Concomitant CIS on TURBT does not impact oncological outcome in patients treated with neoadjuvant or induction chemotherapy followed by radical cystectomy.

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ABSTRACT

Background: Cisplatin-based neoadjuvant chemotherapy (NAC) for muscle invasive bladder cancer has been shown to improve all cause and cancer specific mortality. We evaluate whether a diagnosis of carcinoma in situ (CIS) at the time of initial transurethral resection of bladder tumor (TURBT) has an oncological impact on the response of NAC in patients undergoing a radical cystectomy.

Objective: We aim to compare the pathological response and overall survival between patients with and without CIS receiving NAC followed by radical cystectomy (RC).

Design, Setting and Participants: From 2000 – 2013, data on patients with cT2-T4aN0-3M0 urothelial carcinoma of the bladder who received at least 3 cycles of NAC or induction chemotherapy followed by RC were retrospectively collected from 19 centers across Europe and North America.

Intervention: Neoadjuvant or induction chemotherapy followed by RC.

Outcome Measurements and Statistical Analysis: Our primary outcome was pathological response with secondary outcome being overall survival. Multivariable analysis was performed to determine the independent predictive value of CIS on pathological response.

Results: 1213 patients were included for analysis with 21.8% having concomitant CIS. Baseline clinical and pathologic characteristics of the 'CIS' versus 'no CIS' groups were similar. There was no difference in the pathological response between the two arms when response was defined as pT0N0 (17.9% with CIS vs 21.9% without CIS) or ≤pT1N0 (42.8% with CIS vs 37.8% without CIS). On Cox Regression model for overall survival for the cN0 cohort using clinicopathological data, the presence of CIS was not associated with survival (HR 0.86 (95% CI 0.63-1.18; p=0.35). The presence of LVI (HR 1.41, 95% CI 1.01-1.96; p=0.04), hydronephrosis (HR 1.63, 95% CI 1.23-2.16; p=0.001) and use of ddMVAC regimen (HR 0.57, 95% CI 0.34-0.94; p=0.03) were associated with survival. For the whole cohort, presence of CIS was not associated with any alteration in survival (HR 1.05 (95% CI 0.82-1.35; p=0.70)).

Conclusion: In this multicenter, real-world cohort, CIS status did not affect pathologic response to neoadjuvant or induction chemotherapy. This study is limited by its retrospective nature and lack of concordance with respect to chemotherapy regimens.

INTRODUCTION

Cisplatin-based neoadjuvant chemotherapy (NAC) followed by radical cystectomy (RC) and bilateral pelvic lymph node dissection is considered the standard of care for patients with muscle invasive bladder cancer (MIBC) who are eligible to receive this multimodal therapy. This approach has been shown to improve all-cause and cancer-specific mortality compared to RC alone [1,2]. The pathologic response, defined as either no residual carcinoma (pT0N0) or no residual MIBC (≤pT1N0), is considered a surrogate endpoint for overall survival [3]. Patients with residual MIBC have a high risk of recurrence and subsequent death from bladder cancer [2].

In current clinical practice, the effect on CIS on chemotherapy response and outcomes remains unclear. . with limited and retrospective evidence in current literature. We hypothesize that there is no oncological difference in outcome in patients diagnosed with CIS on initial TURBT who subsequently receive NAC prior to RC. We tested this hypothesis in a large international consortium. We compared the pathologic response to NAC and overall survival in patients with and without concomitant CIS at TURBT undergoing RC.

PATIENTS & METHODOLOGY

Study population

From 2000 – 2013, patients were retrospectively identified with MIBC (cT2-T4aN0-3M0) who were managed with pre-operative systemic chemotherapy followed by RC at 19 centers across Europe, Canada and the USA. These centers collectively agreed to data share and this was approved by their governing Institutional Review Boards. The term neoadjuvant chemotherapy (NAC) is conventionally used only for patients with cN0M0 bladder cancer. Here, we also included patients receiving induction chemotherapy for cN1-3M0 disease under the term NAC.

The study population was divided into patients with and without CIS at TURBT. All patients had urothelial carcinoma of the bladder. Mixed histology with squamous and/or glandular differentiation was allowed, but no other variant histology. All patients received at least three cycles of NAC prior to RC.

