

A single arm phase II trial of neoadjuvant cabazitaxel and cisplatin chemotherapy for muscle invasive transitional cell carcinoma of the urinary bladder.

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Abstract

Background:

Neoadjuvant cisplatin-based combination chemotherapy improves survival in muscle invasive bladder cancer (MIBC). However, response rates and survival remain suboptimal. We sought to evaluate the efficacy, safety and tolerability of cisplatin in combination with cabazitaxel in this patient group.

Methods:

A phase II single arm trial was designed (Simon-2 stage), to recruit at least 26 evaluable patients. This would give 80% power to detect the primary endpoint, objective response rate (ORR) defined as pathological complete response (pCR) plus partial response (pathological downstaging), measured by pathologic staging (T stage) at cystectomy ($p_0 = 0.35$ and $p_1 = 0.60$, setting $\alpha = 0.05$).

Results:

Objective response was seen in 15 out of 26 evaluable patients, 57.7% and over a third of patients achieved pCR (9/26; 34.6%). 78% (21/27) of patients completed all cycles of treatment, with only 6.7% of the reported adverse events (AEs) being graded 3 or 4. There were 6 treatment related SAEs reported but no SUSARs. In the patients who achieved objective response the median progression free (PFS) and overall survival (OS) were not reached (median follow-up of 41.5m). In contrast the median PFS (7.2m) and OS (16.9m) were significantly worse ($p=0.001$, log-rank) in patients who did not achieve objective response.

Conclusions:

Cabazitaxel in combination with cisplatin for neoadjuvant treatment of MIBC can be considered a safe, well-tolerated and effective regimen prior to definitive therapy with higher rates (57.7%) of objective response, which compares favorably to that with

Cisplatin/Gemcitabine (23-26%). These results warrant further evaluation in a larger phase 3 study.

Key words: Muscle-invasive, Bladder cancer, Neoadjuvant chemotherapy, Cabazitaxel, Cisplatin, pathological complete response.

Introduction

Carcinoma of the urinary bladder is the seventh most common cancer in the United Kingdom (ONS, England 2010) with around 10,000 diagnoses annually [1]. The majority of these are transitional cell carcinoma (TCC) with about 30% of cases presenting with disease invading into the muscle wall of the bladder (tumour stage T2 or greater). A further 50% of patients presenting with high risk non muscle invasive (superficial) bladder cancers will later develop muscle invasive disease.

Five-year survival after cystectomy for patients with muscle invasive bladder cancer (MIBC) varies from 36% to 48%, and specifically 17% to 46% for pT3b tumours [2-5]. There was an absolute improvement of 5% in overall survival, 14% decrease in disease specific mortality and 9% improvement in disease specific survival, at 5 years, with cisplatin-based neoadjuvant chemotherapy (NAC) followed by definitive treatment (surgery or radiotherapy) compared with patients who received definitive treatment alone, in patients of good performance status [2, 3].

The choice of neoadjuvant chemotherapy agents is guided by the larger individual trials. The phase III SWOG 8710 (Intergroup 0080) trial [6] demonstrated that 5 year overall survival favoured methotrexate, vinblastine, doxorubicin, cisplatin (MVAC) chemotherapy (57% vs.42%), and was 85% in patients who had a pathological complete response. However, MVAC was toxic with the incidence of grade 4 granulocytopenia of 33% and gastrointestinal complications of 29%. The combination of gemcitabine plus cisplatin (GC) has been shown to be effective with similar response and survival rates compared with MVAC, and less toxic in advanced bladder cancer [7]. Based on these data, GC has become the current standard of care in the neoadjuvant setting in the treatment of MIBC. Despite this obvious benefit, there have been few trials comparing different NAC regimens and few reliable biomarkers that identify patients most likely to benefit from neoadjuvant treatment. Therefore, there is a clear need for new combinations of drugs to improve patient outcomes.

Interest in taxanes (e.g. paclitaxel and docetaxel) in the management of bladder cancer has emerged from trials in metastatic bladder cancer (cancer that has spread to other parts of the body) following failure of platinum-based chemotherapy [8-11]. Taxanes in combination with cisplatin have also been evaluated in the neoadjuvant setting in bladder cancer [12-14].

