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Changes in neoadjuvant chemotherapy utilization in muscle invasive bladder cancer treatment: a tertiary center retrospective study

Katarzyna Gronostaj[1], Anna Katarzyna Czech[1], Jakub Fronczek[2], Tomasz Wiatr[1], Mikołaj Przydacz[1], Przemysław Dudek[1], Łukasz Curyło[1], Wojciech Szczeklik[2], Piotr Chłosta[1]

[1]*Jagiellonian University Medical College, Department of Urology, Cracow, Poland*
[2]*Jagiellonian University Medical College, Department of Intensive Care and Perioperative Medicine, Cracow, Poland*

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Corresponding author
Katarzyna Gronostaj
Jagiellonian University Medical College
Department of Urology
2 Jakubowskiego
30-688 Cracow, Poland
phone: +48 12 424 79 50
katarzynagronostaj@gmail.com

Introduction The year 2015 brought a major shift in the national health care system in Poland – the diagnosis and treatment of patients with malignant diseases became a priority. Close multidisciplinary collaboration was facilitated to optimize patients' care. The aim of this study was to investigate temporal changes in neoadjuvant chemotherapy (NAC) utilization in patients who underwent radical cystectomy (RC) due to muscle invasive bladder cancer (MIBC) in a single academic center in Poland.

Material and methods Patients who underwent planned curative RC with bilateral pelvic lymph node dissection between January 2013 and December 2018 in a tertiary care center were included in the study. To assess the response to chemotherapy, tumor regression grades (TRGs) were included into the standard pathological examination of RC specimens.

Results Out of 183 patients enrolled into the study, 105 (57.4%) underwent NAC before RC. Only 1 (4%) out of 25 patients underwent NAC prior to RC in 2013. The percentage of patients who received NAC in subsequent years were: 4% (1/25) in 2013, 36% (9/25) in 2014, 55.3% (21/38) in 2015, 62.9% (21/35) in 2016, 83.9% (26/31) in 2017 and 89.7% (26/29) in 2018 (p-value for trend <0.001). Thirty patients (28.6%) had complete pathological response to NAC (TRG1), 50 patients (47.6%) showed strong response (TRG2) and 25 patients (23.7%) had weak or no response (TRG3).

Conclusions This study showed an increasing utilization of NAC amongst MIBC patients who underwent RC. Close multidisciplinary collaboration is the key to optimizing perioperative care of patients with MIBC.

Key Words: muscle invasive bladder cancer ‹› neoadjuvant chemotherapy ‹› tumor regression grade

INTRODUCTION

Muscle invasive bladder cancer (MIBC) is a deadly disease. A recent paper concerning the natural history of MIBC showed that 38% of untreated patients developed metastatic disease and 41% died because of the cancer up to 6 months after the diagnosis [1]. These data clearly emphasize the need for therapeutic intervention to increase the patient's chances for survival. Current guidelines recommend cisplatin-based multidrug neoadjuvant chemotherapy (NAC) followed by radical cystectomy (RC) for eligible MIBC patients [2]. Even though the improvement in survival from NAC in the treatment of MIBC is supported by level 1 evidence [3], data concerning the advantage of NAC outside of clinical trials are limited. What is even more bothering, a population-based study using a National Cancer Database failed to demonstrate the survival benefit of NAC [4]. Although these results should be interpreted with caution, they might, among other issues, be the reason why the real life

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utilization of NAC is far from optimal. The largest reports published in the recent years showed that the percentage of patients treated with NAC oscillates around 20% [5, 6]. The situation varies between countries and centers and more encouraging reports with higher NAC usage were published [7, 8, 9]. NAC was first used in our institution in 2013 and its usage has been increasing. The year 2015 brought a major shift in the national health care system in Poland. Due to the introduction of a dedicated pathway of oncological treatment ('oncological package') the diagnosis and treatment of patients with malignant diseases became a priority. A close collaboration between urologists, medical oncologists, radiotherapists, and radiologists was facilitated by weekly tumor board meetings held to optimize patients' care. To provide the assessment of response to chemotherapy, tumor regression grades (TRGs) were included into the standard pathological examination of RC specimens. TRGs, which reflect and quantify pathological response to NAC, were introduced by Fleischmann et al. in MIBC patients who underwent NAC followed by RC [10]. One exploratory study showed prognostic value of TRGs [10]. This finding was recently confirmed in an independent cohort [11]. The aim of the current study was to investigate the changes in NAC utilization over subsequent years and to present the pathological response to NAC in a single academic center in Poland.

