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A phase II trial of cabazitaxel as second line chemotherapy in relapsed locally advanced and/or metastatic carcinoma of the penis

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Abstract

Objectives: To assess the efficacy and tolerability of cabazitaxel in relapsed penile cancer.

Methods: This Phase II single-arm trial was designed to recruit 17 patients with relapsed penile cancer. The primary endpoint was objective (complete + partial) response rate (ORR; Response Evaluation Criteria in Solid Tumours [RECIST] v1.1). Treatment comprised six 21-day cycles of cabazitaxel with restaging after cycles 2 and 4. The planned interim analysis was based upon the premise that if none of the first nine patients achieved ORR, trial would be stopped ($\alpha = 0.05$, Simon's 2-stage design).

Results: Nine patients were recruited from four UK centres between December 2014 and August 2016. The median age was 61 (range, 27–73.6) years, and seven patients had metastases. Patients received a median of two chemotherapy cycles (range, 2–5). None of the nine patients achieved ORR and the trial was stopped. Cabazitaxel was well tolerated with no dose reductions or delays. Three patients had grade 3/4 adverse events (anaemia, vomiting, or neutropenic sepsis). The median progression-free and overall survival were 1.3 and 5.6 months, respectively.

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Conclusions: The trial did not reach the threshold for further continuation of single-agent cabazitaxel. However, the observed tolerability profile supports its further investigation in combination with other agents to improve patient outcomes.

Keywords
Advanced penile cancer, cabazitaxel, second line chemotherapy, metastasis, objective response rate, progression-free survival, overall survival

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Introduction

Penile cancer is rare, and accounts for <1% of male malignancies that are diagnosed each year.[1,2] However, its incidence is increasing, with approximately 637 new cases and 134 deaths per annum in England and Wales in 2015, which is an increase of 21% over the last decade.[3,4] The rarity of penile cancers means that there is a paucity of prospective clinical trial data to guide our management of advanced/metastatic penile cancer, especially in the second-line setting.

Combination chemotherapy has been shown to alleviate symptomatic advanced disease and subjectively improve quality of life, but with no evidence of a survival benefit, although data in this field are limited. Methotrexate and cisplatin in a variety of combinations have shown the most efficacy.[5] Cisplatin and 5-fluorouracil (5FU) have been used to treat advanced penile cancer since 1990. Pooled analyses of three reports, including 19 patients in a first-line setting, demonstrated a response rate (RR) of 63% for this combination (three complete remissions and nine partial remissions).[6–8] The single-agent RR to cisplatin is 23%,[5,9] and this is similar to the overall RR seen in the EORTC study, which used irinotecan and cisplatin combination chemotherapy.[10]

The paclitaxel, ifosfamide, and cisplatin (TIP) regimen;[11] docetaxel/cisplatin/5FU (TPF) triplet combination therapy;[12] and more recently vinflunine[13] have shown benefit in the first-line setting. However, on relapse, there is no UK standard second-line chemotherapy regimen available. Cabazitaxel is an interesting cytotoxic. Its ability to kill taxane-resistant as well as sensitive cells suggests that it can be considered for post-taxane treatment. This was confirmed in the TROPIC prostate cancer trial where patients had increased overall survival when treated with cabazitaxel even if they relapsed during or within 6 months of docetaxel treatment.[14] This coupled with the anticipation of reduced toxicity in a patient population with borderline fitness, making combinations difficult to administer, was the basis of our choice for using single agent cabazitaxel in this study.

This study was primarily designed to establish the effectiveness, safety, and tolerability of cabazitaxel chemotherapy in relapsed advanced penile cancer patients.

Material and methods

Patient characteristics

Between December 2014 and August 2016, nine patients from four UK centres were recruited into this single arm phase II non-randomised multi-centre trial of patients with locally advanced and/or

metastatic penile cancer. The main inclusion criteria were as follows: patients with histologically proven squamous cell carcinoma of the penis staged as M1; TxN3M0; inoperable TxN2M0; or T4, any N, M0, ECOG performance status of ≤ 2, previous platinum-based treatment in radical or palliative settings, and adequate liver and kidney function.