Cabazitaxel is a novel taxane which is well tolerated and effective in tumours that are either sensitive or resistant to other taxanes [15]. Although trials with cabazitaxel have primarily employed it as a single agent treatment in advanced MIBC patients who are cisplatin intolerant [16], benefit has been seen in combination with other platinum-based agents in the treatment of metastatic breast cancer [17]. Recent work in animal models [18] reports synergism when cabazitaxel is combined with cisplatin. Data from phase I studies using cabazitaxel combined with cisplatin are emerging [19]. The combination of platinum and cabazitaxel has been shown to be well tolerated in patients with metastatic prostate cancer [20]. Therefore, cabazitaxel presents a potentially active and tolerable agent, in combination with cisplatin, in MIBC prior to definitive therapy.

Circulating tumour cells (CTCs) as a biomarker may aid selection of therapy [21] and also act as surrogates for overall survival [22]. Detection of urothelial cancer cells using the Cell Search System (CSS) was first described by Naoe et al, in a study of 26 patients with localised and metastatic urothelial cancer [23]. Urothelial cells were defined as those which stained with cytokeratin and EpCAM antibodies but not CD45 (to distinguish them from peripheral blood mononuclear cells or PBMCs). In a study of 50 patients with MIBC, Guzzo et al have shown that the detection rate of CTCs preoperatively in patients with localised MIBC was 30% (15 of 50). The overall survival (OS), progression free survival (PFS) and cancer specific survival (CSS) were shown to be significantly worse in non-metastatic patients with detectable CTCs, compared with those without detectable CTCs [24]. However, there is no study to date in MIBC that has specifically assessed the role of CTCs in chemotherapy response evaluation.

Therefore, this open-label, single arm, phase II, non-randomised single-centre trial was designed to test the effectiveness, safety and tolerability of cabazitaxel in combination with cisplatin as a neoadjuvant regimen in patients with invasive transitional cell carcinoma eligible for radical cystectomy. Optional sub-studies with dynamic contrast enhanced (DCE) MRI and CTCs were also set-up to determine whether, response to neoadjuvant chemotherapy can be predicted early in the course of treatment.

Methods

Patient Characteristics

Between Jul 2012 and Aug 2017, patients with muscle invasive transitional cell carcinoma of the bladder but no nodal or metastatic disease, fit and willing to receive chemotherapy as neoadjuvant treatment and undergo radical cystectomy were recruited. The main inclusion criteria were: patients with histologically proven transitional cell carcinoma of the bladder staged as T2-4N0M0, ECOG performance status of ≤ 1 , and adequate liver and kidney function (eGFR ≥ 55 mL/min).

Patients were excluded if they had previously received treatment for MIBC other than TURBT, active Grade ≥ 2 peripheral neuropathy or had inadequate organ function. Medical history, patient examination, assessment of fitness, computed tomography (CT) scans of the thorax, abdomen and pelvis and blood parameters were required for baseline assessment. Prior to each chemotherapy cycle, physical examination, vital signs, bloods for organ function, concomitant medications and adverse events (AEs) were evaluated. Patients also had a CT scan post 3 cycles of chemotherapy to rule out metastatic disease prior to surgery. The study was approved by South West-Central Bristol Research Ethics Committee.

Regimen

All patients received 4 cycles of i.v. cabazitaxel at $15\text{mg}/\text{m}^2$ followed by cisplatin at $70\text{mg}/\text{m}^2$ on day 1 of a 21-day cycle. Hydration and supportive medicines were prescribed in

accordance with local guidelines for highly emetogenic chemotherapy. Premedication with chlorpheniramine 10mg, Dexamethasone 8mg and Ranitidine 50mg were given 30 min prior to infusion to mitigate allergic reactions. Doses were capped at Body Surface Area of 2.25. Primary prophylaxis with Granulocyte Colony Stimulating Factor (G-CSF) was mandatory for all patients. Cisplatin and cabazitaxel dose modifications for subsequent cycles were made according to the study protocol in the event of predefined toxicity. A delay in treatment of up to 3 weeks was allowed. Patients then underwent radical cystectomy within 8 weeks of the last dose of chemotherapy.

