Chemotherapy in penile cancer

Oliver W. Hakenberg and Chris Protzel

Abstract: Penile cancer is an aggressive disease and after systemic progression it is virtually incurable. While this squamous cell cancer responds to chemotherapy, successful treatment of lymphatic metastases can only be achieved with aggressive surgical treatment in combination with chemotherapy. However, because penile carcinoma is relatively rare there is a paucity of clinical data on the chemotherapy for this aggressive disease. Recent advances have included the establishment of less toxic regimens incorporating taxanes, while cisplatin remains central to all regimens. Multi-institutional studies are urgently needed to advance the multimodal care for patients with penile cancer.

Keywords: penis, neoplasm, penile cancer, lymph node, metastasis, chemotherapy

Penile cancer is an aggressive disease and successful curative local treatment can usually only be achieved at an early stage. Successful treatment of advanced penile carcinoma with regional and systemic metastases remains a grave problem in uro-oncology. In regional lymphatic metastatic disease combined chemotherapy with aggressive surgical treatment may be effective but the rate of local recurrence with further progression is high. In systemic disease chemotherapy remains the only option.

Unfortunately current chemotherapy regimens are unable to cure advanced penile carcinoma. Most of the traditional regimens described are based on data from the late 1990s and are characterized by low response rates and high toxicity [Protzel and Hakenberg, 2009]. Furthermore, due to a lack of clinical data, most patients requiring systemic chemotherapy are treated with very individual chemotherapy regimens since most urologists and medical oncologists have very little experience with penile cancer and consider systemic penile carcinoma incurable. This unfortunate situation in combination with the relatively low incidence of penile cancer leads to therapeutic nihilism and prevents the accumulation of data that might help to improve patient outcome. The results of a nationwide survey on chemotherapy in penile cancer among German urology departments show 18 different chemotherapy regimens were in use for the treatment of systemic penile carcinoma [Protzel *et al.* 2009]. To improve the situation, first, clinical data

need to be collected more comprehensively and multidisciplinary clinical studies are required. Second, the focus of research needs to be a better understanding of the basic pathophysiology of penile cancer. Although no definite results have been achieved so far, several groups are working on penile carcinoma and have focused on this seemingly forgotten malignancy.

Pathology and tumour biology of penile carcinoma

Most penile malignancies are squamous cell carcinomas (SCCs). However, SCC of the penis represents a heterogenous group of histopathological entities which differ in terms of morphology, pathogenesis and prognosis.

The most frequent subtype of penile SCC is the 'conventional' SCC. Other, less common subtypes are the basaloid, verrucous, papillary, condylomatous and sarcomatoid subtypes. These differ in their apparent aetiology: while only 30–50% of conventional penile SCC subtypes are associated with human papilloma virus (HPV), almost all basaloid penile SCCs are associated with HPV [Rubin *et al.* 2001]. Also, some studies have shown different regulations of gene expression in different penile SCC subtypes, which may explain their different biological behaviour [Poetsch *et al.* 2011].

Clinically, the different subtypes carry a different prognosis. The verrucous and condylomatous

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variants rarely metastasize, while systemic spread is common with the basaloid and sarcomatoid subtypes. The systemic progression of penile cancer is clinically characterized by local lymphatic spread to the regional lymph nodes situated in the inguinal region and the superficial inguinal lymph nodes are the first points of spread. The exact pathomechanisms of the development of metastases are not completely understood. Some penile SCCs show an early tendency for metastatic spread even at the T1 stage, while other more locally advanced penile SCCs behave more indolently and do not spread. Vascular and lymphovascular invasion of the primary tumour seen histologically is associated with lymphatic spread and seems to play an important role in the development of metastases. Consequently, both factors – microvascular and lymphovascular invasion – have been incorporated into the new TNM classification of the Union for International Cancer Control for subtyping stage T1 penile carcinoma into T1a and T1b.

The possibility of micrometastatic lymphatic disease in clinically normal inguinal regions even with early local tumour stages has led to the recommendation for invasive lymph node staging for every stage T1b or higher penile carcinoma [Pizzocaro *et al.* 2009]. In cases of regional lymphatic spread of penile cancer, whether clinically apparent or not, complete resection of the primary tumour and all lymph node metastases is paramount to any chance of achieving cure. Clinically advanced regional lymph node metastases with large and perhaps fixed inguinal lymph nodes, recently characterized as N3 stage, have a very high tendency for local recurrence and systemic progression after surgical treatment. In these cases, neoadjuvant chemotherapy administration has recently been proposed as a new therapeutic strategy. However, the chemotherapy regimens used for adjuvant, neoadjuvant and palliative strategies remain under constant discussion and are the focus of this paper.