Table 1. *Patients' characteristics, pre-treatment clinical staging and initial grading*

Variable	Statistics	All patients (n = 183)	RC only (n = 78)	NAC+RC (n = 105)	p (RC only vs. NAC +RC)
Age	Median IQR	65.00 60.00–69.00	66.50 62.00–73.00	64.00 58.00–67.00	0.004
Gender (male)	n (%)	124 (80.0)	60 (78.9)	64 (81)	0.904
BMI	Median IQR	27.17 24.50–29.70	26.95 2 4.49–29.32	27.40 24.50–29.90	0.583
Smokers (current / former)	n (%)	108 (71.6)	42 (58.3)	66 (83.5)	0.001
Occupational exposure	n (%)	26 (18.2)	14 (21.9)	12 (15.2)	0.416
ASA score (%)					
1	n (%)	1 (0.6)	0 (0.0)	1 (1.3)	
2	n (%)	104 (67.1)	48 (63.2)	56 (70.9)	0.381
3	n (%)	49 (31.6)	27 (35.5)	22 (27.8)	
4	n (%)	1 (0.6)	1 (1.3)	0 (0.0)	
CAD	n (%)	37 (23.9)	23 (30.3)	14 (17.7)	0.100
CHF	n (%)	15 (9.7)	10 (13.2)	5 (6.4)	0.254
Aortic stenosis	n (%)	2 (1.3)	2 (2.6)	0 (0)	0.460
PVD	n (%)	9 (5.8)	5 (6.6)	4 (5.1)	0.952
DVT/PE	n (%)	2 (1.3)	1 (1.3)	1(1.3)	1.000
HT	n (%)	104 (67.1)	53 (69.7)	51 (64.6)	0.606
DM	n (%)	32 (20.6)	16 (21.1)	16 (20.3)	1.000
COPD	n (%)	12 (7.9)	9 (11.8)	3 (3.9)	0.133
CVE	n (%)	5 (3.2)	3 (4.0)	2 (2.5)	0.953
Clinical T-stage					
T2-3a	n (%)	99 (54.1%)	42 (53.8%)	57 (54.3%)	0.389
T3b	n (%)	58 (31.7%)	22 (28.2%)	36 (34.3%0	
T4a	n (%)	26 (14.2%)	14 (17. 9%)	12 (11.4%)	
Clinical N-stage					
N0	n (%)	126 (68.9%)	44 (56.4%)	82 (78.1%)	0.003
N+	n (%)	57 (31.1%)	34 (43.6%)	23 (21.9%)	
Grading LG/HG					
LG	n (%)	5 (2.7%)	3 (3.8%)	2 (1.9%)	0.653
HG	n (%)	177 (97.3%)	75 (96.2%)	102 (98.1%)	
Grading G1/G2/G3					
G2	n (%)	65 (35.5%)	33 (42.7%)	32 (30.5%)	0.134
G3	n (%)	118 (64.5%)	45 (67.7%)	73 (69.5%)	

RC – radical cystectomy; NAC – neoadjuvant chemotherapy; IQR – interquartile range; n (%) – number (percentage); BMI – body mass index; ASA score – American Society of Anesthesiologists score; CAD – coronary artery disease; CHF – chronic heart failure; PVD – peripheral vascular disease; DVT/PE – deep venous thrombosis/pulmonary embolism; HT – hypertension; DM – diabetes mellitus; COPD – chronic obstructive pulmonary disease; CVE – cerebral vascular event; LG – low-grade; HG – high-grade

MATERIAL AND METHODS

Medical data of patients who underwent cystectomy between January 2013 and December 2018 in a single academic center was reviewed (n = 282). Only patients with MIBC who were scheduled for planned curative RC with bilateral pelvic lymph node dissection were included for further analysis. Exclusion criteria were: palliative (n = 23), urgent (n = 6) or benign (n = 7) indications for cystectomy, non-muscle invasive bladder cancer (NMIBC) (n = 22) or other than pure urothelial histology of bladder cancer (n = 14), other malignancies (n = 27) except localized adenocarcinoma of prostate.

After obtaining the study protocol approval from the local bioethics committee, the data was collected from hospital records.

