Symbiosis

www.symbiosisonline.org
www.symbiosisonlinepublishing.com
ISSN Online: 2372-0921

Research Article | Cancer Science & Research: Open Access | Open Access

Neoadjuvant Platinum and Gemcitabine Regimens Precede Definitive Radiotherapy in Locally Advanced Bladder Cancer

Engy M Aboelnaga[1], Rasha Hamdy Hamed[1], Amir M zeid[2] and Amrallah A Mohammed[3]

[1]*Clinical Oncology &Nuclear Medicine Department, Faculty of Medicine, Mansoura University, Egypt*

[2]*Surgical Oncology Department, Oncology Center, Mansoura University, Egypt*

[3]*Medical Oncology Department, Faculty of Medicine, Zagazig University, Egypt*

Received: December 31, 2018; Accepted: January 18, 2019; Published: January 28, 2019

***Corresponding author:** Engy M. Aboelnaga, Assistant professor of clinical oncology and nuclear medicine department, Mansoura Faculty of Medicine, 2 El Gomhouria Street, Zip code: 35516, Mansoura-Egypt, E-mail: engyms2007@gmail.com*

Abstract

Background: Trimodality treatment of muscle invasive bladder cancer (MIBC) has a comparable effect to radical cystectomy with maintain of bladder function. Neoadjuvant chemotherapy before definitive treatment either surgery or radiotherapy is a state of art nowadays.

Patients and methods: We targeted sixty patients with locally advanced bladder cancer who weren't candidate for radical cystectomy. Patients received 2 to 3 cycles of Induction chemotherapy based on platinum compound (either cisplatin or carboplatin) according to renal function in combination with gemcitabine followed by definitive radiotherapy 66 Gy (2 Gy per fraction) concurrent with weekly platinum compound in two phases.

Results: The age of patients had a median of 67 years. T3 was the most presenting stage in 68.3% of patients. Forty- eight patients had a clinical positive LN, while 38 patients had grade 3. 73.3% of patients received 3 cycles of NA chemotherapy. 49 patients (81.6 %) received full dose of planned radiotherapy dose, while weekly concurrent chemotherapy was administrated in 95% of patients. Complete response was achieved in 26 patients (43.3 %). After a median follow up period of 16 months, 2-year progression free survival (PFS) was 27.1 % and 2 –years overall survival (OS) was 52.3%. PFS and OS were statistically significant differ in grade 2 vs. grade 3 (p=0.002, p=0.001), tumour size T2 vs. T3 and T4 (p=0.003,p=0.043) and nodal status clinical negative LN vs. clinical positive LN (p=0.02,p=0.006),respectively. Sex and type of chemotherapy had no effect on survival. The toxicities were acceptable.

Conclusion: Neoadjuvant chemotherapy before definitive CRT is feasible and provides acceptable results and tolerable toxicities in locally advanced bladder cancer patients who radical cystectomy isn't suitable for them.

Key words: Neoadjuvant Platinum and Gemcitabine; Definitive Radiotherapy; Concurrent Chemotherapy, Locally Advanced Bladder Cancer

Introduction

Bladder cancer is ranked as the fourth most common cancer in the United States among men while in women it is not included in the top 10 cancers [1].The incidence and mortality varies internationally. In North America, Europe and Egypt was reported a higher incidence [2].The median age at diagnosis being 72 years and before age 40 years, the diagnosis is rare. Men are about 3 times more affected than in women [3].Muscle invasive bladder cancer (MIBC) is locally advanced aggressive disease. The current standard of care for the treatment of MIBC is neoadjuvant cisplatin-based chemotherapy followed by radical cystectomy (RC) with pelvic lymph node dissection [4, 5].

