Original Study

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

Neoadjuvant cisplatin-based combination chemotherapy improves survival in muscle-invasive bladder cancer. 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. This combination can be considered well-tolerated and efficacious with higher response rates (57.7%), which compares favorably to that with cisplatin/gemcitabine (23%–26%).

Introduction: Neoadjuvant cisplatin-based combination chemotherapy improves survival in muscle-invasive bladder cancer. However, response rates and survival remain suboptimal. We evaluated the efficacy, safety, and tolerability of cisplatin plus cabazitaxel. **Methods:** A phase II single-arm trial was designed to recruit at least 26 evaluable patients. This would give 80% power to detect the primary endpoint, an objective response rate defined as a pathologic complete response plus partial response (pathologic downstaging), measured by pathologic staging at cystectomy ($p_0 = 0.35$ and $p_1 = 0.60$, $\alpha = 0.05$). **Results:** Objective response was seen in 15 of 26 evaluable patients (57.7%) and more than one- third of patients achieved a pathologic complete response (9/26; 34.6%). Seventy-eight percent of the patients (21/27) completed all cycles of treatment, with only 6.7% of the reported adverse events being graded 3 or 4. There were 6 treatment-related serious adverse event reported, but no suspected unexpected serious adverse reactions. In the patients who achieved an objective response, the median progression-free survival and overall survival were not reached (median follow-up of 41.5 months). In contrast, the median progression-free survival (7.2 months) and overall survival (16.9 months) were significantly worse ($P = .001$, log-rank) in patients who did not achieve an objective response. **Conclusion:** Cabazitaxel plus cisplatin for neoadjuvant treatment of muscle-invasive bladder cancer can be considered a well-tolerated and effective regimen before definitive therapy with higher rates (57.7%) of objective response, comparing favorably to that with of cisplatin/gemcitabine (23%–26%). These results warrant further evaluation in a phase III study.

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Introduction

Carcinoma of the urinary bladder is the seventh most common cancer in the UK with around 10,000 diagnoses made annually.[1] The majority are transitional cell carcinomas with about 30% of cases presenting as muscle-invasive bladder cancer (MIBC). A

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further 50% of patients presenting with high risk non–MIBCs are at a high risk of developing muscle-invasive disease.

The 5-year survival after cystectomy for patients with MIBC varies from 36% to 48%, and specifically from 17% to 46% for pT3b tumours.[2–5] Cisplatin-based neoadjuvant chemotherapy (NAC) followed by definitive treatment (surgery or radiotherapy) improved absolute overall survival (OS) by 5% and disease-specific survival by 9% at 5 years compared with patients receiving definitive treatment alone.[2,3]

The SWOG-8710 trial[6] showed that methotrexate, vinblastine, doxorubicin, cisplatin (MVAC) chemotherapy had the best 5-year OS (57%) but at the cost of excess toxicity. The accelerated or dose dense MVAC (ddMVAC) regimen has shown improved OS and has less toxicity compared with standard MVAC in advanced bladder cancer.[7] Encouraging results were seen when using ddMVAC in the NAC setting in patients with MIBC.[8–10]

The combination of gemcitabine plus cisplatin (GC) has similar response and survival rates compared with MVAC, and less toxicity in advanced bladder cancer.[11] Based on these data, GC has become the standard of care in the neoadjuvant setting in the treatment of MIBC.[12,13]

Despite the obvious benefit of NAC, there have been few trials comparing different regimens and few reliable biomarkers to identify patients likely to benefit from NAC. Therefore, there is a clear need for new combinations of drugs to improve patient outcomes.

