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Retrospective Review of Chemotherapy Treatment for Locally Advanced and Metastatic Penile Cancer in the North West of England

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Authors' contributions

This work was carried out in collaboration between all authors. Author TE initiated the project, author AB designed the data collection proforma and authors JC, AB and QM carried out all data collection. Authors JC and AB collated and analyzed the data with input from authors HI and TE. Author JC wrote the first draft of the manuscript and carried out literature searches. Authors TE, HI and AB assisted in editing the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Aims: To examine current practices in the UK in the use of chemotherapy in advanced penile cancer and investigate the treatment outcomes of this group of patients.
Study Design: Retrospective series.
Place and Duration of Study: The study population received chemotherapy at Clatterbridge Cancer Centre, The Christie Hospital or Lancashire Teaching Hospital between January 1999 and January 2009.
Methodology: Patients undergoing chemotherapy for histologically confirmed squamous cell carcinoma of the penis within the designated time period were identified retrospectively.
Through case note review, data were collected on chemotherapy regimens, tolerability, response to treatment and survival. Response to chemotherapy was categorized by the investigators

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according to RECIST (version 1.0) criteria.
Chemotherapy given concurrently with radiotherapy was excluded.
Results: 40 patients were treated with chemotherapy for locally advanced or metastatic penile cancer. Prior to the inception of a Supra-regional Multidisciplinary Team (SMDT), seven different chemotherapy regimens were used first line. After introduction of the SMDT Cisplatin/5-Fluoruracil (5FU) was almost exclusively prescribed outside of clinical trials.
12/40 (30%) patients completed the planned course of chemotherapy. 27/40 (67%) discontinued treatment prematurely, 14/40 (35%) due to progressive disease, and 13/40 (32%) due to declining performance status and/or toxicity.
Response to chemotherapy was assessed radiologically in 23/40 patients and categorised by the investigators according to RECIST criteria. There were three complete responses and eight partial responses (objective response rate 28%). Median survival was 15 months from diagnosis and 5 months from commencing first line chemotherapy.
Conclusion: This supra-regional collaboration highlighted varying use of chemotherapy historically in penile cancer. Development of a supra-regional MDT has reduced much of the variability. Response rates are modest and survival outcomes are poor. This reinforces the urgent need for clinical trials to establish a framework for novel, more active regimens and to guide patient selection.

Keywords: Chemotherapy; palliative; penile cancer; retrospective series.

1. INTRODUCTION

Penile cancer is rare in Western countries, with a UK incidence of approximately 1 in 100,000 [1]. Early stage disease is treated primarily with surgery or radiotherapy. Although only a small proportion of patients will present with distant metastases (around 3%), up to a third will have locally advanced disease [2] and around 30% of patients will have recurrent disease after surgery [3]. This risk is much increased if there are bilateral or multiple inguinal lymph node metastases with five year cancer specific survival falling from approximately 80% for N1 disease to 50% in N2 disease. Fixed inguinal nodes and pelvic lymphadenopathy carry a significantly worse prognosis [4].

There is evidence from phase II trials that penile cancer has some degree of chemosensitivity. However, given the rarity of penile cancer the optimal drug regimen and timing of chemotherapy is not established. Practice is therefore varied and based on small, largely retrospective studies.

This heterogeneity was illustrated in a retrospective survey of urology departments in Germany which included 150 patients with penile cancer treated with chemotherapy. On average chemotherapy was used for penile cancer 2.3 times per year per department and 18 different chemotherapy regimens were used. Reported response rates were under 30% overall [5].

The aim of this study was to examine current UK practices in the use of chemotherapy in advanced penile cancer. It was conducted across three large regional cancer centres in the North West of England: The Christie Hospital, Clatterbridge Cancer Centre and The Royal Preston Hospital. Together these hospitals serve a population of 7.1 million.

2. METHODOLOGY

Patients undergoing palliative chemotherapy for advanced squamous cell carcinoma of the penis ie. TNM 7th edition stages IIIb-IV (any T4, N2/3 or M1 disease) between 1999 and 2009 were identified retrospectively using hospital coding systems through computer records at each of the three centres. Data were collected on patient demographics, stage of cancer at presentation, timing of chemotherapy, regimens used, tolerability, response to treatment and survival. The reasons for stopping chemotherapy and mode of assessment of response were recorded. Where possible, radiological response was categorised from original radiological reports by the investigators according to RECIST (version 1.0) criteria. Where radiological assessment was not performed response was categorised into clinical response, clinical progression or not assessable.