Information regarding demographics, clinical staging, chemotherapy regimen, and other treatment parameters was obtained. Additionally, the pathological outcome after cystectomy was retrieved. All centers used the American Joint Committee on Cancer (AJCC) criteria for pathologic assessment. There was no central review.

Statistical Analysis

Clinical and pathologic data were compared between groups. For variables with non-normal distribution, data were presented as median and interquartile range (IQR), and the respective groups were compared using the Mann-Whitney U test. Categorical variables were compared using the $\chi 2$ test. Multivariable logistic regression analysis of selected variables (age, cT stage, gender, and type of chemotherapy regimen) was used to define factors predicting pCR and pPR. For comparison of adjusted pathologic response rates, the odds ratio (OR) was reported, and the 95% confidence interval (CI) was calculated with bootstrapping. The multivariable Cox proportional hazards regression model for survival was used to assess hazard ratios (HRs) for variables of interest (gender, type of chemotherapy regimen, surgical margin, extent of lymph node dissection, and presence of pPR). Significance was set at p value <0.05. Analyses were performed using SPSS v.21 software (IBM SPSS Statistics; IBM Corp, Armonk, NY, USA). The primary outcome was pathologic response defined as either pT0N0 or ≤pT1N0 in RC specimens. Multivariate analysis was performed to identify factors predictive of either outcome. Two multivariable binary regression models were created, one including all cN stages and one only for patients with cN0. A multivariable Cox regression model for overall survival was also generated. Significance was set at p value < 0.05.

RESULTS

After applying our selection criteria from the total of 1865 patients, 1253 met our criteria. The CIS status was not present in 40 patients and they were excluded from the analysis. Overall 1213 patients were chosen, including 823 patients who were cN0, 117 cNx and 273 who were cN1-3. Concomitant CIS was reported in 21.8% of patients. Table 1 shows the clinical and pathological features in both the "CIS" and "no-CIS" cohorts. Seventeen percent of patients who had no CIS on initial TURBT initially were subsequently diagnosed to have CIS on final pathology at the time of RC on final pathology.

The no-CIS patients had a higher baseline risk with respect to cT stage, cN stage, and hydronephrosis, whereas the rate of lymphovascular invasion (LVI) was higher in the CIS patients. The time from NAC to cystectomy was significantly longer in patients with CIS (17 weeks) versus those without CIS (16 weeks; p = 0.006).

	CIS n(%)	**No CIS** n(%)	**P value**
Number of patients	265 (21.8)	948 (72.2)	
Median age (years)	64	64	0.75
Male gender	199 (75.1)	722 (76.1)	0.91
smokers	200 (71.9)	702 (69.7)	0.89
Hydronephrosis at presentation	63 (23.8)	305 (32.2)	0.03*
Clinical stage at initial TURBT			
T2	161 (60.8)	499 (52.6)	0.06
T3	72(27.2)	309 (32.6)	
T4	32 (12.1)	140 (14.8)	
Node negative	188 (70.9)	635 (67.0)	0.05
Node positive	46 (17.4)	277 (23.9)	
Nodal status unknown	31 (11.7)	86 (9.1)	
TURBT pathology			
Urothelial carcinoma (UC)	236(89.1)	839(88.5)	0.94
UC with squamous differentiation	22 (8.3)	85 (9.0)	
UC with glandular differentiation	7 (2.6)	24 (2.5)	
Lymphovascular invasion	59 (22.3)	163 (17.2)	0.04*

Table 1: Baseline demographic and clinicopathological findings at initial TURBT

The NAC regimens employed were gemcitabine-cisplatin (GC) in 608 (50.1%), methotrexate-vinblastine-adriamycin-cisplatin (MVAC) in 401 (33.1%) and 'other' in 196 (16.2%). The NAC regimen was not recorded for the remaining patients (0.6%). The median follow up was 1.6 years (ranged 0.5 – 3.5years).

The pathological response for all patients regardless of cN status showed no significant difference according to CIS status (Table 2). However, when only cN0 patients were considered, the down-staging to ≤pT1N0 occurred more frequently in the CIS group (53.0%) than in the non-CIS group (41.7%; p=0.007). CIS was found more frequently in the RC specimen in patients who had CIS prior to treatment (p = <0.001). Down-staging to pT0N0 did not differ according to CIS status.