Assessments

The primary end point was objective response rate (ORR) (pathological complete response (pCR) or partial response/ pathological downstaging (PR)) in the absence of radiological progression to lymph node or metastatic disease prior to radical cystectomy, measured by histological examination of the radical cystectomy specimen as per American Joint Committee of Cancer (AJCC) 2010 staging manual (AJCC 2010 Cancer Staging Manual). It was acknowledged that accurate pathological T staging of MIBC prior to cystectomy is difficult, therefore it is the absence of MIBC at cystectomy which has been used as a marker of response in this trial. pCR was described as diagnostic stage T2-T4 going to T0 at resection; PR was described as diagnostic stage T2-T4 going to stage T1, Ta or Tis; and persistent disease was described as no change or an increase in T stage from diagnosis to resection. In addition any patient who progressed on treatment and therefore did not have a cystectomy was designated as having persistent disease. All pathology (diagnostic and resection specimens) was assessed by a specialist multidisciplinary team pathologist specialising in the management of urological malignancies. Radiological progression on cross sectional imaging (CT and unenhanced MRI) was defined according to RECIST criteria version 1.1 [25].

Secondary end points were acute toxicity, PFS and overall OS and quality of life (QoL). Response assessments were done every two cycles. Common Terminology Criteria for Adverse Events (CTCAE) v.4.03 were used to grade toxicity after each cycle and for 30 days (acute toxicity) post completion of last cycle of chemotherapy.

Quality of life (QoL) indicators

Patients were asked to complete validated QoL questionnaires (EORTC QLQ-C30 with module BLM-30 and EQ-5D [26]) at baseline, prior to each subsequent cycle of chemotherapy and at 3-5 weeks after receiving the final dose of chemotherapy. The results will be reported in a separate manuscript.

Follow up

Beyond completion of trial treatment, patients have been followed up via telephone at 3, 6, 9, 12, 18, 24, 36, 48 and 60 months, solely for the purposes of recording progression and survival data. Additional clinical follow up was outside of this study and was performed at the discretion of the surgeon performing radical cystectomy.

CTC Sub-study

Patients who took part in the CTC sub study had a blood sample taken at baseline, prior to every cycle of chemotherapy and at the end of treatment visit for analyses of CTCs. The correlation of CTC response with survival was assessed. Each sample obtained for CTC analysis was processed using the CellTracks AutoPrep System and CellTracks Analyzer II System (CellSearch AutoPrep User's Guide (supplied April 2011)). Whilst, there are no existing criteria for interpretation of CTC response to chemotherapy, measurements for each defined time point were compared with the initial (pre-chemotherapy) measurement. Patients with baseline positive CTC measurements undergoing negative change were classed as CTC responders. Patients with initially negative CTC measurements were considered to have undergone 'CTC progression' if the subsequent CTC measurement was positive.

Patients with persistently positive or persistently negative CTC measurements compared with their baseline, were 'CTC stable (positive)' or 'CTC stable (negative)', and were considered as 'non responders' on CTC measurement.

Statistical Analyses

The sample size was calculated on the premise that an objective response rate (ORR) of less than 35% would not warrant further investigation of this regime in an expanded phase II or phase III setting, but that a rate of 60% or higher would warrant further investigation. Using an exact test for a single proportion, $p_0 = 0.35$ and $p_1 = 0.60$, setting $\alpha = 0.05$ (one-sided) and power = 80%, a total of 26 patients were required for the evaluation of ORR. It was deemed that if there is no patient with an ORR among the first 9 patients treated, then the null hypothesis would not be rejected and the trial would be stopped. Allowing for dropouts, a total of 28 patients were recruited.

The data were analysed using intention-to-treat analysis. Descriptive statistics were used for quantitative measurements. The Kaplan-Meier method and log-rank test were used to analyse PFS and OS. PFS was calculated from the date of consent until progression is recorded. OS was calculated from date of consent until date of death from any cause.