Chemotherapeutic agents and regimens for penile cancer

The antitumour activity of single agents against penile cancers was first reported in the early 1970s for cisplatin, bleomycin and methotrexate. The observed response rates were low at 0–27% and major side effects were reported, especially for bleomycin due to pulmonary toxicity [Protzel and Hakenberg, 2009; Ahmed

et al. 1984; Maiche, 1983; Sklaroff and Yagoda, 1979, 1980]. Only one singular case of complete remission under high-dose methotrexate treatment was reported [Garnick *et al.* 1979].

Thus, to improve the poor response rates several combination chemotherapy regimens were tried, usually consisting of double or triple drug regimens [Protzel and Hakenberg, 2009]. The first report of these was by Shamma and colleagues who used 1000 mg/m² 5-fluorouracil (5-FU) and 100 mg/m² cisplatin in a 3-week regimen and achieved a partial response in two out of eight treated cases [Shamma *et al.* 1992]. The reported major side effects were septicaemia and deterioration of renal function, with nausea and vomiting also occurring frequently.

It soon became evident that cisplatin is an important and at least moderately effective chemotherapeutic agent in penile SCC. Cisplatin was thus combined with several other drugs in several smaller studies and case reports. Kattan and colleagues reported one complete response after combined cisplatin (100 mg/m²) and methotrexate (200 mg/m²) treatment in three treated patients [Kattan *et al.* 1993]. The neoadjuvant approach was used with cisplatin in combination with interferon α 2a, with nine of 13 patients achieving a response [Mitropoulos *et al.* 1994]. In another study, cisplatin (80 mg/m²) in combination with irinotecan (60 mg/m²) was used in an European Organisation for Research and Treatment of Cancer (EORTC) protocol [Theodore *et al.* 2008]. In this study, an overall response rate of 30.8% was reported with two patients achieving a complete response. Major side effects were grade 3 diarrhoea and grade 4 neutropenic fever.

As taxane-based chemotherapy regimens have been successfully used in SCCs of different origins, combinations incorporating paclitaxel have been used to treat patients with penile cancer from the early 2000s. A paclitaxel/carboplatin combination has been used experimentally by two groups. Bermejo and colleagues used the neoadjuvant approach in two patients and reported long-term survival after chemotherapy followed by lymph node dissection (50 *versus* 84 months) [Bermejo *et al.* 2007]. Joerger and colleagues reported a 'significant' remission in one patient with advanced disease after three cycles of paclitaxel/carboplatin (75 mg/m² paclitaxel, area under the curve [AUC] 3 carboplatin) [Joerger *et al.* 2004]. Both studies reported that treatment was well tolerated.

The first triple drug regimen was described by Pizzocaro and colleagues [Pizzocaro and Piva, 1988]. They used vincristine 1 mg/m², bleomycin 15 mg/m² and methotrexate 30 mg/m² in a weekly schedule over 12 weeks in a neoadjuvant setting. Three out of five patients achieved a partial response but with severe toxicity, with two of five patients developing pulmonary fibrosis leading to cessation of treatment. In a similar study, one treatment-related death was reported due to pulmonary embolism and pneumonia [Leijte *et al.* 2007].

In 1991 Dexeus and colleagues reported their triple drug chemotherapy regimen, which soon was to become an apparent standard for penile cancer [Dexeus *et al.* 1991]. They used cisplatin (20 mg/m² day 2–6) methotrexate (200 mg/m² day 1 and 15) and bleomycin (10 mg/m² day 2–6) and reported a response in 10 of 14 study patients, with moderate reported side effects. These favourable results led to a fairly widespread use of the ‘Dexeus regimen’. However, the originally reported good results were never confirmed in subsequent studies. On the contrary, other groups reported poorer results and much higher toxicity. In the largest chemotherapy study of penile cancer reported so far, Haas and colleagues using the Dexeus regimen reported five complete and eight partial responses in 40 treated patients, including severe toxicity and five treatment-related deaths [Haas *et al.* 1999]. A similar picture of moderate efficacy with high toxicity and treatment-related deaths was reported in other studies [Hakenberg *et al.* 2006; Corral *et al.* 1998; Leijte *et al.* 2007]. Therefore it was evident that the Dexeus regimen could no longer be regarded as a standard, especially in view of the high toxicity mostly related to bleomycin-induced pulmonary side effects.

