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Cisplatin and 5-fluorouracil in inoperable, stage IV squamous cell carcinoma of the penis

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Study Type – Therapy (case series)
Level of Evidence 4

OBJECTIVE

- To investigate the activity and toxicity of 5-fluorouracil (5-FU) as a first-line treatment in metastatic squamous cell carcinoma of the penis (SCCP).

METHODS

- The medical records of 78 patients with SCCP treated between January 2000 and June 2011 at the four participating centres were reviewed.
- Data regarding patients treated with first-line 5-FU were extracted.
- Patients were included in the study if radiological reports were available for determination of response and progression-free survival (PFS) according to response evaluation criteria in solid tumours (RECIST) 1.1.

RESULTS

- Between January 2000 and June 2011, 25 patients were treated with i.v. cisplatin on day 1 followed by 5-FU as a continuous 24-h infusion for 4 days every 3 weeks until disease progression or unacceptable toxicity. Partial responses and stable disease were observed in eight (32%) and 10 (40%) patients, respectively, with a disease control rate of 72%.
- Severe neutropenia was the most important grade 3–4 side effect observed, occurring in 20% of patients.
- The median (interquartile range [IQR]) PFS was 20 (11–20) weeks and the median (IQR) overall survival (OS) was 8 (7–12) months.

CONCLUSION

- 5-FU is associated with a moderate response rate and is well tolerated in patients with metastatic SCCP.

What's known on the subject? and What does the study add?
Metastatic or locally advanced squamous cell carcinoma of the penis (SCCP) is generally incurable, but it can be palliated with systemic chemotherapy. Two retrospective studies, involving <10 patients each, showed that cisplatin plus continuous infusion of 5-fluorouracil (5-FU) may be effective and well tolerated. Cisplatin, methotrexate and bleomycin, cisplatin and irinotecan and taxanes can also play an important role for patients with locally advanced/metastatic SCCP. Finally, anti-EGFR therapy may also be effective in advanced SCCP.

Although cisplatin plus continuous infusion of 5-FU is widely used in clinical practice for palliation of SCCP, toxicity and efficacy data regarding this schedule include a total of 14 patients with SCCP, treated more than two decades ago. In our retrospective study, cisplatin plus continuous infusion of 5-FU was used for palliative purposes in a homogenous sample of 25 patients with SCCP. Partial responses and stable disease were observed in 8 (32%) and 10 (40%) patients, respectively, with a median progression-free survival of 20 weeks. Neutropenia was the most important grade 3–4 side effect observed, occurring in 20% of patients. These data provide confirmation that such a combination regimen is moderately effective and well tolerated in patients with SCCP.

KEYWORDS

cisplatin-based regimen, chemotherapy, advanced penile cancer

INTRODUCTION

Squamous cell carcinoma of the penis (SCCP), the predominant histological type (>95%) of penile cancer, is rare in the general population. It has a heterogeneous incidence worldwide, which ranges from <1.00 per 100 000 males in Europe and the USA to 0.7–3 and 8.3 per 100 000 men in India and Brazil, respectively [1]. Although survival is influenced by a number of factors, including grade, growth pattern,

presence of vascular embolization, tumour thickness, as well as degree of infiltration of the surrounding tissues [2], the most prominent variable of established prognostic value is pathological lymph node involvement. In the series published by Bezerra *et al.* [3], the 5-year cancer-specific survival was between 90% and 100% in patients with pN0 disease, between 70% and 80% in those with pN1 stage and <30% in those with stage pN2-3 disease. Surgery and radiotherapy are the mainstay of treatment for patients with localized disease and can also be used in combination with adjuvant/neoadjuvant chemotherapy in patients with lymph node involvement, while chemotherapy is the main therapeutic option for patients with distant metastasis [1]. The proportion of patients with stage IV disease is relatively low, ranging from 0 to 14%, but their prognosis is dismal, with the majority of them dying within 1 year of diagnosis [4]. A wide variety of chemotherapy regimens provided radiological responses in either retrospective or prospective studies in this setting, but no phase III trial has ever been conducted, so the benefit of chemotherapy in terms of symptomatic palliation and survival prolongation remains uncertain. Cisplatin, used either alone [5] or in non-bleomycin-containing regimens such as cisplatin-5-fluorouracil (5-FU) [6,7], cisplatin-gemcitabine [8], and cisplatin-irinotecan [9], is the cornerstone of chemotherapy for inoperable disease, with a more favourable toxicity profile with respect to bleomycin-methotrexate-cisplatin [4]. Among cisplatin-based regimens, a combination of cisplatin plus continuous infusion of 5-FU appears especially promising for its safety and efficacy profile, but it has been surprisingly poorly investigated, with a total of only 13 patients with SCCP reported to have received such a regimen in retrospective studies in the neoadjuvant/metastatic setting [6,7]. With the aim of expanding our knowledge of the safety and efficacy of this versatile regimen in patients with advanced SCCP, we conducted a retrospective review of patients treated with this combination at our institutions in the period 2000–2011. Inclusion criteria were defined to select a homogeneous subset of patients with stage IV SCCP, who were not amenable to radical surgery or a neoadjuvant approach at the time they had been treated with cisplatin plus 5-FU, to allow generalization of the results obtained, as we have discussed elsewhere for retrospective studies in kidney cancer [10].