Interest in taxanes has emerged from trials in metastatic bladder cancer after the failure of platinum-based chemotherapy.[14–17] Taxanes in combination with cisplatin have also been evaluated in the neoadjuvant setting in bladder cancer.[18–20]

Cabazitaxel, a novel taxane, is well-tolerated and effective in tumors both sensitive and resistant to other taxanes.[21] Single-agent cabazitaxel has been used in trials with patients with cisplatin-intolerant advanced MIBC.[22] However, benefit has been seen in combining cabazitaxel with platinum-based agents in the treatment of metastatic breast cancer.[23] Recent work in animal models,[24] phase I studies,[25] and in metastatic prostate cancer[26] report synergism and tolerability in combination with cisplatin. Therefore, cabazitaxel combined with cisplatin (which is the most active agent accounting for survival benefit) could potentially improve on the modest efficacy results seen with single-agent cabazitaxel, thus presenting a potentially active regimen in MIBC before definitive therapy. This regimen may also be a suitable combination to test in combination with immunotherapy.

Therefore, our trial was designed to test the effectiveness, safety, and tolerability of cabazitaxel plus cisplatin as a neoadjuvant regimen in patients with MIBC eligible for radical cystectomy. Optional substudies with dynamic contrast enhanced MRI and CTCs were also set up to determine whether response to NAC can be predicted early in the course of treatment.

Methods

Patient Characteristics

Between July 2012 and August 2017, patients with MIBC but no nodal or metastatic disease, fit and willing to receive NAC and undergo radical cystectomy were recruited. The main inclusion criteria were histologically proven transitional cell carcinoma of the bladder (T2-4N0M0), performance status of 1 or less, and adequate organ function (estimated glomerular filtration rate of ≥55 mL/min).

Medical history, patient examination, assessment of fitness, whole body computed tomography, scans and blood parameters were required for baseline assessment. Before each cycle, physical examination, vital signs, bloods, concomitant medications and adverse events (AEs) were evaluated. Patients had a computed tomography scan after 3 cycles of chemotherapy to rule out metastases before surgery. The study was approved by South West-Central Bristol Research Ethics Committee.

Regimen

Patients received 4 cycles of cabazitaxel (15 mg/m^2: chosen in view of the potential for additive/synergistic toxicity on combination with cisplatin) and cisplatin (70 mg/m^2) on day 1 of a 21-day cycle. Hydration and supportive premedications were prescribed as per local guidelines for highly emetogenic chemotherapy and to mitigate allergic reactions. Doses were capped at a body surface area of 2.25. Primary prophylaxis with granulocyte colony stimulating factor was mandated. A treatment delay of up to 3 weeks was allowed for recovery of toxicity. A dose reduction of 20% was considered for grade 3 or higher toxicities. The subsequent cycles were continued at planned dose if toxicities resolved. Patients underwent radical cystectomy within 8 weeks of the last dose of chemotherapy.

Assessments

The primary endpoint was the objective response rate (ORR) (pathologic complete response [pCR] plus partial response/pathologic downstaging [PR]), as measured by histologic examination of the cystectomy specimen. pCR was described as diagnostic stage T2–T4 going to T0 at resection; PR was diagnostic stage T2–T4 going to stage T1, Ta, or Tis; and persistent disease as no change or an increase in T stage from diagnosis to resection. Any patient who progressed on treatment and therefore did not undergo cystectomy was designated as having persistent disease. All pathology was assessed by a specialist uropathologist. Radiologic progression on computed tomography scan was defined according to the RECISTv.1.1 criteria.[27]

Secondary endpoints were acute toxicity, progression-free survival (PFS), OS and quality-of-life (QoL). The QoL results will be reported separately. Common Terminology Criteria for Adverse Events (CTCAE)v.4.03 were used to grade acute toxicity after each cycle and for 30 days after completion of chemotherapy.

Follow-up

Patients have been followed up at 3, 6, 9, 12, 18, 24, 36, 48, and 60 months after cystectomy for the purposes of recording progression and survival data.

