected [53]. In this study, HPV-negative tumors expressed significantly more phosphorylated EGFR than HPV-positive cancers, which correlated with the phosphorylation and activation of Akt signaling. Conversely, HER3 expression was significantly more common in HPV-positive cases, which correlated with cytoplasmic localization of Akt1. PTEN protein expression was reduced in 62% of tumors, but PTEN gene loss occurred only in 4%.

The epigenetic inactivation of thrombospondin-1 and RAS (rat sarcoma) association domain family-1A genes by hypermethylation seemed to confer prognostic significance in one study (n = 24) [54]. LN metastasis was significantly associated with negative p16 and combined LOH (loss of heterozygosity) and promoter hypermethylation, but not with p53 alterations [55]. Similarly, another study of 148 PCs demonstrated that HPV infection may engender p16 and p21 expression and RB suppression, but no association with p53 expression was detected [56]. Nevertheless, p53 protein expression has been related to LN metastasis and poor survival in other studies [57–59]. Moreover, studies indicate the potential importance of cell-cycle regulators and pro-survival proteins, e.g. p16, p21, telomerase and the Bcl-2 family [49, 60–62] (Figure 1).

Another study of 26 cases reported DNA sequence copy number alterations (CNAs) similar to oral and esophageal SCCs [63]. The most frequent copy number gains occurred in 8q24, 16p11-12, 20q11-13, 22q, 19q13 and 5p15, while the most common deletions occurred in 13q21-22, 4q21-32 and the X chromosome. The number of CNAs exhibited a possible correlation with clinical outcome, but the biological mechanisms remain undefined. Increased cyclo-oxygenase (COX)-2 and microsomal prostaglandin E synthase-1 were detected in penile intraepithelial neoplasia and carcinoma in one study, suggesting a pathogenic role for inflammation and a contraceptive role for COX-2 inhibitors [64]. The potential role of angiogenesis was suggested by a case series reporting the activity of sorafenib and sunitinib [65].

prognostic factors

Pathologic TNM staging provides prognostic stratification after surgery (Table 1) [66]. Furthermore, extranodal extension in inguinal LNs and pelvic LN involvement appear to be independently associated with decreased 5-year cancer-specific survival (42% and 22%, respectively) [67]. Nomograms have been reported for patients following penectomy to better predict cancer-specific survival and LN metastasis [68–70]. These nomograms incorporate multiple variables in addition to stage to enhance prognostication including grade, venous or lymphatic embolization and the type of surgery. Other studies have reported LN density, lack of koilocytosis and clear cell subtype to be prognostic [67, 70–84].

Additionally, molecular prognostic markers are suggested by some studies, e.g. p53, Ki-67, E-cadherin, MMP-9 (matrix metalloproteinase-9), annexins I and IV and decreased KAI1/CD82, a metastasis suppressor gene [57, 59, 85–88]. Although HPV has been associated with high-grade tumors, the impact
on outcomes is unclear with one study even demonstrating a favorable impact of HPV and another study showing a positive association with survival of p16, which is related to HPV [17, 46, 89, 90].

surgery

Noninvasive tumors are amenable to local measures, e.g. topical 5-fluorouracil (5-FU) or imiquimod, laser or local excision. A partial and glans-sparing penectomy provides psychosocial benefits, preserves sexual function and is generally feasible for a T1 tumor [91]. A 2-cm margin has been advocated historically, although some recent data suggest a 5- to 10-mm margin may be adequate [92]. Total penectomy is preferred for ≥T2 tumors, although some T2 tumors are amenable to partial penectomy based on location. Penile-sparing surgical modalities including Mohs’ micrographic surgery and laser ablation are considered for small tumors, particularly if located on the glans and margins ≥3 mm can be attained.

