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Chemotherapy in Patients with Penile Carcinoma

Key Words

Penile carcinoma • Chemotherapy

Abstract

The prognosis of patients with advanced penile carcinoma is poor. There are only few studies, mostly with a low number of patients, which show a low response rate with severe toxicity. While adjuvant and palliative chemotherapy for penile cancer is universally characterized by low efficacy, neoadjuvant approaches for patients with fixed lymph node metastases have shown some response. Overall, recent experiences with new chemotherapeutic approaches (i.e. taxane-based combinations) have shown some encouraging results. Therefore, these combinations should be investigated in larger and multi-center studies.

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Introduction

Penile squamous cell carcinoma (PSCC) is a relatively uncommon tumor entity in North America and Europe, while higher incidences are found in South America, Africa and Asia. Although PSCC is characterized by slow regional tumor progression, metastases are frequently found even in early local tumor stages [1]. The prognosis in advanced tumor stages is poor. Due to the low incidence of penile carcinomas there are only a few studies concerning chemotherapy with mostly inhomogeneous patient groups. Furthermore, current chemotherapeutic approaches mostly fail in case of distant metastases and the standard chemotherapy regimens described are characterized by high toxicity profiles making them not feasible for older patients with reduced organ function. So far, chemotherapeutic options are limited to single-center experiences or case reports. Since new chemotherapeutic approaches are highly needed for patients with penile carcinomas, this article reviews the available literature concerning chemotherapy regimens for penile cancer with response rates and survival when reported.

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Evidence Acquisition

A Medline search was performed of the English language literature (1966 to April 2008) using the MeSH terms penile carcinoma, chemotherapy, drug therapy, complications. In addition, we searched the Cochrane Central Register of controlled trials using the term penile carcinoma. Bibliographies of relevant articles and guidelines were additionally used.

Monotherapy

Single agent regimens were initially used in the early 1970s. Moderate response rates were reported for cisplatin, bleomycin and methotrexate, respectively. These

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drugs have become the basic components of combination regimens. Reported response rates were 15–27% for cisplatin, 20–21% for bleomycin and 0–62% for methotrexate [2–7]. Garnick et al. [8] reported on complete remission after high-dose methotrexate chemotherapy. Different dosage regimens were proposed (10–30 mg/m² bleomycin, 30–3,000 mg/m² methotrexate and 50–120 mg/m² cisplatin). Major side effects were reported for bleomycin with pulmonary fibrosis (1 fatal case) and hematological toxicity.

Polychemotherapy with Two-Drug Regimens

The most commonly used two agent combination (cisplatin/5-fluorouracil) was initially described by Hussein et al. [9] and Shammas et al. [10]. In a 3-week interval 960–1,000 mg/m² 5FU were applied on days 1–5 and 100 mg/m² cisplatin on day 1. Two of 8 patients achieved a partial response. Major side effects were septicemia in 2 patients and an increase in serum creatinine in 3 patients attributed to chemotherapy. The most frequent side effects were nausea and vomiting [10]. Kattan et al. [11] reported 1 patient out of 3 treated men who is alive 84 months after receiving 100 mg/m² cisplatin and 200 mg/m² methotrexate for inguinal node and bone metastases (the 2 other patients showed no response).

Mitropolous et al. [12] and Skeel et al. [13] described interferon-based regimens for neoadjuvant treatment and for advanced tumor stages. The combination of interferon-alpha-2a and 13-cis-retinoic acid showed mild side effects but also low efficacy [13]. Neoadjuvant treatment consisted of cisplatin 20 mg/m² given on days 1–5 and 5×10^6 IU interferon-alpha-2b given on days 1–5 and every 2 days in weeks 2–4 in a 4-week schedule. Major side effects were anemia in 5 patients and renal impairment in 3 patients [12].

Recently described two-drug combination approaches are paclitaxel/carboplatin and cisplatin/irinotecan. Bermejo et al. [14] reported 2 patients, one partial response and one stable disease under paclitaxel 80–200 mg/m² and carboplatin AUC6 in a neoadjuvant setting. Both patients showed no evidence of disease in the follow-up after lymph node dissection (LND) (50 and 84 months). Joerger et al. [15] reported one marked regression with three cycles of paclitaxel/carboplatin (28-day schedule, paclitaxel 75 mg/m² and carboplatin AUC3 on days 1, 8 and 15). Treatment was well tolerated with only mild side effects (transient peripheral paresthesia, total alopecia). Our own experiences with this combination

concern 2 patients (one on chronic hemodialysis) in whom the treatment was effective and safe. The combination of cisplatin and irinotecan (80 mg/m² cisplatin on day 1 and 60 mg/m² irinotecan on days 1, 8 and 15) was given in an EORTC protocol [16]. The overall response rate was 30.8% with 2 patients achieving CR while the toxicity was mild. Major adverse events were grade 3 diarrhea in 3 cases and grade 4 neutropenic fever in 2 cases (of which 1 stopped treatment after pneumonia).