Statistical Analyses

The sample size was calculated on the premise that an ORR of <35% would not warrant further investigation of this regime in an expanded phase II/III setting, but that a rate of 60% or higher

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Table 1 Patient Baseline Characteristics

S. No	Sex	Age	TURBT to Chemo (wk)	Consent to Chemo (wk)	No. of Cycles	Reason for Stopping Early
1*	M	61	7.00	2.29	1	PD
2	M	74	6.29	0.29	4	
3	M	78	7.86	4.00	4	
4	M	65	8.86	0.29	4	
5	F	73	8.86	0.00	3	AE
6	M	74	5.57	0.86	3	Patient choice
7	M	48	8.43	0.43	4	
8	M	69	8.86	0.00	4	
9	M	54	3.86	1.14	4	
10	M	61	7.86	1.14	4	
11	M	68	7.14	0.43	4	
12	M	64	5.00	0.14	4	
13†	M	53	9.29	1.14	3	patient choice
14	M	67	5.71	1.00	4	
15	M	64	6.00	0.43	4	
16	F	73	8.29	0.14	1	Patient choice
17	M	73	9.00	0.14	4	
18	M	68	8.71	3.71	4	
19	F	78	8.57	0.14	4	
20	M	78	8.71	0.86	1	AE
21	F	70	7.86	0.14	4	
22	M	76	5.43	0.57	4	
23	M	55	8.43	0.14	4	
24	F	64	6.86	1.57	4	
25	M	55	6.00	1.00	4	
26	M	46	7.43	1.14	4	
Median		67.5	7.86	0.57	4	
Minimum		46	3.86	0.00	1	
Maximum		78	9.29	4.00	4	

Abbreviations: AE = adverse event; F = female; M = male; PD = progressive disease; TURBT = transurethral resection of bladder tumor.
* Patient had progressed on chemotherapy, both in bladder and distantly and classed as a nonresponder.
† Patient was classed as a nonresponder due to N2 disease.

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 of 80%, 26 patients were required for the evaluation of ORR. It was deemed that if in the first 9 patients treated, no patient achieved ORR, then the null hypothesis would not be rejected and the trial would be stopped.

Data were analyzed using an intention-to-treat analysis. Descriptive statistics were used for quantitative measurements. The Kaplan–Meier method and log-rank test were used to analyze PFS (consent date until progression) and OS (consent date until death from any cause).

Results

Patient Characteristics

Twenty-eight patients were recruited. One patient was excluded from analyses, because on review of imaging, this patient was deemed to have had metastases at baseline. Another patient chose to undergo radical radiotherapy rather than cystectomy, leaving 26 patients evaluable for the primary endpoint. This latter patient was however, included in the AE reporting. Therefore, 26 patients were included in efficacy analysis and 27 patients in the toxicity analysis. Baseline characteristics are shown in Table 1. Median (range) time from transurethral resection of the bladder tumor to start of chemotherapy was 7.9 weeks (3.9–9.3 weeks). Patients had their cystectomy in a median of 7 weeks from the end of chemotherapy.

Treatment

The majority of patients (77.7%; 21/27), received all 4 cycles of cabazitaxel/cisplatin (median 4 cycles [1–4]). Cabazitaxel was well tolerated with only 4 patients (14.8%) needing dose reduction (nausea and vomiting [$n = 2$], fatigue [$n = 1$], infection [$n = 1$]). A further 6 patients had a cisplatin dose reduction (low glomerular filtration rate [$n = 2$], fatigue [$n = 2$], infection [$n = 1$], nausea [$n = 1$]). Administration of chemotherapy was delayed for 8 cycles