When patients presented with more advanced stage or more lymph nodes metastases that create the problem of impossibility of radical cystectomy. The use of neoadjuvant chemotherapy or induction chemotherapy before definitive treatment either surgery or radiotherapy give better chance of effective eradication of micrometastasis and increase the feasibility of local treatment [6]. In addition, it has the great potentiality to deliver the drugs with higher doses and lesser toxicities that give more opportunity for better efficacy and response to chemotherapy [7, 8].

Cisplatin combinations in neoadjuvant setting has an absolute survival benefit (approximately 5% at 5 years) in condition precedes cystectomy or radiotherapy [9, 10]. Trimodality therapy (TMT), which included transurethral resection (TUR) of bladder tumor followed by concomitant radiotherapy (RT) with chemotherapy, is considered as alternative therapy for MIBC. However there are no prospective randomized study to directly compare between RC and TMT, the overall survival (OS) was similar achieved in RC and TMT arms in retrospective studies [11,12].

Neoadjuvant chemotherapy or induction chemotherapy before radiotherapy was studied as replacement of radical cystectomy aiming for organ preservation and avoids cystectomy

complications [13, 14]. The efficacy of neoadjuvant chemotherapy in advanced bladder stage was established primarily with regimen of methotrexate, vinblastine, doxorubicin, and cisplatin combination (MVAC), with achievement of pathologically tumour complete response rates (pT0) in about 38% of cases [15]. But based on the comparable efficacy with lesser toxicities and better tolerability of gemcitabine and cisplatin (GC) in patients with metastatic disease, gemcitabine combination with cisplatin has become the most commonly used regimen in the neoadjuvant setting[16-18].

We aimed in our study to assess the outcome of locally advanced unresectable bladder cancer in our institution by using neoadjuvant (NA) chemotherapy based on platinum compound (either cisplatin or carboplatin) according to renal function in combination with gemcitabine(GC or G-carb) followed by definitive radiotherapy concomitant with platinum compound. The Primary end point of study was progression free survival (PFS). Secondary end points were complete response (CR) rate, toxicities assessment and overall survival (OS).

Patients and methods

Sixty patients with confirmed diagnosed of transitional cell carcinoma of the bladder were selected in this prospective trial. The study was conducted in clinical oncology and nuclear medicine department – Mansoura University from July 2016 to July 2018. Informed consent was obtained from all Participants with approval of our local institutional review board.

Patients with clinically stages T2-4N0-3 who weren't suitable for cystectomy, age ≥ 18 years at diagnosis, The Eastern Cooperative Oncology Group (ECOG) performance status PS 0-2, and adequate haematological, renal and hepatic function were included in our study. Patients with second malignancy or previous radiotherapy to pelvis, sever medical problems that affect tolerance to chemotherapy were excluded from the study.

Pretreatment evaluation and assessment

Complete history and clinical examination, complete laboratory evaluation (differential CBC, liver function tests, and serum creatinine, urea and creatinine clearance), complete radiological assessment (CT chest- abdomen and pelvis- MRI on pelvis, bone scan if clinically indicated).

Treatment delivery

Two to three cycles of NA chemotherapy based on platinum compound either cisplatin or carboplatin according to kidney function assessment and general performance of patients in combination with gemcitabine were administrated. Cisplatin was given in dose 70 mg/ m^2 in day 1 and gemcitabine 1250 mg/ m^2 in days 1 & 8 to be repeated every 3 weeks. Adequate hydration and antiemetic was given before cisplatin. Carboplatin was administrated according to area under curve (AUC) = 5 in day 1 and gemcitabine 1000 mg/ m^2 in days 1 & 8 to be repeated every 3 weeks. Radiotherapy was applied after chemotherapy in 2 phases (phase 1 was 46 gray /23 fractions to whole pelvis followed by Phase II 20 gray/ 10 fractions local to the bladder) with weekly chemotherapy (cisplatin 40 mg/m^2 or carboplatin dose (AUC = 2). 3-dimentional conformal radiotherapy was using for radiotherapy delivery according to the Radiation Therapy Oncology Group (RTOG) guidelines.