Polychemotherapy with Triple-Drug Regimens

The combination of cisplatin, methotrexate and bleomycin was originally described by Dexeus et al. [17]. They reported 14 patients treated with cisplatin 20 mg/m² given on days 2–6, methotrexate 200 mg/m² given on days 1 and 15 and bleomycin 10 mg/m² on days 2–6 in a 3-week schedule. With mild side effects response was seen in 10 patients including two complete responses. Haas et al. [18] re-evaluated the protocol in the biggest study on chemotherapy in penile carcinomas so far. Under a modified regimen with cisplatin 75 mg/m² given on day 1, methotrexate 25 mg/m² given on days 1, 8 and bleomycin 10 mg/m² on days 1 and 8 in a 3-week schedule, they reported 5 complete and 8 partial responses in 40 patients. Unfortunately, the side effects were much more severe in this study with a treatment-related mortality rate of 12.5%. Similarly, Hakenberg et al. [19], Corral et al. [20] and Leijte et al. [21] reported toxic deaths under the cisplatin/bleomycin/methotrexate regimen, which were due to mostly pulmonary complications (7 of 9 cases). Interstitial pneumonia was mostly bleomycin associated. Other severe complications and side effects were reported (e.g. pulmonary emboli, deep venous thrombosis and infections during neutropenia). Hakenberg et al. [19] reported grade 4 hematological toxicity in 24 of 45 applied series. Pulmonary changes and increase of serum creatinine level were found in 15 and 33% of the patients.

Another triple combination regimen was initiated by Pizzocaro and Piva [22] (vincristine 1 mg/m² given on day 1, bleomycin 15 mg/m² on days 1 and 2 and methotrexate 30–50 mg/m² given on day 3 with a 1-week interval). Three of 5 patients showed a response. Severe toxicity was also seen with this regimen including one treatment-related death caused by bleomycin-induced pneumonia with pulmonary emboli [21].

A new therapeutic approach is the combination of the cisplatin/5FU regimen with the addition of taxane. Piz-

zocaro et al. [23] demonstrated a high activity of this combination by using paclitaxel 120 mg/m² on day 1, cisplatin 50 mg/m² on days 1 and 2 and 5FU 1,000 mg/m² on days 2–5. Side effects were mild and 5/6 patients achieved response. Hematological toxicity did not exceed grade 2.

Bermejo et al. [14] reported a combination of paclitaxel 175 mg/m² on day 1 for 5 days, 20 mg/m² cisplatin and ifosfamide 1,200 mg/m² on days 1–3. Four of 5 patients received complete response followed by resection of inguinal lymph nodes. One patient showed stable disease. Two patients died of tumor progression within 23 and 30 months, another patient died of unknown causes.

Several chemotherapy combinations have been used for intra-arterial application in penile carcinoma. Roth et al. [24] reported two long-term survivors (inguinal lymph node metastasis and inguinal recurrence) after intra-aortal application of a bleomycin/methotrexate/mitomycin C combination. They reported grade III–IV hematological toxicity and cutaneous toxicity grade II–IV in 5 cases. Huang et al. [25] did not report long-term survival after intra-arterial application of cisplatin/bleomycin/methotrexate. The only patient who reached complete response relapsed with liver metastases after 8 months. Cutaneous and hematological toxicity was reported while nephrotoxicity and pulmonary toxicities were not observed.

Indications and Timing of Chemotherapy

There is an ongoing discussion about the indication and scheduling of chemotherapy in penile carcinomas. Adjuvant, neoadjuvant and palliative approaches are described in the literature as well as in the EAU guidelines.