	CIS	**No CIS**	**P value**
	n(%)	n(%)	
Number of patients	265 (21.8)	948 (72.2)	
Chemotherapy (NAC) regimen			
ddMVAC	50 (18.9)	211 (22.3)	0.18
GC	133 (50.2)	475 (50.1)	
Other	49 (18.5)	147 (15.5)	
Number of chemotherapy cycles			0.07
3	122 (46.0)	371 (39.1)	
4	111 (41.9)	494 (52.2)	
>4	32 (12.1)	83 (8.8)	
Median time between TURBT and NAC (weeks)	6	5	0.13
Duration of NAC (weeks)	9	9	0.35
Median time between NAC and RC (weeks)	17	16	0.006*
	31 (11.7)	86 (9.1)	
Final pathology at RC			
No residual disease (pT0N0)	46(17.9)	204 (21.9)	0.16
Non muscle invasive disease(≤pT1N0)	110 (42.8)	352 (37.8)	0.15
CIS only	43(16.2)	99(10.4)	0.01
Associated CIS	116 (43.8)	248 (26.2)	0.001*

Table 2: Chemotherapy regimens and final pathological results

Table 3 summarizes the multivariable analysis assessing potential risk factors for pathologic down-staging in all patients (cN0-3). cN1-3 status (compared to cN0; OR 0.48, 95% CI 0.32-0.72; p<0.001) was an independent predictor of lower pT0N0 and ≤pT1N0 rates (compared to cN0; 0.44, 95% CI 0.31-0.61; p<0.001). The presence of CIS (OR 0.66 (95% CI 0.45-0.98; p=0.04) was an independent predictor of lower pT0N0 rate. Table 4 summarizes the multivariate analysis assessing potential risk factors for pathologic down-staging for patients with N0 disease.

Variables	≤ypT1N0		ypT0N0	
	OR (95%CI)	p	OR (95%CI)	p
Gender*				
Female	1		1	
Male	0.75(0.66,1.04)	0.08	0.77(0.38,1.55)	0.46
cT stage				
cT2	1		1	
cT3-4	0.83(0.64,1.08)	0.17	0.85(0.63,1.16)	0.31
NAC regimen				
MVAC	1		1	
ddMVAC	1.49(0.93,2.38)	0.09	1.70(0.95,3.03)	0.07
GC	1.39(0.90,2.15)	0.13	1.46(0.84,2.51)	0.17
Other	1.19(0.72,1.97)	0.49	1.54(0.83,2.84)	0.17
cN stage				
N0	1		1	
N+	0.44(0.31,0.61)	<0.001	0.48(0.32,0.72)	<0.001
Nx	0.74(0.47,1.16)	0.19	0.66(0.37,1.15)	0.14
CIS				
No	1		1	
Yes	0.93 (0.67, 1.27)	0.64	0.66 (0.45, 0.98)	0.04

Table 3. Predictors of pT0N0 and ≤ypT1N0 for the entire cohort

Variables	≤ypT1N0		ypT0N0	
	OR (95%CI)	p	OR (95%CI)	p
Gender*				
Female	1		1	
Male	0.73(0.49,1.09)	0.13	0.88(0.56,1.38)	0.58
cT stage				
cT2	1		1	
cT3-4	0.66(0.48,0.91)	0.01	0.71(0.49,1.03)	0.07
NAC regimen				
MVAC	1		1	
ddMVAC	1.32(0.72,2.44)	0.36	1.23(0.62,2.46)	0.54
GC	1.17(0.66,2.08)	0.56	1.03(0.53,1.98)	0.93
Other	0.88(0.45,1.74)	0.72	0.97(0.45,2.11)	0.94
CIS				
No	1		1	
Yes	1.18 (0.81, 1.72)	0.38	0.79 (0.51, 1.23)	0.30

Table 4. Predictors of pT0N0 and ≤ypT1N0 for cN0

On Cox Regression model for overall survival for the cN0 cohort using clinicopathological data (Table 5), the presence of CIS was not associated with survival (HR 0.87 (95% CI 0.64-1.89; p=0.38)). The presence of LVI (HR 1.44, 95% CI 1.04-2.00; p=0.03), hydronephrosis (HR 1.58, 95% CI 1.18-2.11; p=0.002) and use of ddMVAC regimen (HR 0.58, 95% CI 0.35-0.96; p=0.03) were associated with survival outcomes.