Assessment of Toxicity

Toxicities assessment was performed clinically and by laboratory evaluation every cycle using toxicity grading of the common terminology criteria for adverse events (NCI-CTC, version 4.0). During radiotherapy, patients were seen weekly for recording of any toxicity. Early radiation toxicity was reported within 3 months and late toxicities were reported after that time.

Assessment of response

Radiological assessment was done after 8 week after radiotherapy finishing, based on response evaluation criteria in solid tumors (RECIST) criteria after treatment, patient assessed clinically every 2 month for first 2 years then every 3-4 months after that for reporting of any progression and recording of toxicities. Annual radiological evaluation was done, or when indicated.

Statistical analysis

Mean and standard deviation were estimates of quantitative data. Fisher exact test was used for qualitative data. The Kaplan–Meier method was used for survival data, PFS was the time from the date of starting treatment to the date of the evidence of disease progression or death in the absence of disease progression. OS was determined from the diagnosis to the time of the last follow up visit or death whatever the cause with SPSS [Statistical package] (version 23.0). The 95% confidence intervals (95% CIs) were calculated with the exact method. All P values were two-tailed; a value of < 0.05 was considered significant.

Results

In this study, sixty patients with locally advanced non-metastatic bladder cancer patients were treated in Clinical Oncology and Nuclear Medicine department in Mansoura University in Egypt. The age of our patients had a median of 67 years (Range: 51-79 years, mean 66.2 years ±7.64). Males were represented in 44 patients (73.3%) with male to female ratio 2.7 to 1. Most of patients had a score 1 in assessment of ECOG PS (55%). Tumor stage T3 was the most presenting stage in 68.3% patients (48.3% of patients had T3A and 20% staged as T3B). Forty- eight patients had a clinical positive LN (53.3%, 26.7 % of patients had N1 and N2, respectively).

The most presenting symptom is hematuria in 46 patients (76.7 %), followed by dysuria in 65 % of patients. Renal function was elevated in 29 patients (48.3%). The details of patients' characteristics were described in table 1.

Treatment details were mentioned in table 2. It showed that 56 patients (93.3%) underwent TURB for pathological confirmation and maximum tumour eradication. 73.3% of patients received 3 cycles of NA chemotherapy. GC was administrated in 28 patients (46.7%) patients, while rest of patients received G-carb.

Table 1: Patient and tumour characteristics

Variables	No (%)
- **Age**	
• **Median**	67
• **Range**	51-79
- **Sex**	
• **Male**	44(73.3)
• **Female**	16(26.7)
- **ECOG PS Status**	
• **ECOG 0**	15(25)
• **ECOG 1**	33(55)
• **ECOG 2**	12(20)
- **Tumour stage(T)**	
• **T1**	0
• **T2**	6(10)
• **T3 : A**	12(20)
B	29(48.3)
• **T4**	13(21.7)
- **Nodal stage(N)**	
• **N0**	12(22)
• **N1**	32(53.3)
• **N2**	16(26.7)
- **Grading(G)**	
• **G1**	0
• **G2**	22(37.7)
• **G3**	38(63.3)
Associated co-morbidities	
• **Diabetes Melitues**	41(68.3)
• **Hypertension**	38(63.3)
• **Coronary vascular disease**	13(21.6)
presenting symptom	
• **Haematuria**	46(76.6)
• **Dysuria**	39(65)
• **Abdominal pain**	24(40)
• **Incontinence**	4(6.6)
Hydronephrosis	
• **Yes**	37(61.6)
• **No**	23(38.3
Renal impairment	
• **Yes**	29(48.3)
• **No**	31(51.7)
Multiplicity	
• **Solitary**	26(43.3)
• **Multiple**	19(31.7)
• **Diffuse**	15(25)

