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Research Article

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Cabazitaxel in Platinum Pre-treated Patients with Locally Advanced or Metastatic Transitional Cell Carcinoma Who Developed Disease Progression after Platinum based Chemotherapy: Results of the Phase II CAB-B1 Trial

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Abstract

There is a paucity of chemotherapy options for patients with urothelial cancers who have relapsed following platinum based chemotherapy (CT).

CAB-B1 was a single centre phase II randomised controlled trial of Cabazitaxel (CAB; 25mg/m2 q3 week for 6 cycles) versus best supportive care (BSC) in patients with histologically proven transitional cell carcinoma (TCC), locally advanced or metastatic, who had recurred after receiving platinum based treatment. Primary outcome was overall response rate (ORR) using RESIST. Secondary outcomes included Progression Free Survival (PFS) and Overall Survival (OS).

Between January 2013 and October 2016, 20 patients were randomised (10 on each arm). BSC included paclitaxel CT for 9 patients and radiotherapy for 1 patient. 8 patients completed 6 cycles of CT (3 on CAB; 5 on BSC). 2 patients had an ORR on CAB and 1 patient on BSC. Median OS was 5.8 months (95% confidence interval (CI) 0.7-14.6) for CAB patients and 7.5 months (95% CI 1.0-10.8) for BSC patients. Median PFS was 4.8 months (95% CI 0.7-8.3) for CAB patients and 3.7 months (95% CI 1.0-7.0) for BSC patients.

CAB-B1 successfully reached the efficacy target for 1st stage, showing that there could be a role for CAB in these patients.

Keywords: Bladder Cancer, Transitional Cell Carcinoma, Taxane, Cabazitaxel

Introduction

Bladder cancer is the 10th most common cause of cancer in the UK [1]. The majority of bladder tumours occur in men, where it is the 6th most common cause of cancer and 12th most common cause of cancer death in females [1]. The survival of untreated metastatic patients does not exceed 3 to 6 months, and systemic chemotherapy increases overall survival of patients with unresectable disease [2,3,4]. However, the overall survival (OS) of patients with advanced disease treated with chemotherapy remains short (about 14 months) and new agents are needed in this very poor prognosis disease.

There was no standard of care for patients who relapsed after previously receiving neo-adjuvant chemotherapy and there was no standard second line chemotherapy at the time this study was planned.

Cabazitaxel (Jevtana), a semisynthetic compound derived from European yew needles demonstrated activity in cell lines with acquired resistance to doxorubicin, vincristine, vinblastine, paclitaxel, and docetaxel. Cabazitaxel is standard of care in treatment of metastatic prostate cancer following Docetaxel failure [5].

This phase II study was designed to see whether Cabazitaxel had activity in relapsed patients with transitional cell carcinoma (TCC) compared to best supportive care (BSC) (including single agent chemotherapy). Paclitaxel was used as chemotherapy of choice in BSC arm as it showed some activity in advanced urothelial cancers with known safety profile [6,7].

Methods

CAB-B1 was a single centre open labelled phase II randomised controlled trial of Cabazitaxel versus BSC in patients with histologically proven TCC, locally advanced (T4b) or metastatic (lymph node or visceral), who had recurred after receiving platinum based treatment. Eligible patients were aged 18 or above with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and a life expectancy of 12 weeks or more. All patients gave written informed consent. Patients were excluded if they had been treated previously with a taxane, had inadequate organ and

bone marrow function, history of inflammatory bowel disease or had any of the following events within 6 months prior to randomisation: myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft surgery, clinically symptomatic and uncontrolled cardiovascular disease, or clinically significant arrhythmias (grade 3-4).

Eligible patients were randomised centrally on a 1:1 basis using block randomisation with variable block sizes. Randomisation was stratified by the time from last chemotherapy cycle to recurrence (<6 months; >=6 months).

The patients randomised to the Cabazitaxel arm, received 25 to 20 mg/m², administered by IV route, 3 week cycle with maximum of 6 cycles. IV premedication including an antihistamine, corticosteroid, H2 antagonist was given. Primary prophylaxis with Granulocyte Colony Stimulating Factor (G-CSF) was given in patients with high-risk clinical features such as; age > 65 years, poor performance status, previous episodes of febrile neutropenia, extensive prior radiation ports, poor nutritional status, or other serious comorbidities that predispose them to increased complications from prolonged neutropenia.