Variables	OS	
	HR (95%CI)	p
Age	1.00(0.99,1.01)	0.40
cT stage		
cT2	1	
cT3-4	0.14(0.88,1.48)	0.31
NAC regimen		
MVAC	1	
ddMVAC	0.58(0.35,0.96)	0.03
GC	1.00(0.65,1.55)	0.98
Other	1.11(0.68,1.80)	0.68
LVI		
No	1	
Yes	1.44(1.04,2.00)	0.03
Unknown	1.13(0.83,1.54)	0.44
Hydronephrosis		
No	1	
Yes	1.58(1.18,2.11)	0.002
Unknown	1.33(0.93,1.92)	0.11
CIS		
No	1	
Yes	0.87 (0.64, 1.89)	0.38

Table 5. Cox regression model for OS for cN0 cohort using pre-cystectomy data

Assessing survival for the entire cohort (Table 6), cN+ status, presence of hydronephrosis and the use of ddMVAC were the predictors of overall survival. Presence of CIS was not associated with any alternation in survival (HR 1.06 (95% CI 0.83-1.36; p=0.65).

Variables	OS	
	HR (95%CI)	p
Age	1.00(0.99,1.01)	0.23
cT stage		
cT2	1	
cT3-4	1.23(0.99,1.51)	0.06
cN stage		
N0	1	
N+	1.54(1.23,1.92)	<0.001
Nx	0.91(0.54,1.54)	0.73
NAC regimen		
MVAC	1	
ddMVAC	0.66(0.46,0.94)	0.02
GC	0.93(0.67,1.29)	0.66
Other	0.99(0.68,1.43)	0.95
LVI		
No	1	
Yes	1.25(0.96,1.65)	0.10
Unknown	1.13(0.89,1.45)	0.30
Hydronephrosis		
No	1	
Yes	1.35(1.07,1.71)	0.01

Unknown	1.32(0.98,1.77)	0.06
CIS		
No	1	
Yes	1.06(0.83, 1.36)	0.65

Table 6. Cox regression model for OS for the entire cohort using pre-cystectomy data

DISCUSSION

For the management of muscle invasive bladder cancer is important to be able to better prognosticate based on the initial parameters on TURBT in view of a variable response to different neoadjuvant chemotherapy regimens. It is important to identify patients with muscle invasive bladder cancer who are less likely to respond and/or more likely to progress during NAC, and thus have less benefit[1-3]. Current literature indicates progress in research to identify those tumors with specific characteristics on initial TURBT to help prognosticate response rates with NAC [4]. Potential factors associated with lower response to NAC may include tumor location at the bladder neck, and presence of hydronephrosis, sarcomatoid, small cell or micropapillary variant, while genomic alterations in DNA repair genes, e.g. ERCC2, Rb1, FANCC, ATM, also in HER2 gene, as well as the basal molecular subtype based on gene expression predict better response to cisplatin-based NAC. Ongoing clinical trials are evaluating the clinical utility of such molecular biomarkers. [4,5].

CIS alone is regarded as high-risk non-MIBC because it is estimated that >50% of cases will progress to MIBC over time if left untreated. CIS in addition to papillary NMIBC increases the risk of progression. When patients with CIS proceed to cystectomy, upstaging can occur in up to 55% of specimens compared to 6% of cases without CIS [4]. In patients diagnosed with CIS on initial TURBT there is a variable amount of published literature as to whether or not CIS itself may predicit lower response rates to NAC [6].

There are also published reports highlighting that CIS is associated with poorer prognostic implications, however there has been prospective Randomized controlled Trial to address the negative prognostic implications of CIS on pre-NAC TURBT [7]. Based on published data CIS may have potential prognostic impact and thus may be potentialprognostic biomarker for response in patients undergoing RC following NAC. However, isolated CIS at cystectomy is frequently observed and further studies aiming at understanding the biology and clinical effect of CIS in MIBC are warranted [7].

Whilst previous studies indicated a poorer prognosis on response rates with CIS diagnosed at initial TURBT in patients receiving NAC followed by cystectomy [8,9] a recent publication by Thomas et al. [7] and previous by Parker et al. [8] have indicated significantly decreased pCR rates at cystectomy among patients with pre-NAC CIS in their TURBT samples. This finding is

noteworthy, because pCR is a frequently used early endpoint in clinical trial designs in the NAC setting for MIBC.