Table 2: Treatment characteristics

Variables	No (%)
- **TURB**	
• **No**	4(66.7)
• **1 time**	51(85)
• **More than one**	5(8.3)
- **Rang of radiation dose**	46-65 Gy
- **Total radiation dose(gray)**	
• **46 - < 65**	11(18.3)
• **65**	49(81.6)
- **Chemotherapy regimen**	
• **Gem-cisplatin**	28(46.7)
• **Gem-carboplatin**	32(53.3)
- **No of NA Chemotherapy cycles**	
• **2**	16(26.7)
• **3**	44(73.3)
- **Concurrent chemotherapy**	19(31.7)
• **No of cisplatin case**	2-5
Range of cycles	
• **No of carboplatin**	38(63.3)
Range of cycles	4-6

By assessment of patients clinically before starting radiotherapy, we recorded improvement of haematuria in 41 patients out of 46(89.1%) patients, and Dysuria improvement was reported in 33 out 39(84.6%) patients, while 17 out of 24 (70 %) patients felt improvement of abdominal pain.

Planed dose of radiotherapy was 66 gray (2 gray per fraction), 49 patients (81.6 %) received full dose while 11(18.3 %) of our cases did not complete the described plane dose of radiotherapy. 6 patients due to side effects, 3 cases due to disease progression while two others due to social causes.

Weekly concomitant chemotherapy was administrated in 57 of patients (19 cases was received cisplatin and 38 cases was received carboplatin). Three patients who previously received CG refused to receive further chemotherapy and 6 patients were shifted to carboplatin due to intolerance and increase in serum creatinine. Range of chemotherapy cycles was 2 to 6 cycles; median was 3 cycles (range was 2 to 5 and 4 to 6 for no. of cycles of cisplatin and carboplatin, respectively).

Toxicity assessment revealed that: The haematological toxicity were recorded as 32 patients developed anaemia, 8 of them were in grade (G)3. Fourteen patients suffered from neutropenia, mostly G 1-2. While thrombocytopenia was reported in 14 patients 5 of them was in G3.

Other reported toxicities were urinary symptoms mostly presented in cystitis in 52 patients, 49 patients were in G1-2. Forty-one patients recorded G1-2 gastrointestinal toxicity (GIT). Dermatological toxicity was the least reported one (14 patients (23.3%) (Table 3).

Table 3: Acute Toxicities

Acute toxicity	Grade N (%)	
	G 1-2	G 3
Non-heamatological toxicities		
• GU	49(81.7)	3(5)
• GIT	41(68.3)	0
• Skin	14(23.3)	0
Haematological toxicities		
• Anemia	24(40)	8(13.3)
• Neutropenia	11(18.3)	3(5)
• Thrombocytopenia	9(15)	5(8.3)

After completion of treatment, patients were assessed radiologically after 8 weeks to determine the response. 26 patients (43.3 %) had complete response (CR), while 30% and 16.7% had partial response (PR) and stable disease (SD), respectively. Progression of disease (PD) was detected in 6 patients (10%). Patient who experienced progression were shifted to palliative chemotherapy or best supportive treatment. Responding patient who had CR and PR were 22 vs. 23 patients, while nonresponding patients were 6 vs. 9 cases in GC vs. G – carbo subgroups, respectively (p=0.55).

After a median follow up period of 16 months (rang; 6- 27 months), the status of patients was; 23 (38.3%) patients were in CR, 17(28.3%) were alive with disease (4, 7, 5, and 3 patients with residual disease, local recurrence , metastatic disease or both metastasis with local recurrence , respectively). While 20 patients (33.3%) were dead, 15 patients because of bladder cancer, 5 patients with other causes. The details are in table 4.