PATIENTS AND METHODS

INCLUSION CRITERIA

Medical records of patients with SCCP treated with first line i.v. cisplatin plus continuous infusion of 5-FU between 1 January 2000 and 30 June 2011 were reviewed at four participating centres. Patients were included in this retrospective analysis if they met the following criteria: (i) histological diagnosis of SCCP; (ii) newly diagnosed or recurrent disease judged not amenable to either radical surgery or neoadjuvant chemotherapy, followed by surgery with radical intent; (iii) availability of either radiological images or radiological reports of CT scans with contrast of the thorax and abdomen performed at baseline and at least every 4 months during chemotherapy, with sufficient data to allow re-evaluation of response by the investigators according to the response evaluation criteria in solid tumours (RECIST) 1.1 [11]; and (iv) first-line chemotherapy with i.v. cisplatin plus continuous i.v. infusion of 5-FU.

RETRIEVED DATA

Demographic data of eligible patients were retrieved, along with clinical and histological characteristics such as Eastern Cooperative Oncology Group (ECOG) performance status, type of surgical operation before receiving cisplatin+5-FU, histological grade, stage at diagnosis, time from diagnosis to administration of cisplatin+5-FU, dose and schedule used, date of initiation of treatment, date of progression, metastatic sites, date of death. Best response and progression-free survival (PFS) of cisplatin+5-FU treatment were assessed by central review using radiological reports or radiological images according to the RECIST 1.1 criteria. Adverse events occurring within 30 days of the last chemotherapy cycle, defined according to the National Cancer Institute Common Toxicity Criteria (version 3.0), if applicable, were also extracted from reviewed charts. Stage was determined according to the TNM classification 7th edition [12]. If available, mean pain score data, referring to the pain experienced by the patient and measured using a rating scale of 0 to 10 or 100 (0 being no pain and 10 or 100 representing the most intense pain ever experienced) were also retrieved, along with data regarding analgesic use.

DATA ANALYSIS

Descriptive statistics and frequency counts were used to summarize characteristics of the study population. Median numbers are presented with interquartile ranges (IQRs). The overall response rate to cisplatin+5-FU was defined as the percentage of patients who had either a complete response or a partial response as best response at any time during treatment. PFS and overall survival (OS) were calculated using the Kaplan–Meier method. PFS was calculated from the start of treatment to the time of death or radiographic progression, as re-determined by the investigators. Patients were excluded from the PFS analysis if progressive disease, diagnosed by the treating clinician, leading to chemotherapy interruption was not confirmed by the investigators. Patients lost to follow-up, or who were still under treatment as of 1 March 2012, were censored in the analysis. OS was calculated from the start of treatment to the time of death. Patients alive as of 1 March 2012, or who were lost to follow-up, were censored from the analysis. Univariate analysis, performed using Fisher's exact test and the log-rank test, was conducted to seek a relationship between PFS, OS and response to cisplatin+5-FU and variables of interest that included age, performance status, metastatic sites, dose intensity, grade and time from diagnosis to recurrence. A P value <0.05 was considered to indicate statistical significance. Multivariate analysis was not deemed feasible because the expected sample size was not sufficiently large. As described by Buonerba *et al.* [13], 'pain response' was defined as a >50% reduction in analgesic consumption, coupled with a >50% decrease in pain at any time since baseline after at least 1 cycle of treatment. Pain score, measured on a scale from 1 to 10, was multiplied by 10 to allow median calculation. Pain medications were classified as non-opioids (anti-inflammatories, paracetamol, etc.) and opioids. Opioid intake was converted into oral morphine equivalents before analysis.