Chemotherapy given concurrently with radiotherapy was excluded.

3. RESULTS AND DISCUSSION

3.1 Results

3.1.1 Patients and chemotherapy

40 patients were treated with chemotherapy for locally advanced or metastatic penile cancer over the ten year period and were eligible for inclusion. Mean age of the patients was 55 years (range: 34-71). 5/40 were still alive at the time of completion of the study. 29 patients had chemotherapy following prior surgical management of their primary with or without lymph node dissections and five patients underwent surgery post-chemotherapy (Table 1). Six patients presented with advanced metastatic disease and did not undergo an operation.

Seven different chemotherapy regimens were used in the first line setting. Cisplatin/5FU was the most commonly used first line regimen at a dose of cisplatin 80 mg/m^2 day 1 and 5FU 1000 mg/m^2 on days 1-4 of a 21 day cycle. Four patients received second line chemotherapy, and one patient received third line chemotherapy (Table 2). Prior to 2006 there was no formal sub-specialisation in non-surgical penile cancer management in the North West of England. In 2006 a pathway of referral to three penile cancer site- specialised oncologists in Merseyside, Manchester and Preston was instituted. Following the development of this supraregional MDT, consistency of treatment increased and cisplatin/5-FU was almost exclusively prescribed outside of clinical trials.

Table 1. Characteristics of patients

Age of patients: mean/ (range)	**55 years (34-71)**
Grade of tumour: No of patients/ (%)	
1	2 (5)
2	8 (20)
3	16 (40)
Unknown	14 (35)
Stage at initial diagnosis: No. of patients (TNM 7th Edition)	
I	0
II	7
IIIa	2
IIIb	7
IV :	
(T4 or N3M0)	16
(TxNxM1)	3
Unknown	5
Stage at start of chemotherapy: No. of patients	
IIIa	0
IIIb	2
IV :	
(TxN3M0)	19
(TxNxM1)	16
Unknown	3
Performance status prior to chemotherapy: No. of patients (%)	
0	7 (17.5)
1	24 (60.0)
2	5 (12.5)
3	4 (10.0)
Other treatments received: No. of patients	
Surgery to primary +/- nodes upfront	29
Surgery after chemotherapy	5
Radiotherapy	15
Chemoradiation prior to chemotherapy	5
Radical chemoradiation after chemotherapy	1

Table 2. Chemotherapy regimens used

Regimen	Number of patients
First line chemotherapy	
Cisplatin/5FU	26
Docetaxel/Cisplatin/5FU (TPF)	4
Cisplatin/Methotrexate	4
Carboplatin/Gemcitabine	2
Cisplatin/Capecitabine	2
Carboplatin/Paclitaxel	1
Capecitabine	1
Second line chemotherapy	
Carboplatin/Paclitaxel	2
Gemcitabine	1
5FU/Mitomycin	1
Third line chemotherapy	
Weekly Paclitaxel	1

3.1.2 Toxicity

12 of 40 patients (30%) completed the planned course of first line chemotherapy. 14/40 (35%) patients discontinued treatment early due to progressive disease whilst 13/40 (42%) stopped due to early fall in performance status (PS) or toxicity (Fig. 1). One patient died on cycle 1, day 2 of cisplatin/5FU with acute pulmonary oedema.

Seven patients required dose reductions and three needed regimen alterations. 15 patients required 19 hospital admissions during treatment including five brief admissions for electrolyte correction or blood transfusion in addition to potentially more serious indications such as renal failure secondary to cisplatin (three patients), indwelling venous line complications and non-neutropenic infections. There were no cases of febrile neutropenia. Common grade 1-2 toxicities (NCI CTC V3.0) included nausea, constipation and oral mucositis.

3.1.3 Response

Response to first line chemotherapy was assessed radiologically in 23/40 patients. There were three complete responses (CR) and eight partial responses (PR) resulting in an objective response rate (RR) of 48% of those radiologically evaluated (11/23). However the main reason for patients not having formal radiological evaluation was clear clinical progression, therefore a more accurate reflection of response is 28% (11/40). Of the three patients who achieved CR one has died of progressive disease and the other two are alive with recurrence 34 and 45 months after commencing chemotherapy.

Of patients treated with chemotherapy for stage IV disease, those with distant metastases (M1) experienced significantly worse overall survival than those with locally advanced (N3M0) disease; median survival from starting chemotherapy four months compared with 12 months (Fig. 2). Only one of 16 patients with distant metastases (M1 disease) had an objective response to first line chemotherapy.