Table 4: Fate of patients

Response after treatment	No. (%)
• Complete response	
• Partial response	26(43.3)
• Stable disease	18(30)
• Progressive disease	10(16.7)
	6(10)
Fate on follow up	
• No evidence of disease	23(38.4)
• Alive with disease	17(28.3)
• Died of disease	15(25)
• Undercurrent death	5(8.3)

2-year PFS was 27.1 % (the mean: 16.25 months ±0.736months) (figure 1) and 2 –years OS was 52.3 % (the mean: 20.8 months ±0.736 months) (figure 2). In the analysis of survival relation to prognostic factors, PFS was statistically significant differ

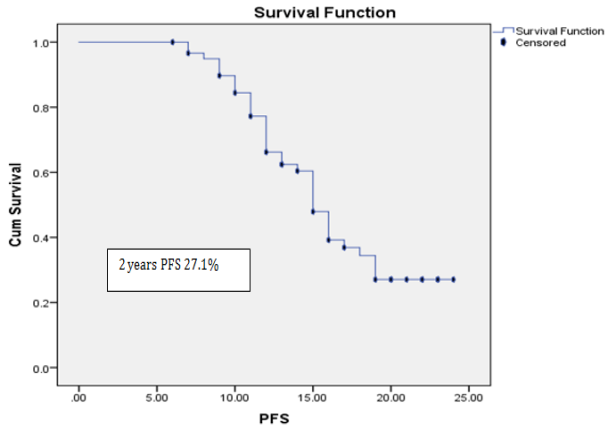

Figure 1: Progression free survival of the studied patients

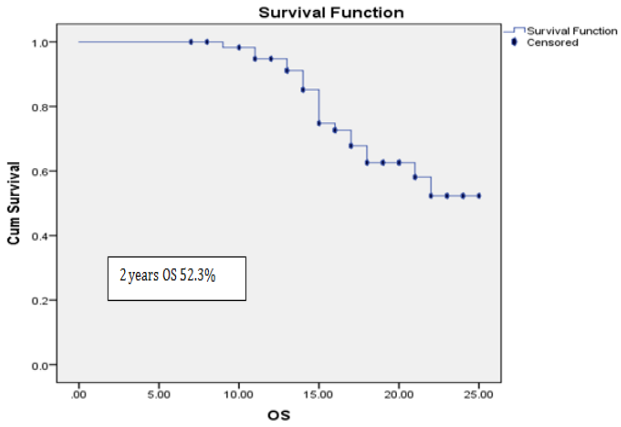

Figure 2: Overall survival of the studied patients

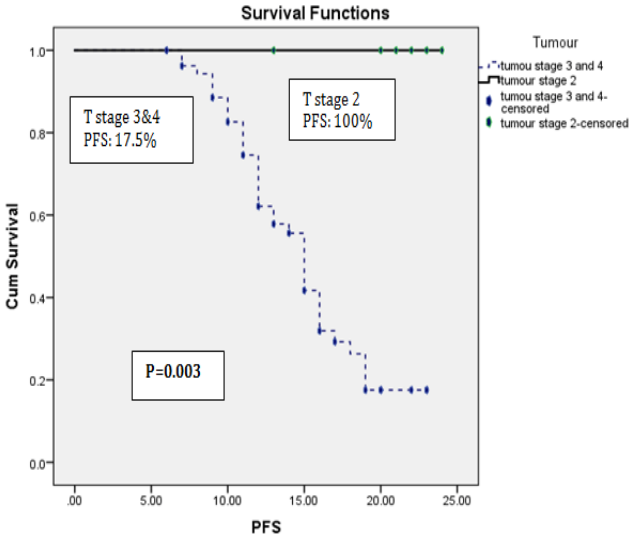

Figure 3A:

