Retrospective analysis of bladder cancer patient outcomes when neoadjuvant chemotherapy is delayed

Zakhar Kanyuka, BSc | Sandy Kassir, MSc, MPH | Nelson Leong, MD, FRCPC | Osama Souied, MD, FRCPC

Introduction

- Canadian Urological Association (CUA) guidelines recommend that muscle-invasive bladder cancer (MIBC) is treated with a course of cisplatin-based mutli-agent neoadjuvant chemotherapy (NAC) followed by radical local therapy.
- We aimed to evaluate the impact of time to treatment initiation (TTI) and compare clinical outcomes among patients treated with NAC followed by radical cystectomy (RC) at the Saskatchewan Cancer Agency (SCA).

Methods

We conducted a retrospective cohort study reviewing the clinical and pathological data of 2104 patients from the SCA electronic registry of those over 18 years old diagnosed with bladder cancer from January 2000 to December 2018. We included patients who received platinum-based NAC and excluded patients with:

- non-MIBC,
- metastatic bladder cancer,
- histologies other than urothelial carcinoma,
- and charts with insufficient data in the EMR.

Then we performed survival analysis using Kaplan-Meier methods and log rank tests to compare the overall survival (OS), disease recurrence, and post-RC surgical pathological staging of patients based on key time intervals in treatment. We investigated the impact of the duration of the following time intervals on the outcomes:

- date of MIBC diagnosis to start date of NAC (≤8 vs. >8 weeks),
- date of MIBC diagnosis to RC (≤25 vs. >25 weeks),
- and date of completion of NAC to RC (≤6 vs. >6 weeks).

Lastly we used univariate Cox regression to determine the factors that were associated with OS.

Table 1. Summary of logistic regression analysis and log rank tests.

Time interval	Outcome															
	Overall survival				Recurrence				TNM Pathological Staging at Cystectomy: T				TNM Pathological Staging at Cystectomy: N			
	relationship	Proportion	95% CI	log rank test p value	relationship	Proportion	95% CI	log rank test p value	relationship	Proportion	95% CI	log rank test p value	relationship	Proportion	95% CI	log rank test p value
Date of muscle-invasive diagnosis to start date of neoadjuvant chemotherapy (within 8 weeks vs. more than 8 weeks)	greater delay to lower overal survival	1.25	(1.09 - 1.35)	0.02	greater delay to increased recurrence	2.77	(1.44 - 4.57)	<0.001	greater delay to higher pathological stage at cystectomy	1.77	(0.43 - 2.5)	0.21	greater delay to higher pathological stage at cystectomy	1.63	(1.03 - 1.77)	0.01
Date of muscle-invasive diagnosis to radical cystectomy (within 25 weeks vs. more than 25 weeks)	greater delay to lower overal survival	2.00	(1.87 - 3.45)	0.02	greater delay to increased recurrence	1.88	(1.04 - 2.47)	<0.001	greater delay to higher pathological stage at cystectomy	1.56	(1.32 - 2.38)	0.04	greater delay to higher pathological stage at cystectomy	1.56	(1.22 - 3.5)	n/a
End date of neoadjuvant chemotherapy to radical cystectomy (within 6 weeks vs. more than 6 weeks)	greater delay to lower overal survival	1.88	(0.48 - 1.95)	0.08	greater delay to increased recurrence	1.50	(1.08 - 3.10)	<0.001	greater delay to higher pathological stage at cystectomy	1.95	(1.3 - 2.09)	0.01	greater delay to higher pathological stage at cystectomy	1.09	(0.76 - 1.3)	n/a

Results

After selecting the patients based on the inclusion and exclusion criteria, our data set consisted of 43 patients. Six (14.3%) patients had pathologically confirmed recurrence of disease and nine (21.4%) patients had died. A total of 37 (88.1%) patients received cisplatin and gemcitabine, 3 (7.1%) patients received carboplatin and gemcitabine, and 1 (2.4%) patient received methotrexate, vinblastine, doxorubicin, and cisplatin NAC regimens.

The key results of the logistic regression analysis and log rank test are as follows:

- OS was 1.25 (95%CI: 1.09-1.35, p=0.02) times more likely to be reduced in patients whose start of NAC was delayed > 8 weeks compared to those who received NAC < 8 weeks of diagnosis.
- Patients who had NAC delayed > 8 weeks also had worse pathological outcomes with higher lymph node metastasis.
- Primary tumour staging (i.e., T) was 1.77 (95% CI: 0.43-2.50, p=0.21) times and the lymph node involvement (i.e., N) was 1.63 (95% CI: 1.03-1.77, p=0.006) times more likely to be at a higher stage.
- Reduction in each of the time intervals was significantly associated with reduced recurrence.
- Univariate Cox proportional hazards regression analysis for OS revealed that neither age, sex, body mass index, NAC regimen, nor prior intravesical treatment were associated with OS.

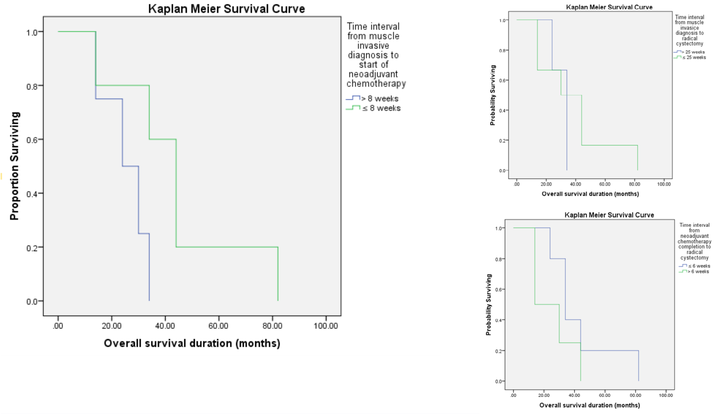

Figure 1. Kaplan Meier Curves comparing overall survival of patients by duration of key intervals in the course of treatment: date of MIBC diagnosis to start date of NAC (left); date of MIBC diagnosis to RC (top right); and date of completion of NAC to RC (bottom right).

Conclusion

Impact of promptness of treatment initiation on pathological outcomes has been reported in previous studies. However, our review demonstrated a significant overall survival benefit by reducing TTI in MIBC patients. Furthermore, the promptness of treatment is congruent with the recommendations of CUA guidelines. While limited in its sample size, this research is an important step in informing treatment planning and resource allocation in the management of patients with MIBC.

Table 2. Univariate Cox proportional hazards regression analysis for overall survival for study cohort cases.

Variable	OS	
	HR (95% CI)	*p* -value
Age (yrs)		0.21
≤70	0.69 (0.13-3.63)	
≥71	0.21 (0.02-2.40)	
Sex		0.45
Male	0.13 (0.01-2.14)	
Female	0.31 (0.02-6.26)	
BMI		0.9
Normal weight	0.87 (0.23-5.78)	
Overweight	1.45 (0.19-11.16)	
Obese	0.57 (0.05-6.62)	
Neoadjuvant chemotherapy agent(s)		0.55
Carboplatin and Gemcitabine	2.53 (0.12-52.17)	
Cisplatin and Gemcitabine	0.70 (0.08-6.32)	
Prior intravesical treatment	3.69 (0.43-31.26)	0.23
Pathological stage: T category		0.33
Tx, T0, Ta, Tis	0.28 (0.10-39.02)	
T1-T4	36.06 (0.26-72.35)	
Pathological stage: N category		0.67
N0	1.45 (0.26-8.01)	
N1-N2	0.69 (0.13-3.80)	

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