Results

Patient Characteristics

Twenty-eight patients were enrolled between Jul 2012 and August 2017. One patient was excluded from analyses of secondary survival and quality of life endpoints, as on review of staging imaging, this patient was deemed to have metastatic disease at baseline. Only 26 of the remaining 27 registered patients were evaluable for the primary endpoint of ORR as one patient chose to undergo radical radiotherapy rather than cystectomy. This patient was however, included in the reporting of chemotherapy related toxicity. Therefore 26 evaluable patients were included in efficacy analysis and 27 patients were included in the toxicity

analysis. Baseline characteristics of the 26 patients are shown in **Table 1**. The median (range) time from transurethral resection of the bladder tumour (TURBT) to start of chemotherapy was 7.9 (3.9-9.3) weeks. Patients had their cystectomy in a median of 7 weeks from the last cycle of chemotherapy.

Treatment

The majority of patients (77.7%; 21/27), received all 4 cycles of cabazitaxel/ cisplatin. A median of 4 cycles were received (range: 1-4). Cabazitaxel was well tolerated with only 4 patients (14.8%) needing dose reduction (nausea & vomiting (2), fatigue (1), infection (1)). A further 6 patients had a cisplatin dose reduction due to low GFR (2), fatigue (2), infection (1), nausea (1). Administration of chemotherapy was delayed for a total of 8 cycles out of 97 given (8.2%). The delay was due to chemotherapy related adverse events (low GFR, deranged liver function, hypersensitivity reactions) for one cycle each in 4 patients (14.8%). All other delays were for short periods due to non-medical issues e.g. scheduling and patient holidays.

Table 1 - Patient baseline characteristics

Trial ID	M / F	Age	TURBT to chemo (wks)	Consent to chemo (wks)	No of cycles	Reason for stopping early	Sx	Sx histology	Length of post-op stay (days)	Clavien-Dindo grade	NP-0, P-1	PFS (m)	Alive-0, dead-1	Cause of death	OS (m)
1†	M	61	7.00	2.29	1	PD	No				1	1.67	1	PD, M1	6.03
2	M	74	6.29	0.29	4		Yes	ypT3a N0Mx	7	0	0	77.50	0		79.20
3	M	78	7.86	4.00	4		Yes	ypTis N0 Mx	14	2	0	74.23	0		75.40
5	M	65	8.86	0.29	4		Yes	ypTisN0Mx	7	0	0	79.20	0		83.80
6	F	73	8.86	0.00	3	AE	Yes	ypT3b N1 Mx	10	1	1	6.33	1	PD, M1	8.63
7	M	74	5.57	0.86	3	Patient choice	Yes	ypT3apN2pMX	13	2	1	18.60	1	PD, M1	20.30
9	M	48	8.43	0.43	4		Yes	ypT2b pN0 pMX	7	0	0	74.53	0		76.67
10	M	69	8.86	0.00	4		Yes	ypT0N0Mx	19	2	0	73.17	0		76.40
11	M	54	3.86	1.14	4		Yes	ypTaN0 (0/33)Mx	9	0	0	68.37	0		69.97
12	M	61	7.86	1.14	4		Yes	ypT0 N0 (0/14)Mx	9	0	0	68.57	0		69.47
13	M	68	7.14	0.43	4		Yes	ypT0N0 (0/13)Mx	6	0	0	68.23	0		69.40
14	M	64	5.00	0.14	4		Yes	ypT2bpN1 (1/5)Mx	6	0	1	6.30	1	PD, M1	13.37
17*	M	53	9.29	1.14	3	patient choice	Yes	ypT0N2 (12/23)Mx	5	0	1	4.67	1	PD, M1	16.90
18	M	67	5.71	1.00	4		Yes	ypT1pN0 (0/24)pMx	4	2	0	59.17	0		61.13
19	M	64	6.00	0.43	4		Yes	yT2bN0 (0/25)Mx	17	2	0	55.60	0		58.30
20	F	73	8.29	0.14	1	Patient choice	Yes	ypT3bN0 (0/9)Mx	7	0	1	7.17	1	PD, M1	9.53
21	M	73	9.00	0.14	4		Yes	ypT0ypN0(0/20)Mx	5	2	0	51.47	0		52.60
22	M	68	8.71	3.71	4		Yes	ypT0yN0(0/9)Mx	4	0	0	44.93	0		50.63