Neoadjuvant Chemotherapy

Seven studies report the concept of chemotherapy in case of fixed inguinal lymph nodes (table 1). Results are encouraging. Pizzocaro et al. [26, 27] were able to achieve partial response in 9 of 16 treated patients followed by a complete resection of lymph node metastases. The best results were achieved with the combination cisplatin/5FU. Leijte et al. [21] reported a response in 12 of 19 patients. Several regimens were used (bleomycin, vincristine/bleomycin/methotrexate, cisplatin/5FU, cisplatin/bleomycin/methotrexate and cisplatin/irinotecan). Eight

of 9 patients resected with curative intent following neoadjuvant chemotherapy were long-term survivors. The combination cisplatin/irinotecan was given in an EORTC study in a neoadjuvant regimen [16]. They reported 1 CR and 1 PR in 7 patients. Three patients who underwent lymph node dissection after chemotherapy showed no histological evidence of residual tumor. Bejermo et al. [14] described 3 patients without histological lymph node metastases after achieving a clinically complete response in 4 patients, partial response in 1, and stable disease in 5 patients. Four patients have been without evidence of disease for 48 months. All other patients died (4 DOD). Culkin and Beer [28] combined the available literature in 2003 for cisplatin-based neoadjuvant chemotherapy and reported a clinical response in 24 of 35 patients (69%). Eight patients (23%) showed no evidence of disease in the follow-up. Additionally, Mitropoulos et al. [12] reported 13 patients who received neoadjuvant treatment with cisplatin and interferon-alpha-2b with a response rate of 75%.

Adjuvant Chemotherapy

There is very little information about adjuvant treatment concepts after radical resection of lymph node metastasis (table 2). Pizzocaro and Piva [22] reported 12 patients who were treated adjuvantly with vincristine/bleomycin/methotrexate. Only 1 of these patients showed progression. Mean remission time was 42 months. In an additional study Pizzocaro et al. [26, 27] demonstrated a 5-year survival of 82% after adjuvant chemotherapy compared to 37% in a historical control group without adjuvant treatment. Hakenberg et al. [19] reported progression in 4 of 8 patients undergoing adjuvant cisplatin/bleomycin/methotrexate treatment with 1 treatment-associated death. The mean duration of remission was 26 months.

Chemotherapy for Advanced Disease

Prognosis of patients with distant metastases is very poor. Most studies failed to show complete remission in this stage. Haas et al. [18] presented the largest group of patients treated in a phase II multi-institutional study. Under cisplatin/bleomycin/methotrexate chemotherapy 5 of 40 eligible patients achieved complete response and 8 partial response. None of the patients with distant metastases achieved complete response except one with

Table 1. Neoadjuvant chemotherapy

Regimen	Dosage	Pa-tients	Number of courses	Response (CR + PR + SD)	CR	Treatment-related deaths	Median survival, months	Reference
Cisplatin Methotrexate Bleomycin	20 mg/m ² , days 2–6 200 mg/m ² , days 1, 15, 22 10 mg/m ² , days 2–6; 4 weeks	3	9	3 SD	0	0	7	Bermejo et al. [14]
Cisplatin Methotrexate Bleomycin	20–30 mg/m ² , days 2–5 200 mg/m ² , day 1 15 mg/m ² , days 2–5; 3 weeks	10	4	6		2	NR	Leijte et al. [21]
Vinblastine Methotrexate Bleomycin	1 mg/m ² , day 1 30–50 mg/m ² , day 3 15 mg/m ² , days 1 and 2; 2 weeks	5	12	3		1	NR	Leijte et al. [21]
Vinblastine Methotrexate Bleomycin	1 mg/m ² , day 1 30–50 mg/m ² , day 3 15 mg/m ² , days 1 and 2; 2 weeks	5	12	3		0	NR	Pizzocaro et al. [22]
Paclitaxel Carboplatin	75 mg/m ² , day 1 AUC 3 days 1, 8, 15; 4 weeks	1	3	1	0	0	NR	Joerger et al. [15]
Paclitaxel Carboplatin	800–200 mg/m ² , day 1 AUC 6 day 1; 3 weeks	2		1 PR 1 SD		0	NA	Bermejo et al. [14]
Paclitaxel Cisplatin Ifosfamide	175 mg/m ² , day 1 20 mg/m ² , days 1–3 1.2 g/m ² , days 1–3; 3 weeks	5	5	4	3	0	30	Bermejo et al. [14]
Paclitaxel Cisplatin 5FU	120 mg/m ² , day 1 50 mg/m ² , days 1 and 2 1,000 mg/m ² , days 2–5; 3 weeks	3	2	3	2	0	11	Pizzocaro et al. [23]
Cisplatin Irinotecan	80 mg/m ² day 1 60 mg/m ² days 1, 8, 15; 4 weeks	7	4	2 4 SD	1	0	NR	Theodore et al. [16]

Treatment regimens and oncological results for published chemotherapy series. CR = Complete remission; PR = partial remission; SD = stable disease; NR = not reported; NA = not applicable.