Transurethral resection of the bladder tumor (TURBt), physical examination, computed tomography (CT) or X-ray of chest and CT or magnetic resonance imaging (MRI) of abdomen and pelvis were used for clinical staging. The final pathology staging was determined according to the 2009 and 2017 TNM classification [12, 13]. TRGs were assessed following the previously described method [10]. TRG1 was assigned when there were no cancer cells, but only fibrosis in tumor bed and reflected complete pathological response to chemotherapy. TRG2 was defined as cancer cells present in less than 50% of tumor bed with predominant fibrosis and indicated strong response to NAC. TRG3 was assigned when there was cancer present in more than 50% of tumor bed and corresponded to weak or no response to NAC. TRGs were evaluated independently for bladder specimen and affected lymph nodes. In the case of varying results the final TRG was the higher (worse) TRG.

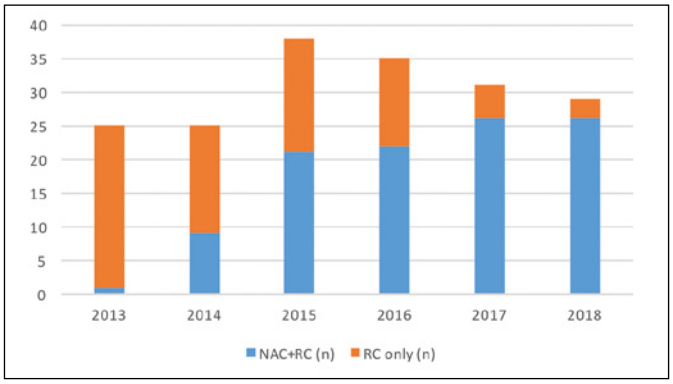

Figure 1. *Changes in neoadjuvant chemotherapy (NAC) utilization among muscle invasive bladder cancer (MIBC) patients who underwent radical cystectomy (RC) between 2013 and 2018. P-value in the Cochran-Armitage test for trend <0.001.*

Table 2. *Characteristics of neoadjuvant chemotherapy (NAC)*

	Total NAC (completed) n = 105 (95)	PG (completed PG) n = 62 (56)	MVAC (completed MVAC) n = 10 (9)	ddMVAC (completed ddMVAC) n = 22 (21)	GemCarbo (completed GemCarbo) n = 11 (9)
2013	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)
2014	9 (7)	3 (2)	1 (1)	0 (0)	5 (4)
2015	21 (20)	20 (19)	0 (0)	0 (0)	1 (1)
2016	22 (20)	19 (18)	1 (1)	0 (0)	2 (1)
2017	26 (23)	11 (9)	4 (3)	8 (8)	3 (3)
2018	26 (25)	8 (8)	4 (4)	14 (13)	0 (0)

NAC – neoadjuvant chemotherapy; PG – cisplatin, gemcitabine; MVAC – methotrexate, vinblastine, adriamycin, cisplatin; ddMVAC – dose-dense methotrexate, vinblastine, adriamycin, cisplatin; GemCarbo – gemcitabine, carboplatin

Table 3. *Tumor characteristics and neoadjuvant chemotherapy (NAC) response*

Variable	Statistics	NAC + RC (n = 105)	RC only (n = 78)	NAC completed (n = 95)	NAC uncompleted (n = 10)
Pathologic T-stage					
T0	n (%)	26 (24.8)	4 (5.1)	24 (25.3)	2 (10)
Ta-1-Cis	n (%)	26 (24.8)	3 (3.8)	25 (26.3)	1 (30)
T2	n (%)	25 (23.8)	19 (24.4)	23 (24.2)	2 (10)
T3-4a	n (%)	28 (26.7)	52 (66.7)	23 (24.2)	5 (50)
Pathologic N-stage					
N0	n (%)	82 (78.1)	44 (56.4)	77 (81.1)	5 (50)
N+	n (%)	23 (21.9)	34 (43.6)	18 (18.9)	5 (50)
TRG1	n (%)	30 (28.6)	–	28 (29.5)	2 (20.0)
TRG2	n (%)	50 (47.6)	–	46 (48.4)	4 (40.0)
TRG3	n (%)	25 (23.8)	–	21 (22.1)	4 (40.0)

RC – radical cystectomy; NAC – neoadjuvant chemotherapy; TRG – tumor regression grade

Statistical analysis

Descriptive statistics on baseline variables are presented as median (interquartile range [IQR]) or count and percentage. Between-group differences were investigated using the Wilcoxon-Mann-Whitney, chi-squared or Fisher's exact tests as appropriate. We performed the Cochran-Armitage test for trend in proportions of patients receiving NAC across subsequent years in the period of interest. A two-sided alpha level of 0.05 was used as a cut-off for declaring statistical significance.