23	F	78	8.57	0.14	4		Yes	ypT3bN0(0/17)Mx	11	2	1	6.70	1	PD, M1	7.90
24	M	78	8.71	0.86	1	AE	Yes	ypTisN0(0/9)Mx	10	0	0	43.13	0		43.70
25	F	70	7.86	0.14	4		Yes	ypT0N0 (0/29)Mx	5	0	0	41.27	0		43.53
26	M	76	5.43	0.57	4		Yes	ypT0ypN0(0/14)Mx	77	3b	0	31.13	0		39.47
28	M	55	8.43	0.14	4		Yes	ypT0pN0(0/13)pMx	4	0	0	9.07	0	went overseas, LFU	13.70
29	F	64	6.86	1.57	4		Yes	ypT2bN0(0/13)M0	6	2	0	24.90	0		25.13
30	M	55	6.00	1.00	4		Yes	ypT1N0 (0/11)Mx	8	2	0	22.63	0		23.50
31	M	46	7.43	1.14	4		Yes	ypT0 ypN0(0/13)Mx	6	0	0	21.47	0		22.00
Median		67.5	7.86	0.57	4				7			42.27			43.6
Min		46	3.86	0.00	1				4			1.67			6.03
Max		78	9.29	4.00	4				77			79.20			83.80

M-Male, F-Female, TURBT- Transurethral resection of bladder tumour, wks - weeks, Sx-surgery, PD - Progressive disease, AE - Adverse event, NP - Non Progressor, P- Progressor, PFS - Progression free survival, OS - Overall survival, m - months, M1 - metastatic disease, LFU - lost to follow up. † patient had progressed on chemotherapy, both in bladder & distantly and classed as a non-responder, *patient was classed as a non-responder due to N2 disease.

Efficacy

Objective response rate (ORR) was 57.7% (15/26 patients). Pathologic complete remission was observed in 9 of these patients (34.6%) and in 6 patients (23.1%) the tumour was down staged (pTa, Tis, T1N0). Seven patients have progressed (26.9%), one during neoadjuvant chemotherapy (3.7%) and a further six subsequent to cystectomy (25.9%). Seven patients have died (26.9%), with median time from progression to death of 2.3 months demonstrating the aggressive nature of MIBC. Of the patients who progressed all had persistent disease at cystectomy. The median PFS and OS in the whole population and in those who achieved ORR has not yet been reached (5-yr estimates of 70% and 100%, respectively in whole population and in those who achieved ORR). Patients who did not have any pathological downstaging after NAC had a significantly worse median PFS (7.2m; $p=0.001$) and OS (16.9m; $p=0.001$; 5-yr estimate of 36% **Figure 1**). There was no significant difference in the PFS or OS between patients who had pCR and patients who had pathological downstaging (pTa, Tis, T1N0).