All chemotherapy was given with palliative intent. However, five patients with stage IV disease (T4 or N3 but M0) who responded well (1 CR, 4 PR) to chemotherapy did proceed to surgery. Two of these five are alive 29 and 45 months from the start of chemotherapy, respectively. The other three patients died of recurrent disease. The median survival for these patients was 16 months.

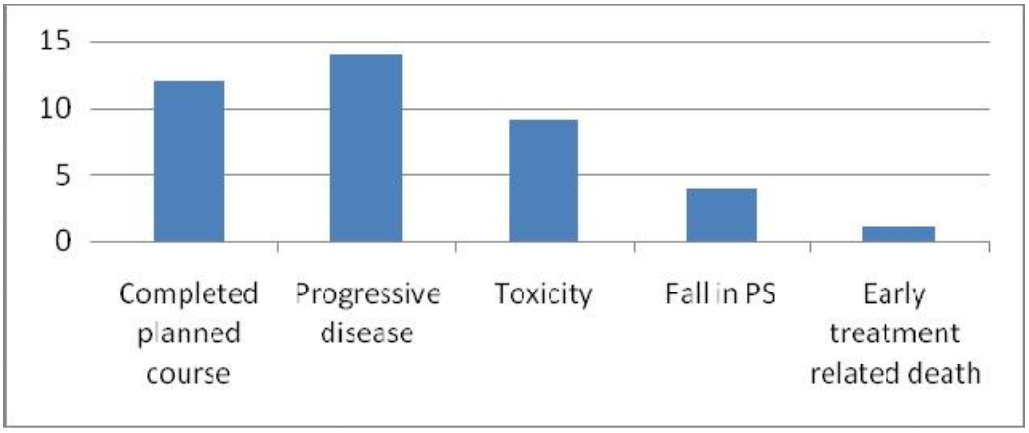

Fig. 1. Reasons for stopping chemotherapy

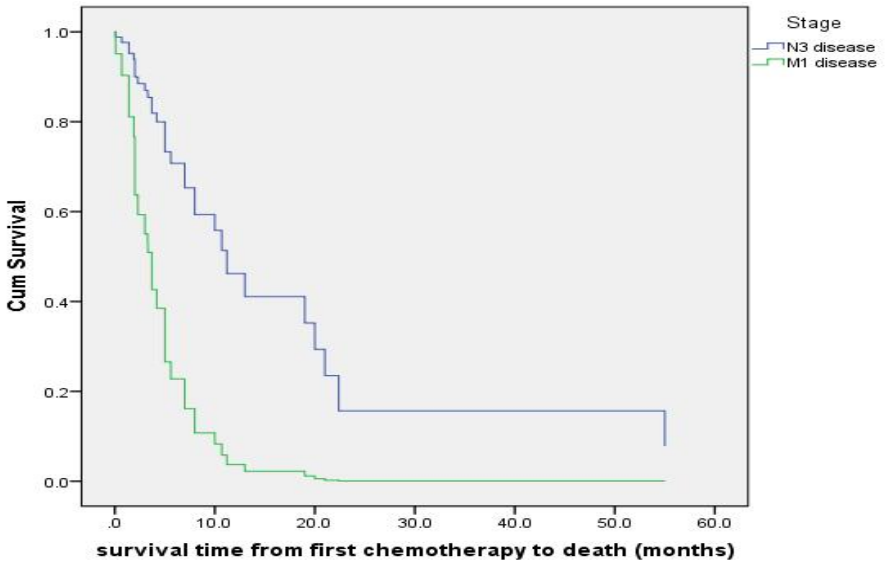

Fig. 2. Survival curves for patients with stage IV disease from commencement of first line chemotherapy; for those with N3M0 disease compared with M1 disease

3.2 Discussion

This study documents the chemotherapeutic management and outcomes of 40 patients with advanced penile cancer over a ten year period and represents the largest series of such patients in the UK. Almost all patients received a platinum-based regimen, most commonly cisplatin/5FU. The introduction of the SMDT in 2006 has substantially reduced the number of doctors involved in chemotherapy delivery and the variation in regimens used.

This data is subject to the limitations of a retrospective casenote analysis and data relating to treatment-related toxicity may be underestimated.

Radiological response was evaluated in only 58% of the patients. This was due to various factors including deterioration in performance status, rapid disease progression or morbidity due to toxicity of treatment.