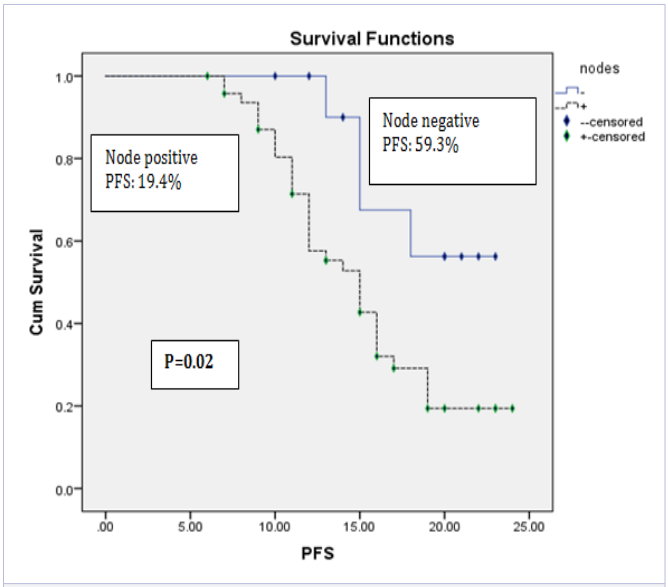

Figure 3B:

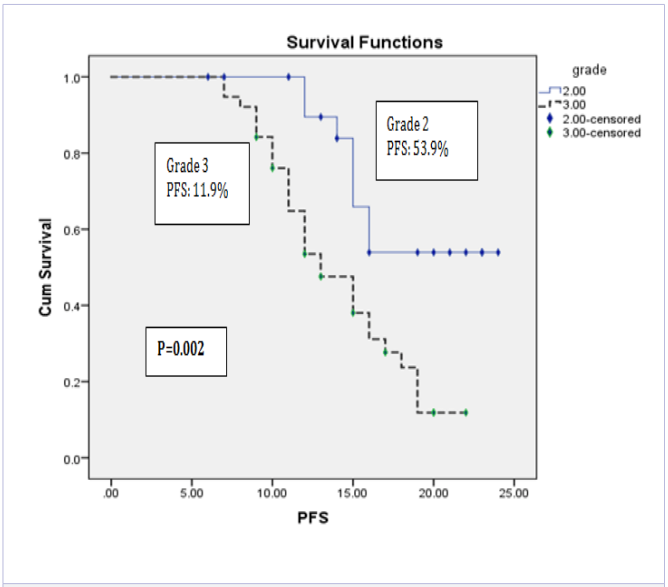

Figure 3C:

Table 5: The survival relation to prognostic factors

Prognostic factors	2-years PFS (%)	P value	2-years OS (%)	P value
Sex				
• Male	32.4	**0.43**	56.1	**0.98**
• Female	15.2		36.5	
Tumors stage (T)				
• T2	100	**0.003**	100	**0.043**
• T3 and T4	17.5		29.6	
Nodal stage (N)				
• N negative	59.3	**0.02**	100	**0.006**
• N positive	19.4		32.8	
Grade				
• Grade 2	53.9	**0.002**	86.7	**0.001**
• Grade 3	11.9		19.7	
Chemotherapy Type		**0.11**		**0.68**
• **GC**	33.5		56.9	
• **G-Carb**	18.6		51.6	

in grade 2 vs. grade 3 (p=0.002), tumour size T2 vs. T3 and T4 (p=0.003) and nodal status clinical negative LN vs. clinical positive LN (p=0.02) (figure 3 A-B-C), with no significant relation with sex (p=0.43) and chemotherapy type (p=0.11). As regards OS, significant relation was found in relation to grade (p=0.001), tumour stage (p=0.043) and LNs (p=0.006). Also no significant relation with sex (p=0.98) and chemotherapy type (p=0.68) (Table 5).

Discussion

Radical cystectomy with pelvic Lymph nodes dissection was the standard treatment with curative intent for long time For MIBC, in spite of development of metastatic disease in about half of patients [4, 21]. With introducing of chemotherapy and advancement of multidisciplinary approach in locally advanced bladder cancer, chemotherapy take wide part in management of bladder cancer as neoadjuvant or adjuvant treatment. NA chemotherapy and radical cystectomy with pelvic lymphadenectomy is the gold standard treatment of MIBC [22].