Patients were excluded if they had previously received cabazitaxel chemotherapy or if they had verrucous carcinoma of the penis or urethral squamous cell carcinoma.

Medical history, patient examination, assessment of fitness, MRI of the pelvis and penis, computed tomography scans of the thorax, abdomen and pelvis, and blood parameters were required for baseline assessment. The study was approved by the South Central Hampshire B Research Ethics Committee (REC). Written informed consent was obtained from all patients.

Regimen

Patients received a 1-hour infusion of cabazitaxel at a dose of 25 mg/m^2 every 21 days. Premedication with 10 mg of chlorpheniramine, 8 mg of dexamethasone, and 50 mg of ranitidine were given 30 minutes before the infusion to mitigate allergic reactions. Six cycles were planned. Treatment was stopped earlier if patients showed progression. Doses were capped at a body surface area of 2.25 m^2. Primary prophylaxis with granulocyte colony stimulating factor (G-CSF) was mandatory for all patients. Only one dose reduction to 20 mg/m^2 was permitted if the patient experienced toxicity.

Assessments

The primary end point was objective response rate (ORR), which included both complete response (CR) and partial response (PR) (as measured radiologically using Response Evaluation Criteria in Solid Tumours [RECIST v1.1]);[15] secondary end points were toxicity, progression-free survival (PFS), overall survival (OS), and quality of life (QoL). Response assessments were performed every two cycles. The Common Terminology Criteria for Adverse Events (CTCAE) v.4.03 were used to grade toxicity after each cycle and at 3 months (acute toxicity) and 6 months (late toxicity). The Kaplan–Meier method was used to analyse PFS and OS.[16]

Patients were asked to complete EQ5D questionnaires before the first, third, and fifth chemotherapy cycles and between 4 and 6 weeks after the last chemotherapy cycle at the end of treatment (EOT).

Statistical analyses

A Simon's two-stage design was used to predict trial patient numbers, with the true RR as $\geq 25\%$ and an alpha and beta error of 5% and 20%, respectively.[17] If there was no patient with CR or PR among the first nine patients who were treated, then the null hypothesis would be true and the trial would be stopped. If, however, there was at least one patient who responded, then the null hypothesis would be rejected. The trial would then continue to recruit to 17 patients, testing the alternative hypothesis that the ORR is $\geq 25\%$. The alternative hypothesis would then be rejected if two or fewer patients responded, and further work with this agent would need to be reconsidered. A planned interim analysis was performed by an independent data monitoring committee after nine patients were recruited. Descriptive statistics were used for analyses, and GraphPad Prism version 4 (GraphPad Software Inc., La Jolla, CA, USA) was used. Statistical significance was not meaningful because the study was stopped after nine patients.

Table 1. Patient characteristics

Age (years)	
Median (Range)	61 (27–73)
M stage	
M0 loco regional	2!
M1 metastatic	7 (subcutaneous nodules^, lung, and liver metastases)
Previous Treatment(s)	
One line	7 (TIP-1; Cisplatin/5FU-2; Vinflunine-3; Cisplatin CT-RT-1)*
Two lines	1 (Cisplatin/5FU & Cisplatin/Methotrexate)
Three lines	1 (Cisplatin/5FU *2 and Cisplatin CT-RT)
Median time from previous PD to start of Cabazitaxel	1.9 (0.5–6.1) months

CT-RT, chemoradiation; PD, progressive disease; 5FU, 5-fluorouracil; TIP, paclitaxel, ifosfamide, and cisplatin

! Had pelvic nodal metastases

^ two patients with sub-cutaneous nodules had no visceral metastases

*four patients progressed while on first line chemotherapy (chemo-refractory)

Results

Patient characteristics are described in Table 1. At recruitment, seven of the nine patients had metastases at the following sites: cutaneous (two patients), lung (four patients), and liver (one patient).

Treatment

A median of two cycles were received (range, 2–5), with a 100% dose intensity. Cabazitaxel was well tolerated with no treatment delays because of side effects or dose reductions in all the nine patients.