Controversies surround the role and extent of immediate inguinal lymphadenectomy with or without sentinel LN dissection in those without clinical lymphadenopathy, as well as the role of pelvic LN dissection [93–105]. In a large surgical series of 688 patients, immediate lymphadenectomy (n = 251) was associated with a better 10-year disease-specific survival than delayed (n = 81) lymphadenectomy (71% vs. 30%, P = 0.002) [99]. The authors reported divergent 10-year disease-specific survivals for low-risk (T1G1-2), intermediate (T2-3G1-2) and high-risk (T1-3G3 and T4G1-3) patients ranging from ~75% to ~40%. The 10-year disease-free survival rates for patients with negative and positive pathological nodal involvement in the immediate lymphadenectomy group were 96% and 35%, respectively. Despite the caveats of a retrospective analysis, these data suggest the powerful favorable impact of inguinal LN dissection. Video-endoscopic inguinal lymphadenectomy appeared feasible without compromising tumor control in those without palpable adenopathy in small retrospective series [106]. However, a larger experience and longer follow-up are necessary before routine adoption.

Similarly, sentinel LN dissection has been carried out to guide additional dissection, although the false negative rate (15%–20%) suggests that further refinement of the methodology is necessary [101].

Both the EAU and NCCN guidelines, which share a number of similarities, suggest adapting the extent of LN dissection to clinical stage [44, 94]. Generally, for low-risk compliant patients (pTis, pTa and pT1G1) without palpable LNs, surveillance was recommended. For all other patients without palpable LNs, a modified bilateral lymphadenectomy or sentinel LN dissection was recommended. Radical inguinal lymphadenectomy was recommended for patients with histologically proven LN metastasis. In addition, pelvic LN dissection was recommended in patients with multiple inguinal LNs, extranodal extension or node of Cloquet involvement.

patterns of recurrence after surgery

In a large retrospective study of 700 patients, the rate of recurrences was compared between patients undergoing penile-preserving treatments and partial/total amputation [107]. Regional recurrences were compared between patients surgically staged as pN0 or pN+ and clinically node-negative (cN0) patients who chose a watchful waiting approach. Of these 700 patients, 205 (29.3%) displayed a recurrence, including 18.6% local, 9.3% regional and 1.4% distant recurrences. The vast majority of recurrences (86%) occurred within 2 years. Local recurrences occurred in a higher proportion (27.7%) after penile-preserving therapy compared with following amputation (5.3%), although this did not appear to compromise survival due to the efficacy of surgical salvage. The regional recurrence rate was 2.3% in patients with pN0, 19.1% with pN+ and 9.1% undergoing a watchful waiting approach. The 5-year diseasespecific survival rate was 92% after a local recurrence and 32.7% after regional recurrence, while all patients with a distant recurrence died within 22 months.

radiotherapy

External beam radiotherapy (XRT) has been employed for localized T1–T2 disease as organ-sparing therapy or as...
adjuvant therapy following surgery [108–113]. In retrospective reports of <100 patients each, local and regional recurrence rates (~20% and ~5%, respectively) appear higher than observed with surgery, but salvage resection is generally effective. However, there are no trials comparing XRT and surgery. Similarly, brachytherapy may be an excellent penile-sparing modality for T1 and T2 tumors <4 cm in size located on the glans [114–116]. The 10-year local recurrence rate in the largest retrospective study of brachytherapy for cancer of the glans penis (n = 144) was ~20% and appeared to be dependent on tumor size. Surgical salvage rescued most recurrences, yielding 10-year cancer-specific survival in 92% [115]. Delayed complications included stenosis, necrosis, fibrosis and ulceration.

Anecdotal reports of the success of concurrent cisplatin or 5-FU-based chemotherapy and radiation for locally advanced unresectable disease suggest that further investigation of this modality is warranted [117, 118]. Prospective studies of concurrent chemoradiation are unavailable at this time, although extrapolation from similar perineal SCCs, e.g. vulvar and anal cancer, suggest the potential efficacy of chemoradiation followed by salvage surgery for persistent or recurrent disease [119, 120].