BSC was administered according to institutional standards (including 6 cycles of single agent chemotherapy, palliative radiotherapy, antibiotics, analgesics, corticosteroids, and transfusion).

Clinical examinations including weight, ECOG performance status, laboratory tests (including complete blood counts, and serum chemistry) and adverse events (NCI CTCAE v.4.03) were obtained prior to drug administration, every cycle before treatment administration and up to 30 days after the last study treatment administration. Treatment response was assessed by computerized tomography (CT) of the whole body (chest, abdomen, and pelvis) at baseline and following cycles 3 and 6 (end of treatment scan) of chemotherapy and whenever disease progression is suspected. Patients completed the Euro QOL EQ-5D at baseline, and every cycle before treatment administration and at the post treatment visit. Patients were followed every 3 months until death or withdrawal of consent to participate in the study.

The primary outcome was overall response rate (ORR) using the Response Evaluation Criteria in Solid Tumours (RECIST) criteria. Secondary outcomes were Progression Free Survival (PFS), OS, Quality of Life assessment, safety and tolerability.

A total of 96 patients (48 patients on each arm) were required to detect differences in ORR from 5% in the BSC arm to 30% in the Cabazitaxel arm with 80% power, a 5% two-sided significance level and allowing for 10% dropouts. Stopping rules were calculated based on the Simon's two stage optimal design to assess the individual effectiveness of Cabazitaxel assuming the lower ORR limit for an ineffective drug at 0.05 and the target ORR for an effective drug at 0.20, With 80% power and a 5% two sided significance level, at least 1 ORR was required from 10 patients on Cabazitaxel at the first stage and 4 ORR from 29 patients on Cabazitaxel at the second stage. An interim analysis was performed after 20 patients in total were recruited into the first stage. However, due to slow recruitment the trial closed after the first stage.

Descriptive statistics with associated 95% confidence intervals (CI) are presented; due to the small numbers of patients no formal statistical tests are performed. OS was calculated as the time from the date of trial entry until the date of death or censored at the date last known to be alive. PFS was calculated as the time from the date of trial entry until the date of documented progression or date of death from any cause or censored at the date last known to be alive and progression free. Kaplan-Meier survival curves were constructed for OS and PFS. A Cox proportional hazards model was fitted to obtain a hazard ratio and associated 95% CI for the treatment effect. Quality of life data from the EQ-5D was analysed by a standardised area-under-the-curve analysis. The worst grade experienced by each patient for each CTCAE category is reported. All analyses are performed on an intention-to-treat basis using the SAS statistical software (version 9.4).

The trial is registered as an International Standardised Randomised Controlled trial, number ISRCTN76947550. The trial was carried out in accordance with the Declaration of Helsinki and approved by research ethics committee and regulatory authorities.

Results

Between January 2013 and October 2016, 47 patients were screened for eligibility; 27 were excluded as they were either not eligible or declined to take part (Figure 1). A total of 20 patients were randomised (10 on each arm). Patient characteristics were similar across trial arms (Table 1): 75% were males; median age 68 years; 65% had recurred within 6 months of previous CT.