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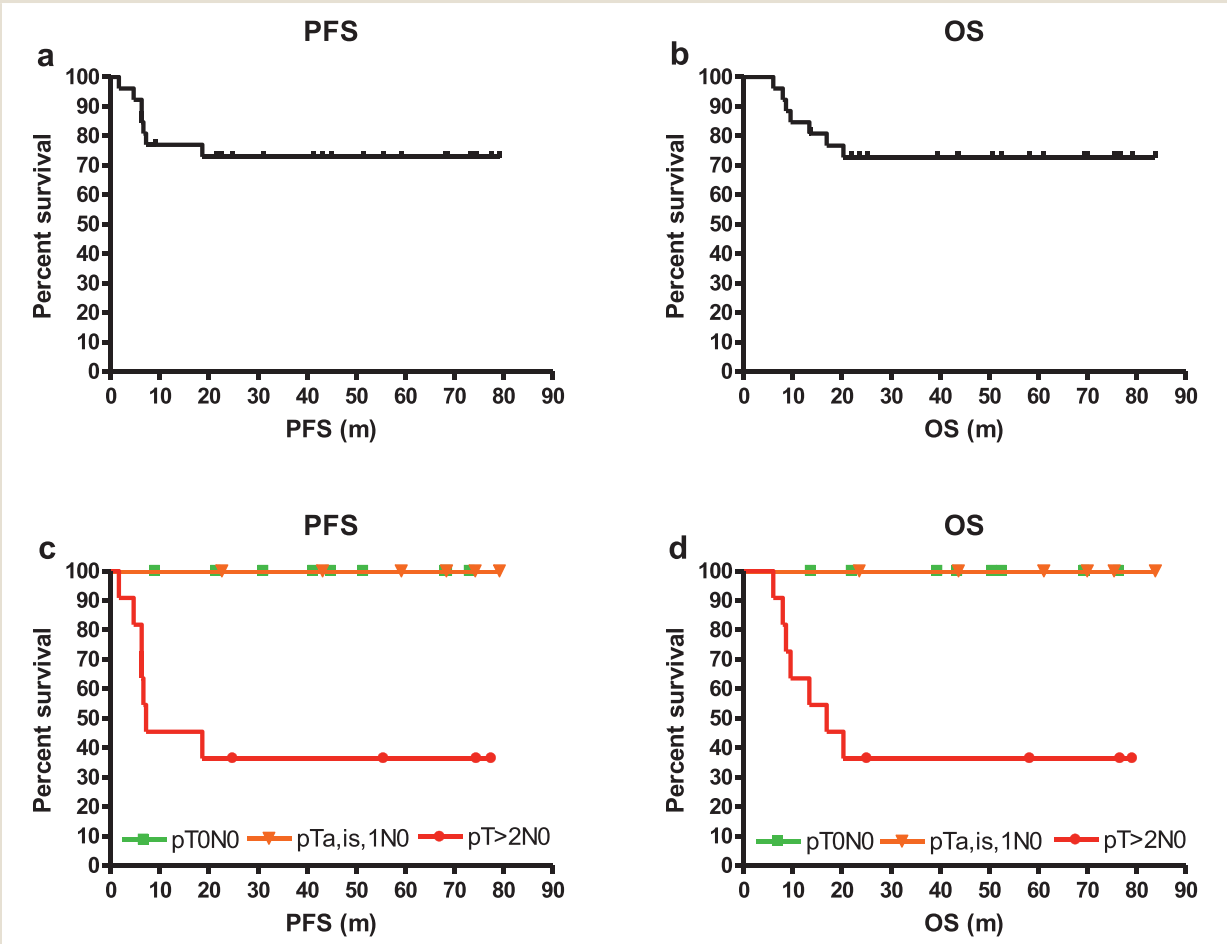
Fig. 1 Survival curves. (a, b) Overall progression-free survival (PFS) and overall survival (OS). The median PFS and OS for the whole population have not yet been reached. (c, d) The median PFS and OS were 7.2 and 16.9 mnoths, respectively for patients with and without pathologic downstaging; significantly worse in patients who did not have pathologic downstaging.



out of 97 (8.2%). In 4 patients (14.8%) the delay was due to chemotherapy related AEs (low glomerular filtration rate, deranged liver function, hypersensitivity reactions). Other delays were for short periods due to nonmedical issues, for example, scheduling and patient holidays.