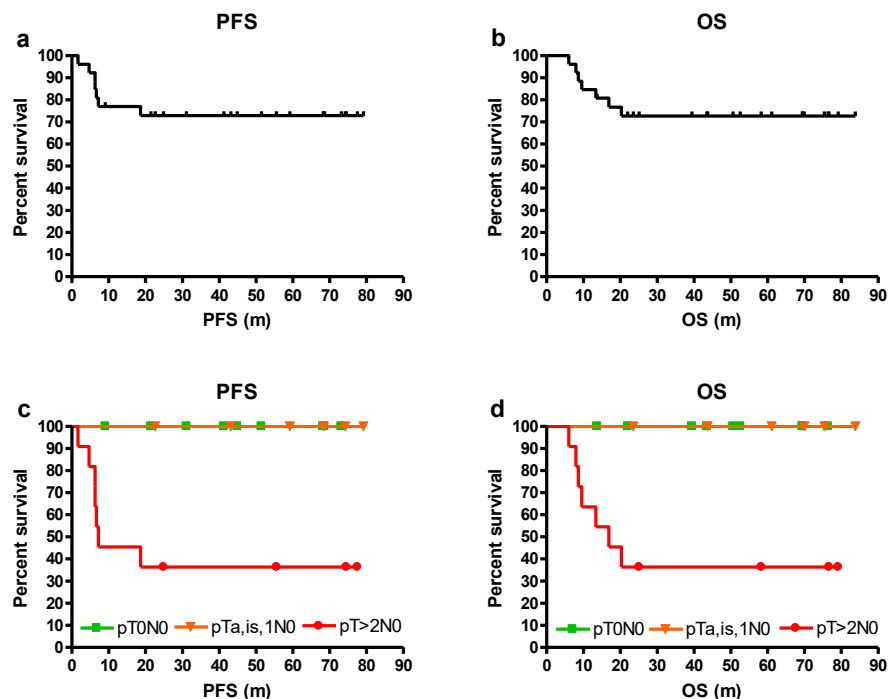


Fig 1: Survival curves. **a, b)** Overall PFS and OS. The median PFS and OS for the whole population have not yet been reached. **c, d)** The median PFS and OS were 7.2 & 16.9m, respectively; significantly worse in patients who did not have pathological downstaging.

Toxicity

Overall, cabazitaxel was well tolerated. There were 253 reported AEs (Gr1: 145/253 (57.3%), Gr2: 91/253 (36%), Gr3: 15/253 (5.9%), Gr4: 2/253 (0.8%)). Of the 253 adverse events 6 (2.3%) were related to cabazitaxel only, 37 (14.6%) were related to cisplatin only whilst 146 (57.7%) were deemed related to both. A quarter of the adverse events 64 (25.3%) were considered not related to either drug. The most common AEs reported were gastrointestinal disorders (30.8%) followed by general disorders (13%) and nervous system disorders (11.9%). Fatigue (11%) was the most common AE in the general disorders whilst nausea and constipation (8.7%) were the most common gastrointestinal disorders. Adverse events \geq grade 3 were reported by 10 patients and represented 6.7% of the total AEs recorded (**Table 2**) and the majority of the patients fully recovered from these episodes. There were no Suspected Unexpected Serious Adverse Reactions (SUSARs) during the course of the study. Post cystectomy, the average length of stay (LOS) was a median of 7 (range:4-77) days. Only one patient had grade 3 or above Clavien-Dindo complications (**Table 1**).

Table 2: Breakdown of AEs grade \geq 3

Patient	Adverse Event	Grade	Related
1	Pelvic pain	3	No
1	Uncontrolled pain	3	No
2	Syncope	3	No
3	Right pulmonary embolus	3	Yes cisplatin
6	Colonic fistula	3	No
19	Vascular access complication	3	No
20	Acute Kidney Injury	3	Yes both
20	Mucositis	3	Yes both
20	Dehydration	3	Yes both
21	UTI	3	No
22	Increased GGT	3	Yes both
24	Thrombocytopenia	4	Yes both
24	Dehydration	3	No
24	Fatigue	3	Yes both
24	Decreased neutrophils	3	Yes both
27	UTI	3	No
27	Urinary sepsis	4	Yes both

CTC Sub-study

Only eighteen patients have had CTCs assessed as per protocol. Overall the CTC yield was very low. Five patients had initial negative CTC measurements with subsequent CTC measurements becoming positive (CTC progression). None of these five have had pCR and three of these CTC progressors have subsequently developed metastatic disease. None of the other 13 patients were CTC responders.