The number of patients in this series is lower than anticipated from incidence data. The most likely explanation is patient selection; many patients with advanced penile carcinoma are elderly and have significant comorbidities that preclude chemotherapy. The low mean age of this cohort supports this premise.

3.2.1 Toxicity and patient selection

Less than a third of patients (12/40) completed their planned course of chemotherapy with chemotherapy-related toxicity contributing substantially to this failure.

A greater proportion of those receiving cisplatin/5FU (11/26) were able to complete the course. Over a third of patients (15/40) required hospital admission during their treatment. Some of these admissions were for blood transfusion or correction of hypomagnesaemia (three patients) and three were for complications due to indwelling lines. However, other more serious reasons for admission included renal failure, non-neutropenic infections and ‘general deterioration’. How much of this early cessation is truly toxicity and how much is due to progressive disease in these patients is difficult to define. Nevertheless, this admission rate is higher than anticipated for a group of patients receiving predominantly cisplatin/5FU. Approximately a quarter of these patients had ECOG performance status 2 or lower and were less likely to complete the planned treatment (11% compared to 35% of patients PS0-1) and required more hospital admissions. Patients who had distant metastases (M1 disease) also stopped therapy more frequently than patients with advanced nodal disease (50% of patients compared with 21%, respectively) and also required more hospital admissions.

3.2.2 Response to chemotherapy

Our estimated radiological RR of 28% using platinum-based regimens is similar to that reported in other series [5,6,7]. Three patients with N2/3 disease achieved CR and two remain alive, albeit with disease, 45 months and 34 after commencing chemotherapy. This demonstrates that selected patients may do well following systemic therapy. Unfortunately, however there are presently no predictive biomarkers to inform better patient selection. Until such markers are identified, patients destined to do poorly with chemotherapy will continue to receive this treatment.

There was a marked difference in response between those with advanced nodal disease (10/24) compared with those with distant metastases (1/16). The median survival for the group with distant metastases was only four months. There is an urgent unmet need for alternative, improved treatment options for this group of patients. On the basis of these data it could be argued that, with the significantly increased toxicity rates, platinum-based chemotherapy should not be routinely given to patients with M1 disease outside of clinical trials, but rather only be offered to those with very good performance status.

3.2.3 Selection of chemotherapy regimen

The majority of patients treated in the North West in the last decade received cisplatin/5FU, with all but one patient receiving an alternative platinum-based regimen. This is in line with other published studies.

Single agent activity has been demonstrated with bleomycin [8,9], methotrexate [10,11] and cisplatin [11,12,13]. However, most studies have focussed on combination regimens. Cisplatin/5FU has shown some success. However, the trials are small, each involving fewer than ten patients. Fisher et al. [14] described two CRs and two PRs in five patients treated with cisplatin/5FU. Hussein et al. [15] similarly treated six patients achieving one CR and two PRs. All six patients proceeded to surgery or radiotherapy. However, all patients experienced progressive disease with a median overall survival of 16 months. A further study of the same drug combination in eight patients with advanced disease reported a lower RR of only 25% [6].

Our data, in a much larger series, support these findings with an overall RR with cisplatin/5FU of approximately 35% (9 radiological PR or CR of 26 patients treated).

Cisplatin with irinotecan has been studied also with a similar RR (30.8%) [7].

There have been several studies of triplet chemotherapy. Dexeus et al. [16] achieved an impressive objective RR in 10 of 14 patients treated with the combination of cisplatin, methotrexate and bleomycin, as did Corral et al. (response rate 55%) [17]. This same combination was the subject of the largest published trial to date in penile cancer, the prospective SWOG multicentre trial achieved a response rate of 32.5% in 40 patients treated. However the toxicity was unacceptable with five treatment-related deaths and a further 17% of patients experiencing life threatening toxicity [18].

In our series all patients who received a triplet regimen received TPF. Interest in adding docetaxel to cisplatin/5FU has arisen from improved outcomes in squamous cell carcinoma of the head and neck [19]. In a recent study six patients with unresectable or recurrent nodal disease received docetaxel with cisplatin/5FU with neoadjuvant intent. Five of the six patients achieved initial response and side effects were moderate [3]. Pagliaro et al. [20] treated 30 patients with N2/3, M0 disease with 4 cycles of neoadjuvant paclitaxel, ifosfamide and cisplatin (TIP). A 50% RR was achieved. A prospective phase II trial of TPF carried out in the UK involving 29 patients has recently reported. Inclusion criteria allowed those with distant metastatic disease as well as patients with locally advanced or nodal disease undergoing neoadjuvant treatment. Ten patients had objective responses (two complete responses) resulting in a response rate of 38.5%. This failed to meet the pre-specified level of 60% considered appropriate to warrant further investigation. Toxicity was high with 68% of patients experiencing grade 3-4 toxicity with an incidence of febrile neutropenia of 21%, despite a protocol amendment to include prophylactic granulocyte colony stimulating factor to be administered at each cycle [21].