New regimens were tried. Pizzocaro and colleagues combined cisplatin with 5-FU and paclitaxel and reported a high activity of this regimen, with five out of six treated patients showing a response [Pizzocaro *et al.* 2009]. The reported side effects of this triple drug regimen (120 mg/m² paclitaxel on day 1, 50 mg/m² cisplatin on days 1 and 2, 1000 mg/m² 5-FU on days 2–5) were moderate, not exceeding grade 2 in severity. More recently, the combination of paclitaxel, cisplatin and ifosfamide has been reported by two groups. Bermejo and colleagues reported a response in four out of five treated patients [Bermejo *et al.* 2007]. Pagliaro and colleagues reported a response with 175 mg/m² paclitaxel

on day 1, 25 mg/m² cisplatin on days 1–3 and 1200 mg/m² 5-FU on days 1–3 for 15 out of 30 patients in a neoadjuvant study [Pagliaro *et al.* 2010]. The neoadjuvant treatment was followed by complete resection of the remaining metastases.

The above findings illustrate the dilemma of research into penile cancer chemotherapy. First, penile cancer as an SCC is usually an aggressive tumour showing limited response to chemotherapy. Second, due to the relatively low incidence of penile cancer and the wide distribution over many treating institutions, there are only a few centres that can accumulate a sufficient number of patients for a study. Available data on chemotherapy in penile cancer are therefore lacking and progress is limited and extremely slow. Centralisation of patients with penile carcinoma to a few centres, as has been done in the UK and is virtually the case in the Netherlands, may be a way to help pool results. However, so far, this has not improved the situation for penile cancer chemotherapy.

What are the valid indications for chemotherapy in penile cancer?

Due to the paucity of data on penile cancer chemotherapy, evidence-based recommendations in current guidelines are scarce. However, in patients with metastatic disease, chemotherapy is undoubtedly the only possible effective treatment. Therefore, chemotherapy is recommended unless treatment is restricted to best supportive care. There are four chemotherapeutic settings which apply to penile carcinoma in the same way as other malignancies: adjuvant, neoadjuvant, therapeutic and palliative.

Adjuvant chemotherapy

The adjuvant setting refers to chemotherapy after complete surgical treatment of the local disease and inguinal lymph node metastases. This treatment is indicated after removal of affected lymph nodes and is recommended by the current European Association of Urology guidelines for lymph node disease of stage N2 (palpable, mobile and multiple lymph nodes, uni- or bilateral). The basis for this recommendation is one retrospective study comparing patients with surgically removed inguinal lymph node metastases who had adjuvant chemotherapy (vincristine, methotrexate, bleomycin) with a historic control group who did not have adjuvant chemotherapy. This study of 12 patients reported a 5-year survival

rate of 82% with adjuvant chemotherapy compared with 37% in the historic control group [Pizzocaro *et al.* 1997]. Also, none of the stage N1 patients (palpable, mobile unilateral lymph node metastases) developed progressive disease in the adjuvant treatment cohort. This finding indicates that adjuvant chemotherapy should be given to all patients after surgical removal of metastatic inguinal nodes. Although the evidence for this recommendation is sparse, we believe that it is beneficial and so it is our current practice to perform this treatment.

Pizzocaro and colleagues also reported 12 patients who underwent adjuvant vincristine/bleomycin/methotrexate combination treatment, with only one patient developing a recurrence [Pizzocaro *et al.* 1988]. Hakenberg and colleagues reported that in a group of eight patients who had adjuvant cisplatin/bleomycin/methotrexate combination treatment, only four patients remained free of recurrence and one patient died as a result of drug toxicity [Hakenberg *et al.* 2006]. At present, there is a clear recommendation that adjuvant chemotherapy is effective and beneficial after inguinal lymphadenectomy, however there is no evidence as to which, if any, chemotherapy regimen is best in this setting.