Efficacy

The ORR was 57.7% (15/26 patients; 95% CI 36.9%–76.6%) leading to the rejection of the null hypothesis. pCR was observed in 9 patients (34.6%) and 6 patients (23.1%) had tumor downstaging (pTa, Tis, T1N0). Seven patients progressed (26.9%), one during NAC (3.7%) and the rest subsequent to cystectomy (25.9%). Of the 7 patients who progressed, 3 patients required dose reductions; cabazitaxel (1 patient for 2 cycles, 1 patient for 1 cycle) and cisplatin (1 for 1 cycle, 1 for 2 cycles). This suggests that progression is due to unfavorable tumor biology. Seven patients have died (26.9%), within a median of 2.3 months from progression to death, demonstrating the aggressive nature of MIBC. All the patients who progressed had persistent disease at cystectomy. The median PFS and OS have not yet been reached either in the whole population or those who achieved ORR (5-year estimate 70% and 100%, respectively). Patients who had no pathologic downstaging after NAC had a significantly worse median PFS (7.2 months; $P = .001$) and OS (16.9 months; $P = .001$; 5-year estimate of 36% Figure 1). There was no significant difference in PFS or OS between patients who had pCR and patients who had PR.

Toxicity

Overall, cabazitaxel was well-tolerated. There were 253 reported AEs (grade 1, 145/253 [57.3%]; grade 2, 91/253 [36%]; grade 3, 15/253 [5.9%]; grade 4, 2/253 [0.8%]). All the AEs have been listed in Supplementary Table 1. Of these 253 AEs, 6 (2.3%) were related to cabazitaxel alone, 37 (14.6%) to cisplatin, and146 (57.7%) were related to both. One-quarter of the AEs, 64 (25.3%) were considered not related to either drug. The most common AEs reported were gastrointestinal (30.8%) followed by general (13%)

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Table 2 Breakdown of AEs Grade 3 or Higher

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

Abbreviations: GGT = gamma glutamyl transferase; UTI = urinary tract infection.

and nervous system disorders (11.9%). Fatigue (11%) was the most common AE in the general disorders, whereas nausea and constipation (8.7%) were the most common gastrointestinal disorders. AEs grade 3 or higher were reported by 10 patients and represented 6.7% of the total AEs recorded (Table 2).The majority of the patients fully recovered from these episodes. No suspected unexpected serious adverse reactions were reported. After cystectomy, the median length of stay in hospital was 7 (4–77) days. Only 1 patient had grade 3 or higher Clavien–Dindo complications (Table 3).

Discussion

We have shown that neoadjuvant cabazitaxel/cisplatin is a well-tolerated and effective regimen before radical cystectomy with a favorable toxicity profile. The ORR was 57.7% with a pCR rate of 34.6%. The median PFS and OS have not yet been reached in the whole population. However, patients who showed no pathologic downstaging had a significantly worse PFS and OS (7.2 months and 16.9 months, respectively; $P = .001$), than those who achieved ORR. The length of stay after cystectomy and the perioperative complications are in keeping with those reported in literature,[28,29] suggesting no adverse impact on surgical outcome. Ninety-day mortality has been used as a surrogate for improved outcomes after radical cystectomy.[30,31] None of our patients died within 90 days of surgery.

Several randomized trials and meta-analyses support the use of neoadjuvant platinum-based multiagent chemotherapy in MIBC. NAC is associated with an absolute improvement of 5% and 9% in OS and disease-specific survival, respectively.[2,3,6] In view of its favorable toxicity profile, GC has become the current standard of care in this setting. The reported 5-year estimated PFS and OS of patients who had pCR are 90% and 80%, respectively, but only 50% and 45% for those without any pathologic downstaging.[32,33] The 5-year estimates in our study are in keeping with this, with ORR providing a 5-year PFS and OS of more than 90%, whereas a lack of response resulted in a 5-year PFS and OS estimate of 36%.