Adjuvant XRT may be considered in high-risk node positive patients following surgery, given the high risk of locoregional recurrence [109]. In a retrospective study, regional failure rates after inguinal LN dissection for pathological inguinal LN metastasis were 11% (1 of 9) and 60% (3 of 5) in patients with and without adjuvant XRT.

**peripheral chemotherapy**

In patients with multiple, fixed or bulky inguinal LNs (≥4 cm), or involved pelvic LNs, multimodality therapy including primary chemotherapy followed by surgery and node resection is preferred. Small retrospective studies including 5–20 patients have examined bleomycin–vincristine–methotrexate (BVM) and bleomycin–methotrexate–cisplatin (BMP; Table 1) [121–124]. A recent prospective trial investigated four cycles of neoadjuvant ifosfamide, paclitaxel, cisplatin (ITP) and demonstrated the feasibility and activity of this regimen (Table 2) [122, 124, 125]. Thirty men received ITP in this trial of whom 15 (50.0%) had an objective response and 22 (73.3%) underwent surgery. Three (10%) patients exhibited a pathologic complete response (pCR), which was a marginally substantial predictor of improved survival. Serious adverse events related to chemotherapy were infrequent, with grade 3 infection being the most common severe toxicity occurring in ~16% of patients. Nine (30.0%) patients remained alive and free of recurrence after a median follow-up of 34 months. The estimated median time-to-progression (TTP) was 8.1 months, and median OS was 17.1 months.

Improved long-term outcomes were substantially associated with response to chemotherapy and the absence of bilateral residual tumor/extranodal extension/skin involvement. Trends toward shorter survival were noted with poor performance status, immobile groin mass, skin ulceration and leukocytosis. Preliminarily, the FDG-PET scan has appeared useful in monitoring response to neoadjuvant chemotherapy in a small study [126].

There are no prospective studies of adjuvant chemotherapy, although small retrospective reports have been presented [44, 121, 127]. Long-term disease-free survival occurred in 84% of 25 consecutive node positive patients treated with adjuvant BVM during 1979–1990 versus 39% of 38 consecutive patients undergoing radical LN dissection (with or without XRT) from 1960 to 1978 [121]. Given the high risk of locoregional recurrence, a potential role may exist for adjuvant combination chemotherapy and XRT. In the absence of randomized trials, clinical judgment and appropriate patient selection are necessary before embarking on adjuvant therapy. The EAU recommends adjuvant chemotherapy only for ≥pN2 disease, whereas the NCCN recommends it for LN size ≥4 cm.

**chemotherapy for advanced disease**

A substantial variability of employed first-line regimens exists in practice [128]. Cisplatin alone displayed modest activity with four partial responses in 26 (15.4%) patients and a median survival of only 4.7 months (Table 3) [129]. Historical data with combination BMP demonstrated a median survival of only 28 weeks [130–132]. In the largest prospective study of this regimen, there were five complete and eight partial responses in 40 assessable patients for a 32.5% response rate [132]. Unfortunately, in this study, five treatment-related deaths occurred and six other patients had 1 or more life threatening toxic episodes. Hence, the toxic effects of

<table>
<thead>
<tr>
<th>Author</th>
<th>Regimen</th>
<th>Design</th>
<th>N</th>
<th>Surgery N (%)</th>
<th>Clinical stage</th>
<th>Clinical response N (%)</th>
<th>pCR N (%)</th>
<th>Median PFS</th>
<th>Median OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pagliaro et al.</td>
<td>ITP</td>
<td>Phase II trial</td>
<td>30</td>
<td>22 (73.3)</td>
<td>Any T, N2–N3</td>
<td>15 (50)</td>
<td>3 (10)</td>
<td>8.1 months</td>
<td>17.1 months</td>
</tr>
<tr>
<td>Leijte et al.</td>
<td>BMP, BVM, CF</td>
<td>Retrospective</td>
<td>20</td>
<td>9 (45)</td>
<td>Any N3 or T4</td>
<td>12 (60)</td>
<td>2 (10)</td>
<td>NR</td>
<td>5 years: 32%</td>
</tr>
<tr>
<td>Bermejo et al.</td>
<td>BMP, PCa, TIP</td>
<td>Retrospective</td>
<td>10</td>
<td>10 (100)</td>
<td>Variable, N1–N3 or M1</td>
<td>5 (50)</td>
<td>3 (30)</td>
<td>NR</td>
<td>26 months</td>
</tr>
</tbody>
</table>

Surgery consisted of bilateral inguinal lymphadenectomy with unilateral or bilateral pelvic lymphadenectomy.