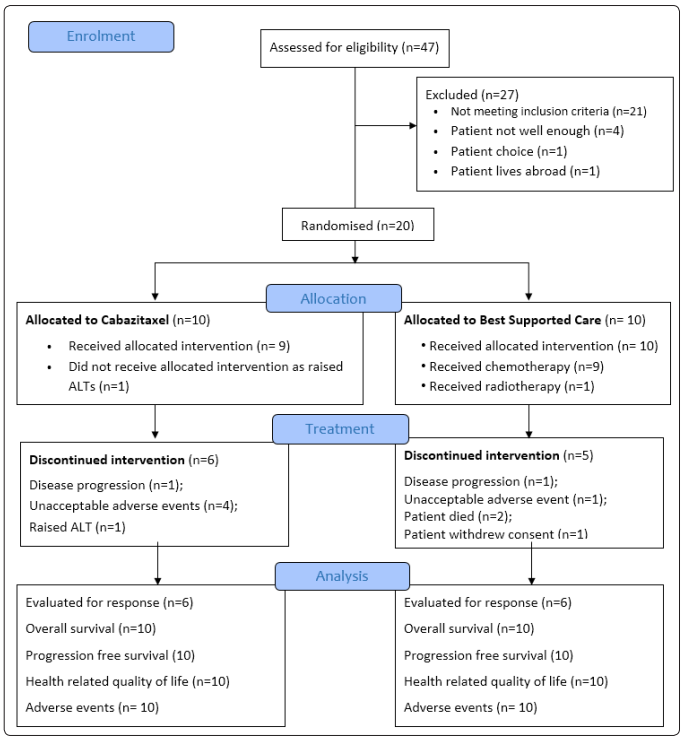

Figure 1: CONSORT diagram

Table 1: Patient baseline characteristics

Characteristic	Cabazitaxel		Best supportive care		Total	
	n	%	n	%	n	%
	10	50	10	50	20	
Gender						
Male	7	70	8	80	15	75
Female	3	30	2	20	5	25
Age years (Median(Range))	70 (41-77)		69 (57-83)		70 (41-83)	
Site of origin						
Bladder	8	80	9	90	17	85
Upper tract	2	20	1	10	3	15
Pathology						
Transitional Cell Carcinoma (TCC)	8	80	10	100	18	90
Mixed pathology with predominately TCC	2	20	0	0	2	10
Disease stage						
Locally advanced (T4b)	1	10	0	0	1	5
Metastatic TCC	9	90	10	100	19	95
Time between last dose of chemotherapy and recurrence						
< 6 months	6	60	7	70	13	65
>= 6 months	4	40	3	30	7	35

Of the 10 patients randomised to Cabazitaxel, 1 patient did not start treatment as had raised ALT and only 3 (30%) patients completed all 6 cycles of treatment. A total of 30 Cabazitaxel cycles were administered. Six patients discontinued Cabazitaxel early due to adverse events (neutropenic sepsis; pyelonephritis; acute kidney disease, abdominal pain and haematuria; fatigue and raised ALTs). One patient stopped treatment early due to disease progression.

Of the 10 patients that randomised to BSC, 9 patients were prescribed paclitaxel chemotherapy and one patient prescribed radiotherapy but died after one fraction. The 9 patients completed 37 cycles of paclitaxel chemotherapy, with 5 (56%) completing all 6 cycles of chemotherapy. The reasons for stopping chemotherapy were due to increased creatinine (n=1), disease progression (n=1), death (n=1) and withdrawing consent (n=1).

Only 3 (5%) cycles of the 67 cycles administered were delayed (2 out of 30 (7%) on Cabazitaxel arm and 1 out of 37 (3%) on the BSC arm), due to requiring a blood transfusion, awaiting results of scan or patient choice. A total of 6 (9%) of the 67 cycles administered involved dose alterations (5 cycles out of 30 (17%)) for 3 patients on Cabazitaxel arm and 1 out of 37 (3%) on the BSC arm), predominately due to clinical decision or toxicity.

Ten serious adverse events (SAEs) were experienced by 6 patients on the Cabazitaxel arm due to adverse events within the following system organ classes: gastrointestinal, renal and urinary, infections and metabolic and nutrition that resulted in hospitalisation. Three patients on the best supported care arm experienced 5 SAEs due to adverse events (renal and urinary, and infections) that resulted in hospitalisation. The worst grade for any adverse event experienced was grade 4 for two patients on Cabazitaxel; one patient experienced grade 4 thrombocytopena and one patient had grade 4 neutropenic sepsis and deteriorated renal function. Grade 3 adverse events were experienced for 5 patients on each arm. The adverse events that was most experienced were from the CTCAE categories blood and bone marrow (e.g. anaemia), metabolic/laboratory (e.g. raised creatinine) and gastrointestinal (e.g. nausea and constipation) (Table 2).