Despite strong evidence,[34] there is low and inconsistent use of NAC in MIBC, owing to the risk of toxicity, risk of progression in nonresponders, and the option of adjuvant chemotherapy.[35,36]

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[13] showed that pathologic downstaging predicts survival and can be used as a surrogate marker. Petrelli et al[37] concluded that pCR is an indicator of better survival. Our results support these

Table 3 Patient Results

S. No	Sx	Sx histology	Length of Postoperative Stay (Days)	Clavien-Dindo Grade	NP-0, P-1	PFS (m)	Alive-0, dead-1	Cause of Death	OS (Months)
1*	No				1	1.67	1	PD, M1	6.03
2	Yes	ypT3aN0 (0/5)Mx	7	0	0	77.50	0		79.20
3	Yes	ypTisN0 (0/2)Mx	14	2	0	74.23	0		75.40
4	Yes	ypTisN0 (0/9)Mx	7	0	0	79.20	0		83.80
5	Yes	ypT3bN1 (1/10)Mx	10	1	1	6.33	1	PD, M1	8.63
6	Yes	ypT3aN2 (2/12)Mx	13	2	1	18.60	1	PD, M1	20.30
7	Yes	ypT2bN0 (0/19)Mx	7	0	0	74.53	0		76.67
8	Yes	ypT0N0 (0/8)Mx	19	2	0	73.17	0		76.40
9	Yes	ypTaN0 (0/33)Mx	9	0	0	68.37	0		69.97
10	Yes	ypT0N0 (0/14)Mx	9	0	0	68.57	0		69.47
11	Yes	ypT0N0 (0/13)Mx	6	0	0	68.23	0		69.40
12	Yes	ypT2bpN1 (1/5)Mx	6	0	1	6.30	1	PD, M1	13.37
13†	Yes	ypT0N2 (12/23)Mx	5	0	1	4.67	1	PD, M1	16.90

(*continued on next page*)

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Table 3 (*continued*)

S. No	Sx	Sx histology	Length of Postoperative Stay (Days)	Clavien-Dindo Grade	NP-0, P-1	PFS (m)	Alive-0, dead-1	Cause of Death	OS (Months)
14	Yes	ypT1pN0 (0/24)Mx	4	2	0	59.17	0		61.13
15	Yes	yT2bN0 (0/25)Mx	17	2	0	55.60	0		58.30
16	Yes	ypT3bN0 (0/9)Mx	7	0	1	7.17	1	PD, M1	9.53
17	Yes	ypT0N0(0/20)Mx	5	2	0	51.47	0		52.60
18	Yes	ypT0N0(0/9)Mx	4	0	0	44.93	0		50.63
19	Yes	ypT3bN0 (0/17)Mx	11	2	1	6.70	1	PD, M1	7.90
20	Yes	ypTisN0 (0/9)Mx	10	0	0	43.13	0		43.70
21	Yes	ypT0N0 (0/29)Mx	5	0	0	41.27	0		43.53
22	Yes	ypT0N0 (0/14)Mx	77	3b	0	31.13	0		39.47
23	Yes	ypT0N0 (0/13)Mx	4	0	0	9.07	0	went overseas, LFU	13.70
24	Yes	ypT2bN0 (0/13)M0	6	2	0	24.90	0		25.13
25	Yes	ypT1N0 (0/11)Mx	8	2	0	22.63	0		23.50
26	Yes	ypT0N0 (0/13)Mx	6	0	0	21.47	0		22.00
Median			7			42.27			43.6
Min			4			1.67			6.03
Max			77			79.20			83.80

Abbreviations: LFU = lost to follow-up; M1 = metastatic disease; OS = overall survival; P = progressor; PFS = progression free survival; NP = nonprogressor; Sx = surgery.
* Patient had progressed on chemotherapy, both in bladder & distantly and classed as a nonresponder.
† Patient was classed as a nonresponder due to N2 disease.