Carcinoma in situ (CIS) is generally considered to be the precursor lesion for nonpapillary MIBCs [9], but comprehensive genomic data for CIS are not yet available, so this assumption awaits further experimental validation. Patients with either high-grade papillary nonmuscle-invasive disease or CIS are currently treated with the same adjuvant therapy (intravesical Bacillus Calmette–Guerin [BCG] immunotherapy) after TURBT, but it is by no means clear that BCG produces comparable benefit in CIS and high-grade papillary tumors [10,11]. Many high-grade papillary tumors ultimately become BCG unresponsive, so clinicians are then faced with the dilemma of whether to continue using a bladder-sparing regimen or to employ definitive surgery. The latter is certainly too aggressive for those patients whose tumors could be controlled by local therapy, but again there are no reliable tools to distinguish the tumors that have the potential to metastasize from those that do not. Muscle-invasive disease is managed with definitive local therapy (chemoradiation) or surgery (cystectomy) with or without perioperative systemic cisplatin-based chemotherapy to treat subclinical metastatic disease, but it is still not possible to further distinguish the patients who warrant chemotherapy from those who will not benefit from it. It would also be tremendously useful to have biomarkers that would enable patients and their physicians to choose between bladder-sparing regimens, such as chemoradiation [9].

A specific concern with respect to CIS in the bladder could relate to disease recurrence in the urethra or upper tracts after RC in the long term [12.13]. Takayanagi A et al. [12] have identified CIS and cancer invading the urethra on final pathology at RC to be risk factors for upper urinary tract recurrence. Volkmer et al. [13] identified the one of the risk factors for upper tract recurrence following RC to be CIS (RR 2.3), history of recurrent bladder cancer (RR 2.6), cystectomy for non-muscle invasive bladder cancer (RR 3.8) and tumor involvement of the distal ureter in the cystectomy specimen (RR 2.7). Patients who underwent cystectomy for urothelial carcinoma and with at least 1 risk factor for upper urinary tract recurrence should have closer follow-up than those with non-urothelial histology or without any of these risk factors [13]. The overall rate of upper urinary tract recurrence at 5, 10 and 15 years were 2.4%, 3.9% and 4.9%, respectively [13]. It is also important to note that CIS of the bladder has an inherent sampling error and tumor heterogeneity, which can make the identification of TURBT CIS difficult, in addition to the less judicious reporting of CIS in the past [7,13]. Once we have longer follow up in our series we plan to present data on urethra and upper tract recurrence in due course.

It has been shown that pT0 rates post RC are influenced by NAC regimens and prior TURBTs being performed [14]. Kukereja et al. [14] evaluated pT0 status following NAC on final pathology can be attributed to the absence of residual disease (cT0) on transurethral resection

of bladder tumor (TURBT) or to the effects of NAC. The authors found [14] that a complete TURBT may not predict pT0 at RC. A notable fraction of patients with cT0 bladders have locally advanced and/or lymph node-positive disease. These findings may be of value when counseling patients on bladder preservation strategies for muscle-invasive BC.

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In our study, we evaluated the pathologic and clinical outcomes in patients diagnosed with or without CIS on the initial TURBT prior to NAC followed by a RC. We found no difference in the pathologic response between the two groups when response was defined either as pT0N0 or ≤pT1N0. On Cox Regression model for overall survival for the cN0 cohort using clinicopathological data, the presence of CIS was not associated with survival (HR 0.87 (95% CI 0.64-1.89; p=0.38). The presence of LVI at TURBT (hydronephrosis and less use of ddMVAC regimen were associated with shorter overall survival. For the whole cohort, presence of CIS was not associated with survival. We found that CIS status at initial TURBT did not affect pathologic response to NAC. We also acknowledge that the study is limited by its retrospective nature, and variability of NAC regimens, schedules and number of cycles given, as well as surveillance follow up logistics. As a multi-institutional study, it lacks of consistency with respect to surgical technique in TURBTs and RC, and histopathological reporting since there was no central pathology review. Essentially all patients in this study underwent white light cystoscopy, although this was not captured explicitly. The rate of CIS detection would likely be higher if patients had been evaluated with blue light cystoscopy CIS [15,16], and the latter would allow for a more complete analysis of the impact of CIS in the context of NAC.

In conclusion, our multicenter retrospective data did not indicate worse outcome after neoadjuvant or induction chemotherapy and RC in patients with concomitant CIS of the bladder at TURBT. This study suggests that these patients may not be treated differently than patients without CIS at TURBT.

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