Neoadjuvant chemotherapy

For patients with palpable lymph nodes and especially with large, immobile inguinal nodal metastases, recent studies have shown promising results for neoadjuvant chemotherapy followed by surgical node dissection. In a retrospective analysis, 12 out of 19 patients receiving neoadjuvant chemotherapy with different regimens (vincristine/bleomycin/methotrexate, cisplatin/bleomycin/methotrexate, cisplatin/5-FU or cisplatin/irinotecan) were reported to show a response and eight of these patients achieved long-term survival after subsequent resection of the inguinal lymph node metastases [Leijte *et al.* 2007]. Bermejo and colleagues reported a complete response in four out of five patients receiving neoadjuvant treatment with paclitaxel/cisplatin/ifosfamide, three of whom had a histologically proven complete response [Bermejo *et al.* 2007]. Similarly promising data with the same neoadjuvant regimen were reported by Pagliaro and colleagues, with 15 of 30 patients achieving a response and nine patients long-term survival [Pagliaro *et al.* 2010]. Pizzocaro and colleagues used a neoadjuvant regimen of paclitaxel/cisplatin and 5-FU and reported a response in

all three patients treated [Pizzocaro *et al.* 2009]. Therefore, a clear recommendation for patients with penile carcinoma and fixed inguinal lymph node metastases (N3) is that neoadjuvant chemotherapy followed by lymph node dissection should be given to patients whose disease responds to treatment. There is also likely to be a benefit in patients with N2 disease but data are lacking. Again, while the principle seems to be established, it is unclear which if any of the possible chemotherapy regimens is most suitable, how many cycles should be given and what the time interval should be between chemotherapy and surgery. Data about the relative rate of complications in patients undergoing inguinal lymphadenectomy with or without neoadjuvant chemotherapy are also lacking.

Therapeutic and palliative chemotherapy in advanced penile cancer

The results for chemotherapy in advanced penile cancer with systemic metastases are very poor. There is at best only a minimal chance for curative treatment in patients with non-resectable lymph node metastases or systemic disease, including lymph node recurrence after surgical treatment. Haas and colleagues reported complete remission in only five out of 40 patients with advanced penile cancer disease and none of these five patients had distant metastases [Haas *et al.* 1999]. In the same series, only two of the patients with distant metastases showed a partial response, and altogether, 36 of the 40 patients died. Hakenberg and colleagues reported five patients with M1 disease treated with the Dexeus regimen (cisplatin/bleomycin/methotrexate) with only minimal response. All patients died of the disease with a median survival of 5 months after chemotherapy [Hakenberg *et al.* 2006]. The use of taxane-based regimens may improve on these poor results in the future. Pizzocaro and colleagues reported a partial response in two out of three patients with regional recurrence after inguinal lymphadenectomy [Pizzocaro *et al.* 2009]. Some of the newer drugs (targeted therapies) have reportedly been used in a few patients with advanced penile cancer disease [Zhu *et al.* 2010; Necchi *et al.* 2011]. In one case report, panitumumab used as a second-line treatment was reported to show a relevant response [Necchi *et al.* 2011].

Second-line treatment

There are again virtually no data on second-line strategies for the systemic treatment of penile

cancer. Recently, Di Lorenzo and colleagues reported the results of a phase II trial of 25 patients with progression after pretreatment with different chemotherapy regimens treated with a single agent paclitaxel [Di Lorenzo *et al.* 2011]. They observed a response in five of 25 patients, with grade 4 neutropenia reported in seven patients and a median progression-free survival of 11 weeks (median overall survival 23 weeks).

Because patients with progression do not survive long term there are no data and most clinical investigators are concerned with looking at effective first-line treatment. However, studies on second-line treatment are also needed in view of the often low response rate of first-line regimens.

Conclusions

The field of penile cancer treatment remains difficult due to the paucity of data and the aggressive nature of penile SCC. Multiple drug regimens must be used. Previous regimens with cisplatin/bleomycin/methotrexate or vincristine/bleomycin/methotrexate are increasingly being abandoned because their high toxicity profile makes them unsuitable for older patients. The newer taxane-based regimens have shown promising results in recent studies, with equal or better efficacy and lower toxicity. Neoadjuvant treatment for patients with advanced inguinal lymph node metastases (N3) is recommended and can result in long-term survival after surgical resection of the residual tumour. Systemic penile cancer remains incurable. Some response with prolongation of survival may be achieved with chemotherapy. In these patients, the potential benefit to be gained by the use of chemotherapy must be weighed against the remaining quality of life.

The main problem remains a lack of data. Thus, it would be extremely helpful if all patients with penile cancer requiring chemotherapy are treated under study protocols, which are urgently needed to improve results.

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