Table 4 Pathologic Complete Response Rates (pCR) after Neoadjuvant Treatments

Agent/trial	pCR rate
TURBT (resection of bladder tumor)[33]	12%–15%
Cisplatin-based chemo	
MVAC trial[6]	38%
ddMVAC[43–45]	41%
Pooled analysis of gemcitabine/cisplatin[33]	25.6%
Real-world data[13]	23%
Bristol bladder trial (cabazitaxel/cisplatin) (this study)	34.6%
Immunotherapy	
ABACUS trial ($n = 68$); atezolizumab[42]	29% - all comers 40% in PDL1 + patients
PURE-01 trial ($n = 43$); pembrolizumab[41]	39.5% - all comers 50% in PDL1 + patients

Abbreviations: ddMVAC = dose dense methotrexate, vinblastine, doxorubicin, cisplatin; PDL1, programmed death ligand 1; MVAC = methotrexate, vinblastine, doxorubicin, cisplatin; TURBT = transurethral resection of the bladder tumor.

conclusions. Similar to Zargar et al[13] and Sonpavde et al,[38] we also found no significant difference in the survival of patients who had pCR vs. PR. Additionally, 4 patients who had no pathologic downstaging have not progressed and are disease free (Table 3). This suggests disease heterogeneity and highlights the importance of evaluating molecular biomarkers for predicting outcomes to NAC.[39,40]

The rates of pCR after various agents are as listed in Table 4.[6,13,33,41–45] The pCR rates with GC are 23%–26%.[13,33] The pCR rates with ddMVAC are around 40%.[43–45] Despite the higher pCR rates, ddMVAC regimen has significantly higher rates of grade 3 or higher toxicity, with no significant difference in OS.[43,44] In view of the favorable toxicity profile, GC has been the standard of care regimen for NAC, in majority (if not all) of the centers in the UK. Our study has shown a better pCR rate, than GC, of 34.6%, with a favorable toxicity profile. Although our results are from a single-center phase II study with a modest sample size they show it is a suitable comparator for further evaluation in a large multicenter phase II/III trial, especially given the favorable toxicity profile.

To further improve the outcomes of NAC, new strategies are being explored, including immunotherapy alone or immunotherapy in combination with chemotherapy. A proportion of patients with MIBC are ineligible for platinum-based chemotherapy. This, along with no improvements in standard NAC over the last 2 decades, has provided the impetus to explore other agents, for example, immunotherapy. The introduction of immunotherapy has resulted in a paradigm shift in the therapeutic landscape of urothelial carcinoma.[46]

Integrating short courses of immunotherapy in nonmetastatic resectable lung cancer has shown promise and a potential new strategy for neoadjuvant therapy.[47] This strategy was tested in MIBC in 2 phase II single-arm trials with single agent immunotherapy. A trial of 2 cycles of atezolizumab before cystectomy, reported a pCR rate of 29% (20/68) in all 68 evaluable patients and 40% (10/25) in the programmed cell death ligand 1–positive patients.[42] A second study using pembrolizumab had a pCR rate of 40%.[41] However, there was an increased incidence of postoperative complications with pembrolizumab (35% grade 2–4) and 2 treatment-

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related deaths with atezolizumab. Further research is needed to assess combination chemotherapy and immunotherapy regimens.

Although single-agent immunotherapy has shown promise in the neoadjuvant setting, only a proportion of patients show benefit from these therapies (30%–40%).[41,42] To further improve these outcomes, combinations of immunotherapy and chemotherapy are being explored.[48] Three trials evaluating combination of immunotherapy (NCT02365766 pembrolizumab, NCT03294304 nivolumab, and NCT02989584 atezolizumab) with GC are underway. 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 novel combination of cisplatin and cabazitaxel alongside the standard of care, GC regimen with or without immunotherapy in the neoadjuvant setting, in a large phase III randomized trial.

Conclusions

Cabazitaxel in combination with cisplatin for neoadjuvant treatment of MIBC can be considered a well-tolerated and effective regimen before radical cystectomy. The higher pCR rate warrants further evaluation of the cabazitaxel/cisplatin regimen in a larger phase III trial.

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Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clgc.2021.02.001.

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