Efficacy of cabazitaxel

None of the nine patients recruited achieved the primary endpoint of ORR, which included the CR and PR after completion of six cycles, and the trial was stopped. Seven patients had progressive disease after two cycles of cabazitaxel and the remaining two patients had stable disease after two cycles (these two patients had lung and liver metastases) and progressed after two further cycles. The median PFS and OS were 1.3 and 5.6 months, respectively.

Quality of life

Only three patients completed the EQ5D questionnaires at multiple time points, two of whom completed it before the first, third, and fifth chemotherapy cycles and at EOT, and one patient completed it before the first cycle and at EOT (this patient only had two cycles). There was no difference in the scoring in individual domains and in the global health score in these three patients at the various time points.

Toxicity

Overall, cabazitaxel was well tolerated with no dose reductions or treatment delays in the nine patients. Four patients had six serious adverse events (SAEs), among which four were treatment-related (neutropenic sepsis, hypercalcemia, sepsis, fever). All of these patients completely recovered. Two SAEs were fatal (pulmonary embolism and bleeding from the penile wound), but they were judged to be unrelated to the

treatment. There were no suspected unexpected serious adverse reactions.

Three patients developed grade 3/4 adverse events (anaemia, sepsis, and vomiting), which were treatment-related.

Discussion

This trial showed that cabazitaxel was well tolerated and has a favourable safety profile in relapsed penile cancer patients. The adverse events of cabazitaxel were manageable. The trial, however, did not reach the pre-determined threshold (because statistically, there was a <5% chance of achieving a greater than a 25% response) to warrant continuation of this study of single agent cabazitaxel as a second- or subsequent-line treatment in relapsed penile cancer. These results are consistent with the overall disappointing results from other case series with the use of different therapeutic agents in pre-treated metastatic penile cancer.[18] The median time from progression of the previous line of treatment to start of cabazitaxel was only 1.9 (range, 0.5–6.1) months, reflecting an aggressive disease. Additionally, four of the seven patients who had cabazitaxel as a second-line treatment had progressed while on first-line therapy (chemo-refractory). Therefore, we feel that single-agent cabazitaxel is ineffective for treating relapsed penile cancer after first line therapy and future studies should include combination regimens.

There is paucity of data on second-line chemotherapy in penile cancer (Table 2)[19–23]. Additional salvage chemotherapy has been shown to induce an objective response. A retrospective review of the 19 patients (among the initial 30 patients) who relapsed in the TIP study,[11] demonstrated responses in five patients treated with bleomycin, methotrexate, and cisplatin (BMP), but serious toxicity in the form of fatal pneumonitis means that BMP is no longer recommended for routine use.[23]

A phase II trial has reported outcomes (response rates under 30%) for 25 patients who received second-line single-agent paclitaxel chemotherapy.[21] All patients had received cisplatin combination chemotherapy regimens (neoadjuvant or adjuvant) in the first-line setting, and the observed response rate to paclitaxel was 20%. The median PFS and OS were 11 and 23 weeks, respectively. These results were similar to those reported by Wang et al.[23] and in our current study. Thus, paclitaxel may be a reasonable second-line option for patients who are taxane-naive.

Taxanes have been shown to be efficacious as part of a multidrug regimen in the front-line setting.[11,12] Despite this proven efficacy, a retrospective chart review by Buonerba et al.,[19] which included 65 patients across North America, Europe, and Japan, reported that 74% of the patients received taxanes as second-line chemotherapy. This is consistent with the fact taxanes are not universally used in a first-line setting. Thus, there is a role for taxanes in the relapsed setting. Single-agent taxane is preferable to a combination regimen because it is less toxic, especially in the relapsed setting. Therefore, in pretreated patients, further evaluation of single-agent taxane was warranted. The favourable toxicity profile in our study supports the use of cabazitaxel in a future combination regimen, especially because of the lack of therapeutic options for advanced penile cancer patients. Moreover, because of the poor outcomes in the relapsed setting, these data also support our belief that the further optimisation of first-line regimens, including taxane, platinum, and/or immunotherapy combinations are required, despite the moderate success of current first-line chemotherapy regimens.