Discussion

We have, in this phase 2 single arm study, shown that cabazitaxel in combination with cisplatin as neoadjuvant treatment of MIBC is a well-tolerated and effective regimen prior to radical cystectomy with a favourable toxicity profile. The overall response rate (ORR) was 57.7% (15/26) with a pathological complete response (pCR) rate of 34.6% (9/26). The median PFS and OS in the whole population has not yet been reached. Patients who did not have any pathological downstaging after NAC had a significantly worse PFS and OS (7.2m and 16.9m, respectively; $p=0.001$), than those who had an objective response. The LOS post cystectomy and the peri-operative complications are in keeping with what is reported in the literature [27, 28] suggesting that NAC did not have an adverse impact on surgical outcome. Ninety-day mortality has been used as a surrogate for improved outcomes after radical cystectomy [29, 30]. None of our patients died within 90 days of surgery.

Several randomized controlled trials and meta-analyses support the use of neoadjuvant platinum-based multi-agent chemotherapy in MIBC. NAC is associated with an absolute overall survival improvement of 5% in 5 years, 14% decrease in disease specific mortality and 9% improvement in disease specific survival in patients of good performance status [2, 3, 6]. In view of the favourable toxicity profile, Gemcitabine and Cisplatin (GC) combination has become the current standard of care in the neoadjuvant setting in the treatment of MIBC. The 5-yr estimated PFS and OS of patients who had pCR reported in

literature are 90% and 80%, respectively. The corresponding estimates for those who did not have any pathological downstaging are 50% and 45% [31, 32]. The 5-yr estimates in our study are in keeping with the literature with pCR/ pathological downstaging providing a 5yr PFS and OS of over 90% whereas a lack of response resulted in a 5-yr PFS and OS estimate of 36%.

Despite the strong evidence [33], there is low and inconsistent use of NAC, due to risk of toxicity, the risk of progression in non-responders, and the fact that adjuvant chemotherapy could be used instead [34, 35]. Zaid et al, in a retrospective review of over 5000 patients with MIBC in the USA, reported that the overall use of NAC increased from 7.6% in 2006 to about 20.9% in 2010, with 10.6% achieving complete pathologic downstaging [36]. In a European survey, the uptake of NAC was around 12% [37].

The lack of response in a significant proportion of patients with NAC probably explains the low rates of uptake. Therefore, there is a need for predictive biomarkers to assess response to NAC. Zargar et al [38], showed that, pathological downstaging predicts survival and can be used as a surrogate marker. Petrelli et al, concluded that pathologic complete response (pCR) is an indicator of better survival [39]. Our results of better survival in patients with pathological downstaging, are also in keeping with this conclusion. Additionally we found no significant difference in the survival of patients who had pCR vs. patients with pTa/Tis/T1, N0, in keeping with Zargar et al and Sonpavde et al [38, 40]. Four patients who did not have any pathological downstaging have not progressed and are alive and disease free (**Table 1**). This suggests disease heterogeneity and the importance of evaluating molecular biomarkers for predicting response to NAC [41, 42].

The rates of pCR after various agents is as listed in **Table 3 [6, 32, 38, 43, 44]**. The pCR rates with GC chemotherapy are in the range of 23-26% [32, 38]. Our study has shown a pCR rate of 34.6% which is better than that seen with the GC regimen. This shows promise and requires further evaluation in a large multicentre phase 2/ phase 3 study.

Table 3: Pathological complete response rates (pCR) after Neoadjuvant treatments.

Agent/ trial	pCR rate
TURBT (resection of bladder tumour) [32]	12-15%
Cisplatin based chemo	
MVAC trial [6]	38%
Pooled analysis of Gemcitabine/Cisplatin [32]	25.6%
Real world data [38]	23%
Bristol bladder trial (Cabazitaxel/Cisplatin) (This study)	34.6%
Immunotherapy	
ABACUS trial (n=68); Atezolizumab [44]	29% - all comers 40% in PDL1 + pts
PURE-01 trial (n=43); Pembrolizumab [43]	39.5% - all comers 50% in PDL1 + pts

However, there are a proportion of patients who are ineligible for platinum based chemotherapy. There have been no further improvements in the standard neo-adjuvant strategies over the last 2 decades. This provided the impetus to explore other agents such as immunotherapy. To date, immunotherapy outside of trials has only been used to treat metastatic bladder cancer. The introduction of immunotherapy has resulted in a paradigm shift in the therapeutic landscape of urothelial carcinoma (UC). Several anti-programmed cell death (PD)-1/ligand- 1 (PD-L1) agents have been approved for locally advanced or metastatic UC both in the post-platinum setting and as first line treatments in PDL1 enriched population [45]. Out of the 5 agents showing promise, pembrolizumab is the only therapy to have been approved by both the US Food and Drug Administration and European Medicines Agency based on level 1 evidence.