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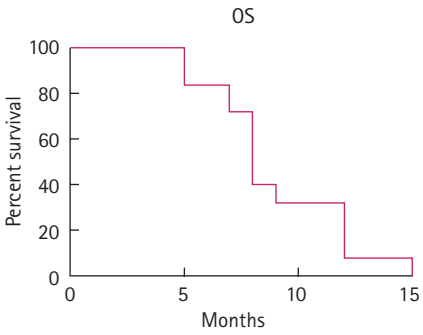
TABLE 1 Patient characteristics

No. of patients	25
Median age (range), years	63 (57–65)
ECOG performance status, *n*	
0	7
1	11
2	7
Previous loco-regional therapy, *n*	
Total amputation	10
Partial amputation	13
Radiotherapy	5
Radical inguinal lymphadenectomy	16
Radical lymphadenectomy for recurrent disease	2
Pathological T stage at diagnosis, *n*	
T1	4
T2	15
T3	5
Pathological N stage at diagnosis, *n*	
N0	11
N1	4
N2/N3	1
Not available	9
Time from first diagnosis to treatment start, *n*	
≤6 months	11
>6 months	10
Not available	4
Metastatic site at the time of treatment, *n*	
Lymph node only	15
Bone	2
Lung	5
Liver	3
Median oral mg morphine equivalents in 16 patients on opioids (range)	60 (30–80)
Median baseline pain score in 12 assessable patients on a scale from 1 to 100 (range)	45 (40–60)

TABLE 2 Responses and survival rates according to the follow-up

Response, *n* (%)	
Complete response	0
Partial response	8 (32)
Stable disease	10 (40)
Progression	7 (28)
Median (IQR) number of cycles	6 (4–6)
Median (IQR) PFS, weeks	20 (11–20)
Median (IQR) OS, months	8 (7–12)

FIG. 1. OS of the study population.



RESULTS

STUDY POPULATION AND TREATMENT SCHEDULE

Of the 78 medical records evaluated for this retrospective review, 25 patients were finally included in the study. All patients presented with inoperable stage IV SCCP at the time they received cisplatin+5-FU. All of them presented with adequate baseline renal, hepatic and bone marrow function (at least 1500 neutrophils and 100 000 platelets per μLwith minimum haemoglobin 90 g/L; creatinine clearance calculated by the cockcroft-gault equation >60 mg/mL/min; total bilirubin <1.5× upper limit of normal; aspartate aminotransferase (AST) and alanine amino transferase (ALT) <3× upper limit of normal). Cisplatin was delivered at a median (IQR) dose of 75 mg/m^2 (70–80) on day 1, while 5-FU was delivered via continuous infusion at the median (IQR) dose of 900 (800–1000) mg/m^2 for 4 days after cisplatin infusion in all patients every 21 days (one cycle). Patients were generally seen by physicians every 3–4 weeks and radiological evaluation was performed every 3–4 cycles. Information regarding pain levels was available for 12 patients, while data on analgesic consumption were available for all patients. All patients received some kind of analgesic medication, and 16 of them were taking opioids at the time of initiation of chemotherapy. Patient characteristics are shown in Table 1.

EFFICACY OF CISPLATIN PLUS CONTINUOUS INFUSION OF 5-FU

All included patients were evaluable for both response and PFS. Eight patients (32%; 95% CI 13.7–50.3) had a confirmed radiological response according to the RECIST criteria. Stable disease was observed in 10 (40%) patients, while the remaining patients (28%) had progressive disease (Table 2). No data regarding quality of life were available. Of 12 patients assessable for response to pain, all presented a baseline pain score ≥30 on a scale from 0 to 100 and required opioids for pain control. Four of them showed a pain response after 3, 4, 4 and 7 weeks, respectively. All four of them also showed radiological response. All patients presented a baseline whole body CT scan with contrast and were evaluated every 3 cycles, except for three who were evaluated every 4 cycles. A median (IQR) of 6 (4–6) cycles were administered, with a median relative delivered dose intensity of cisplatin of 81.8%. Median (IQR) PFS was 20 (11–20) weeks, while median (IQR) OS was 8 (7–12) months (Figs 1,2).

TOXICITIES OF CISPLATIN PLUS CONTINUOUS INFUSION OF 5-FU

Treatment was well tolerated overall. The most common grade 3–4 toxic effects were

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FIG. 2. PFS of the study population.