Table 2: Adverse events: Worst grade experienced

N(%)	Cabazitaxel					Best supportive care				
Grade	**0**	**1**	**2**	**3**	**4**	**0**	**1**	**2**	**3**	**4**
Worst grade experienced	**1 (10)**	**0**	**2 (20)**	**5 (50)**	**2 (20)**	**0**	**2 (20)**	**3 (30)**	**5(50)**	**0**
CTCAE categorisations										
Auditory/ear	10 (100)	0	0	0	0	9 (90)	1(10)	0	0	0
Blood/bone marrow	1 (10)	3 (30)	1 (10)	4 (40)	1 (10)	0	6 (60)	2 (20)	2 (20)	0
Constitutional symptoms	4 (40)	4 (40)	1 (10)	1 (10)	0	5 (50)	3 (30)	0	2 (20)	0
Dermatology/skin	6 (60)	4 (40)	0	0	0	4 (40)	3 (30)	3 (30)	0	0
Gastrointestinal	2 (20)	1 (10)	4 (40)	3(30)	0	3 (30)	3 (30)	4 (40)	0	0
Hemorrhage/										
bleeding	10 (100)	0	0	0	0	9 (90)	1 (10)	0	0	0
Infection	7 (70)	0	1(10)	1(10)	1(10)	7 (70)	0	1(10)	2(20)	0
Lymphatics	9 (90)	1 (10)	0	0	0	9 (90)	1 (10)	0	0	0
Metabolic/										
laboratory	3 (30)	2 (20)	4 (40)	1 (10)	0	5 (50)	4(40)	0	1 (10)	0
Neurology	8 (80)	2(20)	0	0	0	5 (50)	3(30)	1 (10)	1 (10)	0
Pain	7 (70)	1 (10)	1 (10)	1 (10)	0	5 (50)	0	4 (40)	1 (10)	0
Pulmonary/upper respiratory	8 (80)	1 (10)	0	1 (10)	0	8 (80)	2 (20)	0	0	0
Renal/										
Genitourinary	5 (50)	2 (20)	1 (10)	1 (10)	1 (10)	6 (60)	3 (30)	1 (10)	0	0
Sexual/reproductive function	10 (100)	0	0	0	0	9 (90)	1 (10)	0	0	0

Twelve patients were evaluated for radiological response (six on each arm; Table 3). One patient had the 3 months scan after 2 cycles instead of 3 cycles. Four patients on each arm were not evaluated for response, as either the patient died of progression within 3 months (2 on Cabazitaxel arm, 3 on BSC arm) or the patients stopped treatment after 1 cycle and did not go on to have the CT scan and be assessed for response (2 patients on Cabazitaxel; 2 on BSC). Two patients (20%) on the Cabazitaxel arm had a partial response; one patient had a partial response after 3 months but subsequently progressed by the 6 month assessment and one had stable disease at 3 months and then a partial response at 6 months. One (10%) patient on BSC arm had a partial response at 3 months but subsequently progressed by the 6 month assessment. Thus the ORR was 2 (20%) patients on Cabazitaxel and 1 (10%) patient on BSC.

Table 3: Response to treatment

Characteristic	Cabazitaxel		Best supportive care		Total	
	n	**%**	**n**	**%**	**n**	**%**
	10		**10**		**20**	
Response at 3 months						
Complete response (CR)	0	0	0	0	0	0
Partial response (PR)	1	10	1	10	2	10
Stable disease (SD)	3	30	4	40	7	35
Progressive disease (PD)	2	20	1	10	3	15
Not evaluated for response	4	40	4	40	8	40
Response at 6 months						
Complete response (CR)	0	0	0	0	0	0
Partial response (PR)	1	10	0	0	1	5
Stable disease (SD)	1	10	3	30	4	20
Progressive disease (PD)	1	10	2	20	3	15
Not evaluated for response	7	70	5	50	12	60
Overall best response						
Complete response (CR)	0	0	0	0	0	0

Partial response (PR)	2	20	1	10	3	15
Stable disease (SD)	2	20	4	40	6	30
Progressive disease (PD)	2	20	1	10	3	15
Not evaluated for response	4	40	4	40	8	40

Seventeen patients are known to have died of their disease 9 patients on the Cabazitaxel arm; 8 on BSC arm). Three patients (1 patient on the Cabazitaxel arm; 2 on BSC arm) are still alive and have been followed up between 13.0 and 19.6 months. All patients have progressed. The median overall survival was 5.8 months (95% confidence interval (CI) 0.7-14.6) for Cabazitaxel patients and 7.5 months (95% CI 1.0-10.8) for BSC patients (hazard ratio 1.06 (95% 0.40-2.78), Figure 2). Median progression free survival was 4.8 months (95% CI 0.7-8.3) for Cabazitaxel patients and 3.7 months (95% CI 1.0-7.0) for BSC patients (hazard ratio 0.71 (95% CI 0.29-1.77), Figure 3).