Integrating short courses of immunotherapy in nonmetastatic resectable lung cancer has shown promise, thus exploring the potential to become a new strategy for neoadjuvant therapy [46]. This strategy was tested in muscle invasive bladder cancer in a couple of phase 2 single arm trials with single agent immunotherapy to see if it improves the pCR rates compared to NAC. A phase 2 exploratory trial of 2 cycles of atezolizumab prior to cystectomy, reported a pCR rate of 29% (20/68) in all the 68 evaluable patients and 40% (10/25) in the PD-L1 enriched patients [44]. In another study by Necchi et al, a pCR rate of

40% was seen with Pembrolizumab [43]. However, there was an increased incidence of post-operative complications (35% Gr2-4) with pembrolizumab and 2 treatment related deaths with atezolizumab. This needs further research in assessing both chemotherapy regimens with immunotherapy in a multi-centre phase 3 setting.

Our findings from the CTC analyses, although limited, are hypothesis generating. The CTC yield is very low and the presence of CTC's is likely to be associated with predicting non-response to NAC. This warrants further exploration, along with molecular subtyping using gene expression analysis and differences in responses and toxicity profile depending on the treatment modalities (chemotherapy vs immunotherapy).

Although single agent immunotherapy has shown promise in the neoadjuvant setting among many tumour types, only a proportion of patients show benefit from these therapies (about 30-40%) [43, 44]. In order to further improve the outcomes, combination of immunotherapy and chemotherapy is being explored. The combination of chemotherapy and immunotherapy has a synergistic effects and has been shown to improve outcomes in metastatic lung cancer [47]. In this regard, three phase 2 trials evaluating the combination of immunotherapy (NCT02365766 Pembrolizumab, NCT03294304 Nivolumab and NCT02989584 Atezolizumab) with gemcitabine and cisplatin are underway. However, there are also concerns over the cost of immunotherapy and the rapid introduction of new drugs that have not been tested in randomized controlled trials. The cost of new drugs often does not reflect the benefits experienced by patients. Moreover, it is paramount that chemotherapy regimens considered for combination with immunotherapy are those with the best efficacy and tolerability. Our study provides the rationale to evaluate the standard Cisplatin-Gemcitabine combination and the proposed novel combination of Cisplatin-Cabazitaxel with or without immunotherapy in the neoadjuvant setting, in a large phase 3 randomised trial.

There is paucity of data on QoL outcomes in patients undergoing systemic therapy for MIBC. Our results on the impact of NAC on QoL, will be reported separately. Tumour staging evaluation in MIBC presents a challenge for uro-oncologists. There is a lack of a reliable radiological test for T staging in this disease. Computed tomography (CT) imaging cannot be relied upon to demonstrate tumour stage reliably. Moreover, it is often not possible to determine the exact T stage of these tumours from the diagnostic biopsy due to the nature of the diagnostic pathological sampling. This is reflected in the fact that the majority of patients in this trial were staged 'pT2 at least' at diagnosis. This leads to a real possibility of under-staging at diagnosis. Hence we have evaluated the role of multiparametric MRI in the staging and response assessment with NAC. The results of these will be the subject of a separate manuscript.

The main limitation of this study is that this is a single centre phase 2 observational study with a modest sample size. These results will need further validation in a larger phase 3 study, especially given the favourable toxicity profile and improved pCR rates of cabazitaxel and cisplatin.

Conclusions

Cabazitaxel in combination with cisplatin for neoadjuvant treatment of MIBC can be considered a safe, well-tolerated and effective regimen prior to radical cystectomy. The higher pCR rate warrants further evaluation of the Cabazitaxel/ Cisplatin regimen in a larger phase 3 trial.

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