Table 2. Adjuvant chemotherapy

Regimen	Dosage	Pa-tients	Number of courses	Pro-gression	Treatment-related deaths	Mean duration of remis-sion, months	Reference
Vinblastine Methotrexate Bleomycin	1 mg/m ² , day 1 30–50 mg/m ² , day 3 15 mg/m ² , days 1 and 2; 1 weeks	12	12	1	0	42	Pizzocaro et al. [22]
Cisplatin Methotrexate Bleomycin	20 mg/m ² , days 2–6 200 mg/m ² , days 1, 15, 22 10 mg/m ² , days 2–6; 4 weeks	8	6	4	1	26	Hakenberg et al. [19]

Treatment regimens and oncological results for published chemotherapy series. CR = Complete remission; PR = partial remission; SD = stable disease; NR = not reported; NA = not applicable.

Table 3. Advanced disease

Drug	Regimen	Pa- tients	Number of courses	Response (CR + PR + SD)	CR	Treatment related deaths	Median survival, months	Reference
Cisplatin Methotrexate Bleomycin	20 mg/m ² , days 2–6 200 mg/m ² , days 1, 15, 22 10 mg/m ² , days 2–6; 4 weeks	14		10	2	0	NR	Dexeus et al. [17]
Cisplatin Methotrexate Bleomycin	75 mg/m ² , day 1 25 mg/m ² , days 1 and 8 10 mg/m ² , days 1 and 8; 3 weeks	40	6	13	5	5	28	Haas et al. [18]
Cisplatin Methotrexate Bleomycin	20 mg/m ² , days 2–6 200 mg/m ² , days 1, 15, 22 10 mg/m ² , days 2–6; 4 weeks	21	4	12	4	1	32.7 (CR) 15.8 (PR)	Corral et al. [20]
Cisplatin Methotrexate Bleomycin	20 mg/m ² , days 2–6 200 mg/m ² , days 1, 15, 22 10 mg/m ² , days 2–6; 4 weeks	5	6	5 SD	0	1	17.9	Hakenberg et al. [19]
Cisplatin Methotrexate Bleomycin	20 mg/m ² , days 1–5 200 mg/m ² , days 1, 15, 22 10 mg/m ² , days 1–5; 4 weeks	3	4	1 SD	0	0	6	Kattan et al. [11]
Cisplatin 5FU	100 mg/m ² , day 1 960 mg/m ² , days 2–5	5	4	5	0	0	15	Hussein et al. [9]
Cisplatin 5FU	100 mg/m ² , day 1 1,000 mg/m ² , days 2–5	8		2	0	0	NR	Shammas et al. [10]
Cisplatin 5FU	100 mg/m ² , day 1 1,000 mg/m ² , days 2–5	4	5	1	0	0	5	Kattan et al. [11]
Cisplatin 5FU Paclitaxel	50 mg/m ² , days 1 and 2 1,000 mg/m ² , days 2–5 120 mg/m ² , day 1	3	5	2	1	0	NA	Pizzocaro et al. [23]
Cisplatin Irinotecan	80 mg/m ² day 1 60 mg/m ² day 1, 8, 15; 4 weeks	21	4	6 4 SD	1	0	NR	Theodore et al. [16]

Treatment regimens and oncological results for published chemotherapy series. CR = Complete remission; PR = partial remission; SD = stable disease; NR = not reported; NA = not applicable.

retroperitoneal lymph node metastases. Only 2 patients with pulmonary metastases achieved partial response. The median duration of response was 16 weeks and estimated median progression-free survival 14 weeks. 36 patients died (31 deaths of disease, 5 treatment-associated deaths). In another phase II trial Corral et al. [20] reported 21 patients with penile carcinoma within a group of 30 patients with different squamous cell carcinoma entities. Four of 21 patients achieved complete response (1 patient with distant metastases) while another 8 patients showed partial response. Median response duration for the CR group was 20.9 months and in the PR group 3.8 months. All patients died of disease (me-

dian survival for CR 32.7, PR 15.8 and for nonresponders 6.7 months).