Table 4. *Basic characteristics, pre-treatment clinical staging, initial grading and chemotherapy used according to tumor regression grade group*

Variable	Statistics	TRG 1 (n = 30)	TRG 2 (n = 50)	TRG 3 (n = 25)	p
Age	Median IQR	62.5 (58–67)	64.5 (60–69)	63 (60–67)	0.322
Gender (male)	n (%)	21 (70.0)	45 (90.0)	19 (76.0)	0.068
BMI	Median IQR	27.4 (26.8–29.5)	27.5 (24.5–29.9)	26.1 (23.4–30.8)	0.882
Smoking status					
Current smoker	n (%)	0 (0.0)	1 (2.0)	0 (0.0)	
Non-smoker	n (%)	25 (83.3)	30 (60.0)	19 (76.0)	0.309
Former smoker	n (%)	5 (16.7)	19 (38.0)	6 (24.0)	
Occupational exposure	n (%)	4 (13.3)	4 (8.0)	6 (24.0)	
ASA score					
1	n (%)	0 (0.0)	1 (2.0)	0 (0.0)	
2	n (%)	25 (83.3)	30 (60.0)	19 (76.0)	0.142
3	n (%)	5 (16.7)	19 (38.0)	6 (24.0)	
CAD	n (%)	4 (13.3)	10 (20.0)	3 (12.5)	0.653
CHF	n (%)	0 (0.0)	5 (10.0)	2 (8.3)	0.229
Aortic stenosis	n (%)	0 (0.0)	1 (2.0)	0 (0.0)	1.000
PVD	n (%)	1 (3.3)	4 (8.0)	0 (0.0)	0.504
DVT/PE	n (%)	1 (3.3)	1 (2.0)	0 (0.0)	1.000
HT	n (%)	16 (53.3)	37 (74.0)	15 (62.5)	0.161
DM	n (%)	5 (16.7)	12 (24.0)	6 (25.0)	0.692
COPD	n (%)	2 (6.7)	1 (2.1)	1 (4.2)	0.809
CVE	n (%)	0 (0.0)	2 (4.0)	0 (0.0)	0.720
Clinical T-stage					
cT2-3a	n (%)	20 (66.7)	29 (58.0)	8 (32.0)	0.010
cT3b	n (%)	10 (33.3)	16 (32.0)	10 (40.0)	
cT4a	n (%)	0 (0.0)	5 (10.0)	7 (28.0)	
Clinical N-stage					
cN0	n (%)	30 (100.0)	41 (82.0)	11 (44.0)	<0.001
cN+	n (%)	0 (0.0)	9 (18.0)	14 (56.0)	
Grading LG/HG					
LG	n (%)	1 (3.4)	1 (2.0)	0 (0.0)	1.000
HG	n (%)	28 (96.6)	49 (98.0)	25 (100.0)	
Grading G1/G2/G3					
G2	n (%)	9 (30.0)	18 (36.0)	5 (20.0)	0.365
G3	n (%)	21 (70.0)	32 (64.0)	20 (80.0)	
Type of NAC					
PG	n (%)	18 (60.0)	31 (62.0)	13 (52.0)	
MVAC	n (%)	1 (3.3)	5 (10.0)	5 (20.0)	0.137
ddMVAC	n (%)	9 (30.0)	10 (20.0)	2 (8.0)	
GemCarbo	n (%)	2 (6.7)	4 (8.0)	5 (20.0)	
NAC completed	n (%)	28 (93.3)	46 (92.0)	21 (84.0)	0.519

TRG – tumor regression grade; RC – radical cystectomy; NAC – neoadjuvant chemotherapy; IQR – Interquartile range; n (%) – number (percentage); BMI – body mass index; ASA score – American Society of Anesthesiologists score; CAD – coronary artery disease; CHF – chronic heart failure; PVD – peripheral vascular disease; DVT/PE – deep venous thrombosis/pulmonary embolism; HT hypertension; DM – diabetes mellitus; COPD – chronic obstructive pulmonary disease; CVE – cerebral vascular event; LG – low-grade; HG – high-grade; PG – cisplatin; gemcitabine; MVAC – methotrexate, vinblastine, adriamycin, cisplatin; ddMVAC – dose – dense methotrexate; vinblastine; adriamycin; cisplatin; GemCarbo – gemcitabine, carboplatin

RESULTS

Out of 183 patients enrolled into the study, 105 (57.4%) underwent NAC before RC. Patients' characteristics, pre-treatment clinical staging and initial grading obtained from TURBt specimen are presented in Table 1. Except for younger age, higher percentage of positive smoking history and lower percentage of clinically suspicious lymph nodes in NAC+RC patients, the groups were similar (Table 1).