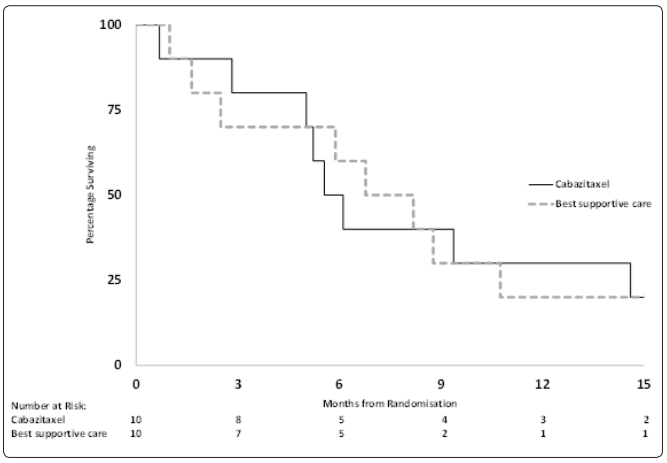

Figure 2: Overall survival

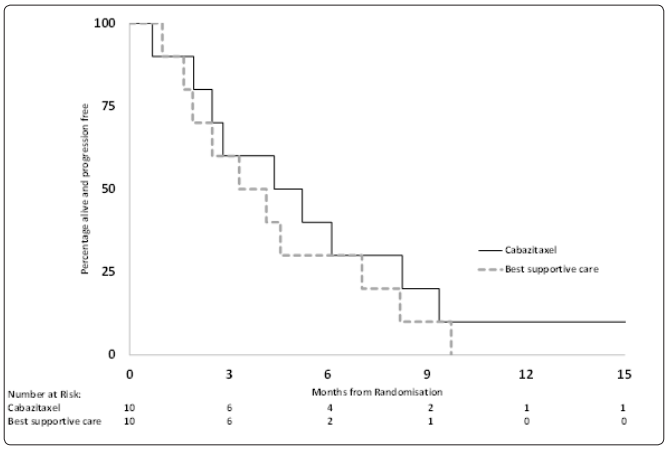

Figure 3: Progression free survival

The median area under a curve using the EQ5D health today scores for those on Cabazitaxel was 71 (IQR 59-83, range 44-89) and 77 (IQR 73-89, range 32-91) for those on BSC (Figure 4). The median area under a curve using the EQ5D utility scores for those on Cabazitaxel was 0.72 (IQR 0.59-0.77, range 0.34-0.92) and 0.76 (IQR 0.71-0.89, range 0.64-0.91) for those on BSC.

Discussion

Muscle invasive bladder cancer treatment options remain limited in spite of recent availability of the immunotherapy options in the second line setting [10]. After platinum based chemotherapy, median overall survival remains poor and therefore effective options are still needed in this patient group. However, this patient group is usually elderly with multiple co-morbidities, which has resulted in the lack of large phase III trials in the second line setting using chemotherapeutic options.

There has been limited number of randomised phase III/ II trials showing a meaningful benefit of second line treatment compared with other active treatment [6,7,9-12].

Our study achieved its primary endpoint and is the second phase II study confirming the safety profile of the Cabazitaxel in the second line treatment [13]. The median OS in our study of 5.8 months for Cabazitaxel and 7.5 months for Paclitaxel (BSC) were similar to those observed in other clinical trials [13,14].

Limitations of the study were mainly the small numbers of patients being recruited and the high numbers of patients from both arms not being evaluable for response due to toxicity of treatment, early progression and withdrawal from the study.

In spite of newer options such as monoclonal antibodies against programmed death 1 (PD-1) and it's ligands (PD-L1 and PD-L2) being available in the second line setting, we have to remember that there are group of patients where immunotherapy may not be an option of treatment due to co-existing condition. This phase II study confirms safety profile of Cabazitaxel in second line treatment of urothelial carcinoma following platinum based treatment in this patient population.

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