3.2.4 Timing of chemotherapy

There is evidence suggesting that in a selected group of patients with advanced nodal disease,

chemotherapy before or after radical surgery may improve outcomes for patients.

The experience of the Netherlands Cancer Institute using neoadjuvant chemotherapy was reported with five different chemotherapy regimens utilised. Leijite et al. [22] reported an objective response in 12 of 19 evaluable patients with inoperable disease due to fixed lymph nodes or irresectable locally advanced disease. Following chemotherapy nine patients proceeded to surgery and eight patients achieved long term survival (five year survival 32%). Those patients who did not respond to treatment all died within nine months. Pizzocaro et al. [23,24,25] published both pilot and longer term follow up data using chemotherapy in the neoadjuvant and adjuvant settings with some evidence of increased disease free survival. In their pilot study 12 patients were treated postoperatively with vincristine, bleomycin and methotrexate (VBM). Only one of the 12 patients had relapsed at a median follow up period of 42 months. Their neoadjuvant data show that 56% of 16 patients treated with chemotherapy for fixed lymph node disease were able to proceed to surgery with five patients surviving disease-free for over five years [26].

Of the small cisplatin/5FU studies, two focussed on neoadjuvant treatment with responses in 2/5 patients [15] and 4/5 patients [14] respectively who proceeded to surgery. In the TIP study described above 22/30 patient proceeded to surgery following chemotherapy [20]. Based on these response rates, current EAU guidelines now recommend neoadjuvant chemotherapy for non-resectable or recurrent lymph node metastases or adjuvant treatment for patients with resected N2-3 disease [27].

In our series a small number of patients with N2/3 disease underwent this multimodality approach. The median survival for this group was 16 months compared with 5 months for the entire cohort. This is similar to some of the above neoadjuvant chemotherapy trials [15,20]. Our data does therefore support prior studies showing that delivery of chemotherapy in the neoadjuvant setting is feasible and may lead to modestly improved outcomes. However, a major problem facing patients and treating physicians is the relatively low response rate to chemotherapy. In other cancer treatment situations where chemotherapy has been proven to be useful in the neoadjuvant or adjuvant setting, it is on a background of high response rates in the metastatic setting. These high response rates with acceptable toxicity have yet to be achieved in penile cancer and the therapeutic ratio for benefit in neoadjuvant/adjuvant settings will therefore be lower. It could be argued that until more effective systemic therapies are made available, neoadjuvant chemotherapy should be reserved for surgically inoperable patients (eg. T4, fixed nodes) and adjuvant chemotherapy should preferably be delivered in the context of clinical trials. Given the patient numbers required for these studies international collaboration will be required.

4. CONCLUSION

This supra-regional series demonstrates historic variability in chemotherapy treatment but also demonstrates that this can be significantly reduced by the introduction of SMDTs. Cisplatin/5FU is now almost exclusively prescribed outside clinical trials. Overall response rates are disappointingly low and survival outcomes poor. Response rates in locoregional disease are superior to those in the presence of distant metastases suggesting possible benefits from the use of chemotherapy earlier in the course of the disease. Using these platinum-based regimens, toxicity is significant and patient selection is crucial.

These results highlight the urgent need for collaborative national and multi-national prospective trials to inform future practice and improve outcomes for patients. The role of targeted agents in penile cancer is yet to be explored. Recent findings that epidermal growth factor receptor (EGFR) is over-expressed in a majority of invasive penile squamous cell cancers [28,29], suggest that the EGFR targeting monoclonal antibodies and tyrosine kinase inhibitors may be useful therapeutic agents to study in this population. Given the high toxicity seen with triplet chemotherapy regimens, combining EGFR directed therapy with cisplatin/ 5FU or using them as single agent therapies are most likely to be avenues to explore.

CONSENT

Not applicable.

ETHICAL APPROVAL

Not applicable.

DECLARATION

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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