Table 2. Reported studies of ≥10 patients receiving preoperative therapy
bleomycin–containing regimens have been recognized and considered to be prohibitive.

Thereafter, other cisplatin-based regimens were employed that omitted bleomycin. Small retrospective reports of regimens containing cisplatin–5-FU with or without taxane have demonstrated modest activity [132–139]. In the largest retrospective study employing cisplatin–5-FU, 25 patients exhibited a response rate of 32%, and median PFS (progression-free-survival) and OS of 20 weeks and 8 months, respectively [138]. In contrast to BMP, cisplatin–5-FU displayed excellent tolerance, with a 20% incidence of grade 3–4 neutropenia and an 8% incidence of grade 3–4 anemia. One trial investigated the combination of cisplatin and irinotecan in locoregionally advanced or metastatic disease [140]. Patients were treated in the neoadjuvant setting for T3 or N1–N2 disease either with up to four cycles before surgery or up to eight cycles for T4 or N3 or M1 disease. There were eight clinical responses in 26 assessable patients (30.8%) including two complete clinical responses, and three pCRs at LN dissection were noted. Anecdotal benefit has been observed when employing cisplatin–gemcitabine [141].

ITP may also be a rational regimen in metastatic disease, based on the activity in the neoadjuvant setting [125].

Second-line therapy is also not established, and taxanes have been used with marginal activity [142]. In a prospective, multicenter phase II trial, 25 patients were enrolled and treated with paclitaxel 175 mg/m² every 3 weeks [142]. Partial responses were observed in 20%. The median PFS was only 11 weeks, and the median OS was 23 weeks. The anticipated, but manageable, toxic effects of paclitaxel were observed.

### novel systemic regimens and biological agents

A potential role may exist for EGFR inhibiting monoclonal antibodies (panitumumab and cetuximab) [143–145]. In one retrospective study, all 13 patients with advanced PC expressed EGFR with 77% exhibiting 3+ levels of expression and received EGFR-targeted therapies, including erlotinib (n = 1), cetuximab (n = 3) or cetuximab, combined with platinum-based regimens (n = 9) [143]. The patients showed a median TTP of 3.2 months and a median OS of 9.8 months. Four (31%) patients survived between 13 and 48+ months, comparing favorably with historical survival when utilizing conventional chemotherapy. Anecdotal responses have been reported with panitumumab or combination docetaxel–cetuximab after cisplatin-based chemotherapy [144, 145]. EGFR monoclonal antibodies appear to warrant further study in combination with chemotherapy and radiation, given these promising signals.

Angiogenesis is also a promising target; in a retrospective report of six chemorefractory patients following at least two prior regimens treated with sunitinib or sorafenib, one patient achieved a partial response and four had stable disease [65]. Reduction in microvessel density and Ki-67 labeling index was observed in paired specimens. Serious adverse events were fatal infection and rupture of the femoral vessel.

### future perspectives

Better understanding of the basic biology of the malignancy should guide the design and conduct of future clinical trials. Currently, a dominant molecular driver of the disease remains unknown. A large international consortium may overcome the barrier of slow accrual and has been demonstrated to be successful in other uncommon or rare malignancies [146–148]. In this context, the International Rare Cancer Initiative (IRCI) has been launched, which is composed of the UK National Cancer Research Network, Cancer Research UK, US National Cancer Institute (NCI) and the European Organization for the Research and Treatment of Cancer (EORTC). Given the rarity of the disease, referral to centers with demonstrated excellence in the management of PC should be considered, particularly with reported improvement in outcomes with this approach [149]. Simultaneously, the cooperation and partnership of regulatory bodies is essential in the early stages of drug development. There is a need to incentivize industry and a role for disease advocacy and venture philanthropy.