The percentage of patients who received NAC in subsequent years were: 4% (1/25) in 2013, 36% (9/25) in 2014, 55.3% (21/38) in 2015, 62.9% (21/35) in 2016, 83.9% (26/31) in 2017 and 89.7% (26/29) in 2018 (Figure 1; p-value for trend <0.001).

NAC regimen details are presented in Table 2. Ten patients did not complete planned chemotherapy due to the treatment toxicity. All these patients received less than half of planned infusions. The decision concerning NAC termination was made by a medical oncologist. Ninety-four patients underwent cisplatin-based combination. The most popular schedule was cisplatin-gemcitabine (PG), however in the last two years of the analyzed period, ddMVAC (dose-dense methotrexate, vinblastine, adriamycin, cisplatin) was prescribed more often.

Final pathology results including histopathological response to chemotherapy are presented in Table 3. Nearly half of the patients who underwent NAC did not show muscle invasive disease in final surgical specimen. More than three-quarters of NAC patients showed either complete (TRG1) or partial (TRG2) pathological response to chemotherapy.

Patients characteristics, pre-treatment staging, initial grading, type of NAC used and tumor characteristics according to TRG group are presented in Table 4 and Table 5.

DISCUSSION

The study showed a major increase in NAC utilization since its introduction in 2013. In 2015, due to changes in the national health care system in Poland, tumor board meetings became mandatory, which resulted in the close collaboration between medical oncologists, radiotherapists, radiologists and urologists. One of the observed effects of this multidisciplinary cooperation was an increased accessibility to medical oncologist's consults and subsequent rapid increase in NAC utilization. A similar phenomenon has been described before [14].

The percentage of NAC utilization reaching nearly 90% in 2018 is one of the highest reported up to date. To our best knowledge, only one study from Japan reported comparably high results [7]; however, in this study the predominant schedule of NAC was carboplatin-based. In the current study the NAC regimen was assigned at the discretion of a medical oncologist and the eligibility criteria for cisplatin-based chemotherapy were extended to patients with glomerular filtration rate over 50 ml/min, which might be one of the reasons for such high NAC utilization.

Data concerning the assessment of response to chemotherapy published to date was limited to complete (ypT0N0) or non-invasive (ypTa-T1-Tis N0) downstaging [15, 16, 17]. Introducing TRGs gave the possibility not only to quantify the response to NAC but also to assess the response to NAC in more advanced pathological stages. Over 75% of patients in our study had complete (TRG1) or strong (TRG2) response to NAC, which was higher than in the original Fleichmann's cohort used to derive this system [10]. In the Fleichmann et al., most of the patients had locally advanced disease [10], whereas the currently described sample was more balanced. These data might suggest a better response to chemotherapy in less advanced disease stages.

Our study has several limitations. First, this is a retrospective study from one tertiary care academic center, thus obtained results may not be fully transferable into daily clinical practice. Second, the prognostic value of TRGs had been shown only in retrospective setting [10, 11] and these findings need validation in prospective studies. Third, histology other than pure urothelial carcinoma was not

Table 5. *Tumor characteristics in neoadjuvant chemotherapy group and according to tumor regression grade group*

Variable	Statistics	NAC + RC (n = 105)	TRG 1 (n = 30)	TRG 2 (n = 50)	TRG 3 (n = 25)
Pathologic yT-stage					
yT0	n (%)	26 (24.8)	24 (80.0)	1 (2.0)	1 (4.0)
yTa-1-Cis	n (%)	26 (24.8)	6 (20.0)	20 (40.0)	0 (0.0)
yT2	n (%)	25 (23.8)	0 (0.0)	16 (32.0)	9 (36.0)
yT3-4a	n (%)	28 (26.7)	0 (0.0)	13 (26.0)	15 (60.0)
Pathologic yN-stage					
yN0	n (%)	82 (78.1)	30 (100.0)	41 (82.0)	11 (44.0)
yN+	n (%)	23 (21.9)	0 (0.0)	9 (18.0)	14 (56.0)

NAC+RC – neoadjuvant chemotherapy and radical cystectomy; TRG – tumor regression grade; n (%) – number (percentage)

included in the study. Moreover, not all the patients had a pre-treatment CT chest scan, only chest X-ray, which might be the cause of a potential understaging.

CONCLUSIONS

This study showed an increasing utilization of NAC amongst MIBC patients who underwent RC in tertiary academic center. The probable reason for that might be the shift in the national health care system facilitating regular tumor board meetings. The close multidisciplinary collaboration is the key to optimizing care of patients with MIBC.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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