Emerging Systemic Therapies for the Management of Penile Cancer

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KEYWORDS

• Penile squamous cell carcinoma • Combined modality therapy • Chemotherapy • Targeted therapy • EGFR • PD-1 • VEGF

KEY POINTS

- Penile squamous cell carcinoma (PSCC) is a rare cancer in men in developed countries and more common in developing countries.
- Prognosis of metastatic PSCC is dismal, and responses to chemotherapy are short-lived.
- There is an urgent need to incorporate novel targeted and immunotherapy agents in the treatment paradigm.

INTRODUCTION

Penile squamous cell carcinoma (PSCC) is a rare cancer in men in developed countries, with an estimated 2030 new cases of PSCC and 340 deaths in the United States in 2016.[1] The incidence of PSCC is higher in the developing countries of Asia, Africa, and South America.[2] The most common age of presentation is between 50 and 70 years.[3]

PSCC is an aggressive disease, spreading locally through lymphatic channels and subsequently to distant sites. The survival outcomes of patients with penile cancer depend on the presence or absence of lymph node involvement.[4,5] The 5-year survival rate is more than 85% for patients with negative lymph nodes and 29% to 40% with positive nodes and 0% for those with pelvic lymph node involvement.[5] Although surgical excision is the standard of care for patients with palpable inguinal lymph nodes less than 4 cm in size, for those with inguinal lymph nodes greater than 4 cm, fixed nodes, or involvement of pelvic lymph nodes, multimodality treatment with systemic chemotherapy, surgery, and radiation is generally offered.[6] Notably, multiple therapeutic conundrums exist because of the absence of randomized trials. The International Rare Tumors Initiative has launched the International Penile Advanced Cancer Trial (InPACT) trial for patients with inguinal lymph node metastases to elucidate the role of neoadjuvant therapy using chemotherapy or chemoradiotherapy compared with no neoadjuvant therapy. Additionally, the role of pelvic lymph node dissection following surgery and inguinal lymph node dissection will be investigated (NCT02305654).[7]

Successful treatment of advanced PSCC with regional and systemic metastases remains a challenge; given the lack of randomized trials in PSCC,

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current therapy options are based on small prospective trials and retrospective studies.[8,9] Cisplatin-containing multi-agent systemic chemotherapy regimens are commonly used as first-line treatment of patients with advanced/metastatic PSCC. There are no standard second-line treatment options, and only marginal responses are observed with single-agent paclitaxel.[10] Novel treatment approaches with targeted therapies and immunotherapies are urgently required to improve the outcomes in PSCC refractory to standard therapy. This review highlights the current standard therapies and the role for novel therapies that warrant further studies.

SYSTEMIC CHEMOTHERAPY

Chemotherapy for Advanced/Metastatic Penile Squamous Cell Carcinoma

First-line chemotherapy

Monotherapy with cisplatin, bleomycin, and methotrexate in PSCC was attempted in the early 1970s; but response rates were modest between 0% and 27% (**Table 1**).[11–13] Cisplatin displayed a 15.4% response rate with a median survival of 4.7 months.[11] Bleomycin had modest activity as well and caused major side effects, including pulmonary toxicity.[12,14] One case of complete response was seen with high-dose methotrexate.[15]

Combination chemotherapy regimens with 2 or 3 chemotherapeutic agents was attempted to improve outcomes. There were small studies and case reports of patients treated with cisplatin-based combination chemotherapy. Shammas and colleagues[16] showed a partial response in 2 out of 8 patients treated with cisplatin and 5-fluorouracil. The efficacy of cisplatin-5-fluorouracil was evaluated more recently in a larger retrospective study in patients with metastatic PSCC (see **Table 1**).[17] Among the 25 patients with metastatic PSCC treated with cisplatin plus 5-fluorouracil, partial responses and stable responses were observed in 8 (32%) and 10 (40%) patients, respectively, with a disease control rate of 72%. The median progression-free survival (PFS) was 20 weeks, and the median overall survival (OS) was 8 months. The incidence of grade 3 to 4 neutropenia was 20%.[17]

Kattan and colleagues[18] reported one complete response after treatment with combined cisplatin and methotrexate in 3 patients with metastatic PSCC. In a phase 2 European Organization for Research and Treatment of Cancer study by Theodore and colleagues,[19] 28 patients with advanced/metastatic PSCC were treated with the combination of cisplatin and irinotecan (**Table 2**). Patients were treated either in the neoadjuvant setting for T3 or N1-N2 disease with up to 4 cycles or up to 8 cycles for T4 or N3 or M1 disease. Twenty-six eligible patients were evaluated for response; there were 8 responses (30.8%; 2 complete responses and 6 partial responses).[19] The combination of paclitaxel and carboplatin (PCa) demonstrated significant remission in an anecdote of a single patient and the regimen was well tolerated.[20] In a phase II trial, patients with unresected locoregional lymph nodes and/or distant metastases were administered gemcitabine and cisplatin every 2 weeks.[21] The median time to progression (TTP) was 5.48 months, and

Table 1
Key reported studies of chemotherapy for advanced/metastatic penile squamous cell carcinoma

Author	Regimen	Line of Therapy	N	Response
Shammas et al,[16] 1992	Cisplatin, 5-FU	First	8	PR 3 patients
Di Lorenzo et al,[17] 2012	Cisplatin, 5-FU	First	25	PR 8 patients, SD 10 patients
Gagliano et al,[11] 1989	Cisplatin	First	26	PR 4 patients
Dexeus et al,[23] 1991	Bleomycin, methotrexate, cisplatin	First	14	PR 10 patients
Haas et al,[24] 1999	Bleomycin, methotrexate, cisplatin	First	40	CR 5 patients, PR 8 patients
Theodore et al,[19] 2008	Cisplatin, irinotecan	First	26	CR 2 patients, PR 6 patients
Nicholson et al,[28] 2013	Docetaxel, cisplatin, 5-FU	First	26	CR 2 patients, PR 8 patients
Pizzocaro et al,[81] 2009	Paclitaxel, cisplatin, 5-FU	First	3	PR 2 patients
Di Lorenzo et al,[10] 2011	Paclitaxel	Second	25	PR 5 patients

Abbreviations: CR, complete response; 5-FU, 5-fluorouracil; PR, partial response; SD, stable disease.

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