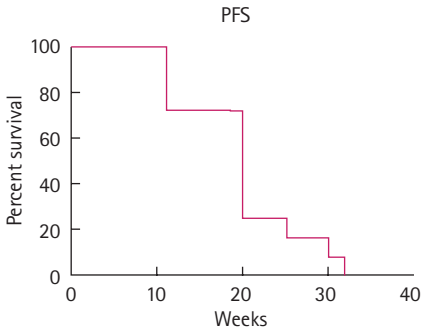

TABLE 3
Toxicity data from the 25 patients

Toxicity	Grade 1–2, *n* (%)	Grade 3, *n* (%)	Grade 4, *n* (%)
Neutropenia	11 (44)	4 (16)	1 (4)
Anaemia	6 (24)	2 (8)	1 (4)
Thrombocytopenia	5 (20)	1 (4)	1 (4)
Oral mucositis	8 (32)	1 (4)	0
Nausea/vomiting	8 (32)	1 (4)	0
Peripheral neuropathy	6 (24)	1 (4)	0
Constipation	6 (24)	1 (4)	0
Alopecia	5 (20)	1 (4)	0
Hypercreatininaemia	5 (20)	0	0
Diarrhoea	1 (4)	1 (4)	0

neutropenia, occurring in 5 (20%) patients, and anaemia, occurring in 3 (12%) patients. There was no death or interruption of treatment for toxicity. Dose reductions were necessary in seven patients (28%, two, two and three patients after 3, 4 and 5 cycles, respectively). Among grade 1–2 side effects, neutropenia, oral mucositis and nausea/vomiting were the most frequent, occurring in 11 (44%), 8 (32%) and 8 (32%) of patients, respectively (Table 3).

TABLE 4 Univariable analysis of response rate, PFS and OS

Variable	Response rate	PFS, weeks	OS, months
Age	75% vs 0%	22.5 vs 20	10.5 vs 8
<63 vs ≥63 years	$P < 0.001$	$P = 0.009$	$P = 0.022$
T at diagnosis	35% vs 20%	20 vs 20	8 vs 8
T1–T2 vs T3	$P = 1$	$P = 0.32$	$P = 0.49$
Grade	33.3% vs 28.5%	20 vs 11	8 vs 6
G1–2 vs G3–4	$P = 1$	$P = 0.025$	$P = 0.001$
Lymphnode involvement only vs visceral disease	33% vs 30%	20 vs 20	8 vs- 8
	$P = 1$	$P = 0.298$	$P = 0.486$
Recurrence	0% vs 80%	20 vs 25	8 vs 12
≤6 months vs >6 months	$P = 0.001$	$P = 0.004$	$P = 0.005$
ECOG performance score	44% vs 0%	20 vs 11	9 vs 5
0–1 vs 2	$P = 0.057$	$P = 0.002$	$P < 0.001$

PROGNOSTIC FACTORS

At univariate analysis, a younger age and a longer time to recurrence were significantly associated with an improved response, longer PFS and OS. Conversely, a lower histological grade and better performance status were significantly associated with longer PFS and OS (Table 4).

DISCUSSION

Although cisplatin can be considered the mainstay of first-line treatment for patients with advanced penile cancer, it is presently uncertain whether its use is associated with a survival advantage or symptomatic improvement, given the lack of phase III trials in this setting. In an effort to increase the activity of single-agent cisplatin, which yielded a response rate of only 15.4% and an OS of 4.3 months in a sample of 26 patients, a number of cisplatin-based combination regimens have been experimented in SCCP [4]. In a phase II trial by Theodore *et al.* [9], men with locally advanced (25%) or men (75%) with metastatic SCCP received combination cisplatin and irinotecan, with a response rate of 30.8% (80% CI 18.8–45.1) in 26 assessable patients. While survival was not reported, three patients treated in the neoadjuvant setting, who underwent a lymphadenectomy after chemotherapy, demonstrated no pathological evidence of malignancy. Additionally, a favourable toxicity profile was seen. A similar response rate of 32.5% with a median OS of 28 weeks was obtained in the largest phase II trial conducted in patients with penile cancer, with 40 assessable patients treated with the combination of cisplatin-methotrexate-bleomycin [14]. Although this regimen was considered active according to the study design, toxicity was unacceptable, with five treatment-related deaths and six of the 36 remaining patients experiencing one or more life-threatening side effects. Recently, a phase II trial has shown a response rate of 50% (95% CI 31–69%) with the combination of cisplatin, ifosfamide and paclitaxel in 30 patients treated in the neoadjuvant setting, which was accompanied by a favourable safety profile [15]. However, only nine patients (30.0%) were free of recurrence after a median follow-up of 34 months. No data are available for the cisplatin-ifosfamide-paclitaxel regimen in the metastatic or unresectable setting, where the therapeutic index may not be as favourable as in the neoadjuvant setting. Notably, as far as the use of paclitaxel in SCCP is concerned, we have shown that this drug administered as single agent at 175 mg/m^2 every 3 weeks exhibited modest activity in the second-line setting, with a response rate of 20% (five of 25 patients), and a median survival of 23 weeks [16]. Paclitaxel has also been used in the neoadjuvant setting with excellent preliminary results in a small experience involving six patients with recurrent or inoperable nodal disease treated with a combination of cisplatin 5-FU paclitaxel, with three of them achieving a complete or near-complete pathological response and