Hakenberg et al. [19] reported a subgroup of 5 patients with M1 disease. All 5 patients showed stable disease under cisplatin/bleomycin/methotrexate chemotherapy (3 patients with minor response). However, all patients progressed and died of disease after a mean interval of 5 months. Pizzocaro et al. [23] reported 3 patients treated with paclitaxel/cisplatin/5FU for recurrence after initial inguinal lymph node dissection. One patient suffered progression while the remaining 2 patients showed nearly complete response. Both are alive after resection of the remaining tumor (one histologically without tumor). The

activity of cisplatin/5FU combination was demonstrated by Hussein et al. [9] in 5 cases of advanced penile carcinomas. All patients showed partial response but died of disease after a median survival of 15 months (6–20 months). The activity of the combination cisplatin/irinotecan was proved for patients with advanced disease in a recent EORTC trial. The overall response rate was 31.6% with 1 CR and 5 PR in 19 included patients [21].

Discussion

The prognosis of patients with metastasized penile carcinomas is extremely poor. Due to the small number of patients with advanced penile carcinomas in North America and Western Europe there are only few and small studies about effective chemotherapy options for these patients. Most reports are single-center experiences with low numbers of patients. Only a few phase II studies show biological activity of different drugs and regimens resulting mostly in partial responses, while long-term survival is very poor under the current regimens.

The best results were shown for neoadjuvant and adjuvant strategies. Encouraging reports about long-term survivors after neoadjuvant chemotherapy followed by inguinal lymph node dissection of previously fixed lymph nodes make this concept reasonable. Thus, a neoadjuvant treatment for all patients with suspected lymph node metastases should be discussed. This could probably be followed by additional (adjuvant) chemotherapy in case of histologically positive inguinal lymph nodes.

Experiences concerning adjuvant treatment compared with historical control groups without chemotherapy demonstrated a clear indication for the adjuvant concept. Interestingly, no patient with N1 status after inguinal node dissection showed progression independent of whether adjuvant treatment was given. Therefore, adjuvant treatment in N1 patients is not recommended by the EAU guidelines.

The relatively large number of patients with progression after adjuvant chemotherapy highlights the major problem of chemotherapy in penile cancer. The biological activity of the current regimens has no long-term effect in many cases. Furthermore, it is associated with high toxicity leading to dose reduction and incomplete application of regimens. This is especially obvious for patients with advanced disease. Haas et al. [18] reported a 13% toxicity-related mortality with only 10% long-term survivors. Of 66 patients reported in literature only 11 patients reached complete response including only 1 patient with

distant metastases. Only Haas et al. [18] and Dexeus et al. [17] reported long-term survivors after chemotherapy for lymph node metastases.

Adverse effects of the current chemotherapy regimens are serious. Hakenberg et al. [19] reported hematological toxicity grade 4 in 24 of 45 series. Especially pulmonary toxicity with a remarkable number of treatment-associated deaths and nephrotoxicity make the actual regimens not feasible for older patients [20]. This is an important concern since the highest incidence of penile cancer is found in the 6th and 7th decades.

The EORTC trial was focused on the prevention of adverse effects by the use of the better-tolerated irinotecan instead of bleomycin/methotrexate. The efficacy of this combination was comparable to previous regimens with lower toxicities [16].

With recent developments in chemotherapy for squamous cell carcinoma of other origins (e.g. HNSCC and cervical cancer) showing positive results for taxane treatment [29, 30], the addition of taxanes to regimens in penile carcinoma seems reasonable. The first reports about paclitaxel in penile carcinomas are encouraging [14, 15, 23]. Especially the studies of Bermejo et al. [14] and Pizzocaro et al. [23] demonstrated a high biological activity with moderate side effect. Furthermore, current developments in chemoradiation and monoclonal antibody treatment in HNSCC need to be discussed in the following years concerning their possible value in penile carcinoma.

Conclusions

Current chemotherapy in penile carcinomas is characterized by high toxicities and poor prognosis of metastasized patients. Recent studies show promising results for new combinations of irinotecan and cisplatin and high efficacy of taxane-based combinations. Neoadjuvant treatment should be given in all cases of fixed lymph node metastasis and possibly for all patients with suspected lymph nodes metastasis. Adjuvant treatment should be proven with new regimens, which might also be able to improve the poor prognosis of patients with distant metastasis.

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