There is emerging evidence that epidermal growth factor receptors (EGFRs) are overexpressed in penile squamous carcinoma,[24] leading to evaluation of

Table 2. Literature review of therapeutic agents in pre-treated patients

Author	n, Study Drug	Efficacy	Comments
Di Lorenzo et al.[21]	25, Paclitaxel (2nd line)	20% PR, 16% SD Median PFS, 11wks Median OS, 23 wks	Well tolerated and acceptable efficacy Slow accrual over 7 yrs
Carthon et al.[20]	24, (2nd or 3rd line) 8, Cetuximab/Erlotinib/Gefitinib 13, Cetuximab+Platinum 3, Cetuximab+TIP	PR, 20–25% Median PFS, 11.3wks Median OS, 29.6 wks	No responses seen with Erlotinib/Gefitinib Visceral metastases (VM) had a detrimental effect on OS
Wang et al.[23]	5, Bleomycin, Methotrexate, Cisplatin (BMP) 2, Gemcitabine combinations 6, EGFR targeted therapy	1, CR; 1, PR; ORR, 40% High treatment related mortality Median OS, 4 m No durable response No response	Overall poor response to salvage therapies with median OS $<$6 m. No difference in outcomes with platinum/non-platinum based regimes Fatal pneumonitis, and thus, BMP is not recommended for routine use
Necchi et al.[22]	11, Panitumumab (2nd or 3rd line)	2, CR; 1, PR; 2, SD 6, PD Clinical benefit, 45.5% Median PFS, 1.9 m Median OS, 9.5 m	VM had a detrimental effect on OS Skin toxicity was not predictive of benefit
Buonerba et al.[19]	65, (retrospective chart review) 48, Taxane regimen 17, Cetuximab regimen	Median PFS, 12 wks Median OS, 20 wks	VM and Hb $\leq$10 were predictors of poor PFS and OS Cetuximab based regimes had better response rates

PR, partial response; SD, stable disease; PFS, progression-free survival; OS, overall survival; ORR, objective response rate; TIP, paclitaxel, ifosfamide, cisplatin; EGFR, epidermal growth factor receptor; VM, visceral metastases; Hb, Haemoglobin; m, months; wks, weeks; yrs, years

EGFR-targeted therapies for this disease (Table 2). Immunotherapy is also a current focus for further clinical research. The rationale for using immunotherapy in advanced penile cancer is based on the PD-L1 expression that is seen in 40% to 60% cases of primary penile cancer.[25–28]

Although there have been a few studies in the relapsed setting in penile cancer, its rarity makes it difficult to conduct such large, phase 3 trials. One of the future challenges is the slow accrual of patients for these studies, which is partially because of the elderly population, significant comorbidities, high screen-failure rates, and poor performance score. A paradigm change is required for us to keep up with the advancements in penile cancer.

One way of overcoming this challenge is the development of prognostic nomograms/models, which may be beneficial for analysing study outcomes and tailoring aggressive salvage regimens for a specific patient group, e.g., those with worse outcomes. Buonerba et al.[19] retrospectively analysed 65 patients who received second-line systemic therapy. The presence of visceral metastases and haemoglobin $\leq$10 g/dL were associated with poor outcomes. They have demonstrated that cetuximab-based regimens were associated with better responses compared with other agents, but this did not translate into a survival benefit.

Another way of improving the results could be administration of more active treatments concurrently or sequentially with standard systemic therapy. We feel that the observed favourable tolerability profile of cabazitaxel in pre-treated patients supports further investigation of cabazitaxel in combination with other agents in this patient group to improve patient outcomes for this area of unmet need. Optimal utilisation of EGFR-receptor blockers in combination with chemotherapy or radiation is another strategy to be considered. These strategies need to be balanced carefully with the ability to maintain dose intensity in the context of poor performance score or organ function.

Conclusion

The trial did not reach the pre-determined threshold for further continuation of the study of single-agent cabazitaxel as second- or subsequent-line treatment in patients with relapsed penile cancer. However, the observed tolerability profile in this group supports the conclusion that cabazitaxel was well tolerated and further investigation of cabazitaxel in combination with other agents in this patient group should be considered to improve outcomes for this area of unmet need.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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