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two of them achieving a complete clinical remission [17].

The rationale for the use of cisplatin and 5-FU in patients with cancer is strong, and includes synergy of cisplatin and 5-FU in animal models, different mechanisms of action and different dose-limiting toxicities of the two drugs [7]. No prospective trial has been conducted with this regimen in patients with penile cancer. In one retrospective study, all of the five patients with SCCP treated with cisplatin+5FU showed partial radiological response, with one of these patients receiving radical surgery after chemotherapy. The primary toxicities (nausea/vomiting, renal injury, mucositis) were manageable and transient [6]. Another retrospective study conducted in eight patients with advanced SCCP reported radiological responses in two patients, with three patients showing 'poor tolerance' to treatment [7]. The present retrospective study, to the best of our knowledge, represents the largest report of patients with penile cancer receiving this regimen. In the present study, we were able to include 25 men with homogeneous characteristics, all of them receiving first-line treatment for palliative purposes in the setting of inoperable disease. As evaluation of response was critical for our aims, we reviewed and re-assessed response to treatment on the basis of either radiological reports or radiological images. The response rate of 32% (CI 95% 13.7–50.3) was in line with that of bleomycin-cisplatin-methotrexate, with no toxic deaths and no patient interrupting treatment because of toxicity.

In the present study, we also reported an association of simply assessable clinical and pathological variables, such as age, performance status, time to recurrence and histological grade with both PFS and OS. Most of the available data regarding prognostic factors in patients with penile cancer concern surgical series, which identified tumour stage and grade as sufficient alone to predict survival after surgery [18]. Although multivariate analysis was not performed in the present study, owing to the limited sample size, the variables that we identified (age, grade, time to recurrence and performance status) may be helpful for stratification purposes in clinical trials and also in clinical practice, provided confirmation from larger trials is obtained.

Recently, cetuximab [19] and panitumumab [20] have been shown to provide responses in SCCP, employed in combination with docetaxel and as a single agent, respectively. In this regard, we believe that the positive results obtained in this retrospective study, coupled with the high expression of EGFR on immunohistochemistry [21], and the proved synergism of cisplatin, 5-FU and cetuximab in head and neck squamous cell carcinomas [22], should prompt the investigation of such a regimen in SCCP.

In conclusion, the present retrospective study is currently the largest study providing evidence that a combination schedule, widely used in oncological practice, is active and safe in patients with inoperable SCCP. By contrast to the limitations of previous reports [6,7], the present study included a sufficiently large, homogeneous sample of patients treated with similar doses and schedules of cisplatin plus continuous infusion of 5-FU. Although data presented here are still affected by the typical biases of retrospective studies, such as lack of study protocol, study design and data incompleteness, our effort to re-evaluate response according to the RECIST criteria strengthened the quality of our results, suggesting that this combination regimen is a valid first-line therapeutic option in the metastatic setting. Prospective trials are required to confirm the efficacy and tolerance of this combination, and also to explore the additional therapeutic advantages of its combination with biological agents (e.g. cetuximab, HPV vaccination) or chemotherapy (e.g. taxanes). The neoadjuvant paradigm may enable the early identification of signals of activity, i.e. pathological remission. Given poor long-term outcomes despite initial chemosensitivity, the switch maintenance paradigm may also be worthy of consideration. Additionally, the discovery of biomarkers predictive of activity is important [2]. Finally, prevention remains critically important.

CONFLICT OF INTEREST

Giuseppe Di Lorenzo is a Paid Consultant to Janssen, Teva, Sotio and Sanofi.

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Abbreviations: **5-FU**, 5-fluorouracil; **SCCP**, squamous cell carcinoma of the penis; **RECIST**, response evaluation criteria in solid tumours; **PFS**, progression-free survival; **OS**, overall survival; **IQR**, interquartile range; **ECOG**, Eastern Cooperative Oncology Group.

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