In addition, the classic paradigm of randomized trials may be difficult to execute in this rare malignancy. Therefore,
Figure 2. Proposed strategy to manage local and locoregional invasive penile cancer. "Consider LN biopsy to exclude false positive lymphadenopathy, "brachytherapy/external bean radiation/Mohs micrographic surgery/laser, *except for T1G1 where a role for surveillance exists, "potential role for sentinel LN dissection followed by LN dissection if positive, "consider pelvic LN dissection based on risk.

conclusion

A logical and effective therapeutic approach to PC is possible despite the lack of randomized trials (Figure 2). For localized disease, there are sophisticated approaches beyond mere amputation, such as glans-sparing partial penectomy, brachytherapy and reconstructive surgery. For metastatic disease in LNs, a curative neoadjuvant multidisciplinary paradigm is feasible instead of a palliative approach. Nevertheless, despite excellent outcomes in localized disease, locoregional and metastatic disease portend poor outcomes. Important research questions remain, such as the role of chemoradiation, and opportunities for targeted therapy. Unfortunately, in view of the rarity of the disease and little interest among pharmaceutical companies, few clinical trials have been conducted. Prevention and early detection appear critical. In particular, neonatal circumcision, smoking cessation and HPV vaccination may substantially reduce the incidence of PC. Indeed, HPV vaccination is already approved in the USA for males aged 9–26 years for preventing genital warts and anal cancer. Global collaboration is urgently necessary to make advances.
disclosure

GS: Research support and/or advisory board of Pfizer, BMS, Novartis, Celgene, and Sanofi-Aventis. LCP: Consultant for Janssen and Research support from Pfizer and Celgene. CB and RJL: these authors have declared no conflicts of interest. TBD: speaker for Pfizer and Bayer. GDL: research support from Pfizer and advisory board of Sanofi, Janssen, Cilag and Novartis.

references


Diagnosis and management of gastrointestinal complications in adult cancer patients: evidence-based guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO)

M. J. G. T. Vehreschild¹*, J. J. Vehreschild¹, K. Hübel¹, M. Hentrich², M. Schmidt-Hieber³, M. Christopeit⁴, G. Maschmeyer⁵, E. Schalk⁶, O.A. Comely¹,⁷ & S. Neumann⁸

¹1st Department of Internal Medicine, University Hospital Cologne, Cologne; ²Department of Infectious Diseases, Oncology, Palliative Care, Harlaching Hospital, Munich; ³Department of Hematology, Oncology and Tumor Immunology, HELIOS Klinikum Berlin Buch, Berlin; ⁴Department of Oncology and Hematology, University Hospital and Medical Faculty of Martin-Luther-University Halle, Halle; ⁵Department of Hematology, Oncology, and Palliative Care, Ernst-von-Bergmann Klinikum, Potsdam; ⁶Department of Haematology and Oncology, Medical Center, Otto-von-Guericke University, Magdeburg; ⁷Clinical Trials Centre Cologne, ZKS Köln, University of Cologne, Cologne; ⁸Department of Haematology and Oncology, Georg-August-University Göttingen, Göttingen, Germany

Received 14 July 2012; revised 2 November 2012; accepted 14 December 2012

Background: Cancer patients frequently suffer from gastrointestinal complications. However, a comprehensive, practical and evidence-based guideline on this issue is not yet available.

Patients and methods: An expert group was put together by the Infectious Diseases Working Party (AGIHO) of the German Society of Haematology and Oncology (DGHO) to develop a guideline on gastrointestinal complications in the penis: updates and molecular analyses. J Clin Oncol 2010; 28 (Suppl): e15022.

© The Author 2013. Published by Oxford University Press on behalf of the European Society for Medical Oncology. All rights reserved. For permissions, please email: journals.permissions@oup.com.