Anan et al, reported in a multicenter study in Japan a significantly increase in administration of NA chemotherapy from 10 % in period between 1996-2004 to 83% from 2005 to 2016[23]. Moreover based on the result of several meta-analysis [18, 21], they conclude that NA chemotherapy before definitive local treatment either with surgery or radiotherapy create survival advantage. The same benefit in term of pathological

down staging, 5- year PFS and 5- year OS was obtained in another study using NA platinum compound plus gemcitabine before RC in MIBC [23].

In comparison between, MVAC and gemcitabine with platinum compound either cisplatin or carboplatin in neoadjuvant is setting before RC, no significant difference in pathological complete response between them. However, MVAC was associated with a significantly higher overall survival, but the difference was no longer statistically significant after exclusion of carboplatin data [18]. However, GC had gained favor in view of less toxicity profile and easy to administration [24].

With consideration of organ preservation and maintain bladder function, the role of radical radiotherapy treatment is take a chance in management of bladder cancer. But in comparison to RC, the results came poor as regards local control and survival with less affection of quality of life of patients especially the functional quality of the neo-bladder [25-26]. These leads to development of TMT by applying TURB followed by chemoradiation , providing the possibility of cure with preservation of bladder function and comparable survival outcomes of patients after TMT in comparison to RC[27-29]. Fahmy et al, analyzed the result of a 10-year disease specific survival(DSS) and 10-year OS were 50.9% and 30.9% for TMT and 57.8% and 35.1% for RC (P = 0.26), (P = 0.32), respectively) [27].

The definitive treatment by radical radiotherapy combined with chemotherapy sensitizer provides an alternative approach in those group of patients who had associated co- morbidities , advanced stage , or positive clinically lymph nodes. In our study, we targeted that group of patients who weren't candidates for surgery and presented with clinical stage T2-T4 with or without clinical positive LN. Two to three cycles of NA chemotherapy was administrated; gemcitabine combined with platinum compound either cisplatin or carboplatin, depending on renal function assessment.

We found the application of chemotherapy before definitive treatment with radiotherapy concomitant with chemotherapy is alternative approach to its application before surgery. These provide several advantages ; rapid control of patients symptoms, early introduction of chemotherapy before radiotherapy allow for more better delivery of treatment and control of micrometastasis [6-8,30], and provide a line of treatment till availability of radiotherapy delivery to overcome delay of radiotherapy starting especially in low income countries with long list of patients.

Carboplatin usage in bladder cancer revealed comparable results to cisplatin, Moreover there were no clear evidence of superiority of Cisplatin –compound protocol in NA setting [31-32].

In our series no significant difference in response between patient receiving carboplatin and cisplatin (p=0.55), but tolerance to carboplatin was in advantage. We reported 6 patients received Cisplatin in NA setting shifted to carboplatin, also the range of concurrent number of cycles was more with carboplatin (4 to 6 vs. 2 to 5 cycles).

The role of NA chemotherapy was discussed in two large randomized trial that were conducted by the Medical Research Council/European Organization for Research and Treatment of Cancer and Southwest Oncology Group's study [33-34], they concluded the significant benefit of survival of NA chemotherapy before definitive local treatment and was considered as state of art [34]. In the updated study, most of patients stage were in T3 and had Nx , they received 3 cycles on CMV followed by surgery or RT without randomization. Twenty percent reduction of death and 9% reduction of risk of loco-regional recurrence. The outcome NA chemotherapy before RT in comparison with NA chemotherapy before cystectomy is worse, but it is mostly attributed to difference in patients' criteria and absence of randomization and selection of local treatment depend on physician choice [34].

In ours, CR was achieved in 43% of patients, 2 –years PFS and OS were 27 %and 52%, respectively. Survival data was comparable to result obtained from a German study [35]. They reported 3-year OS was 56.9%, however CR was achieved in 66.7% of the patients and lower response rate in our series, may be attributed to enrolment of more patients had T3 and T4 with positive LNs. The report from another study was CR in 60%, PR in 26%, 2 year survival were 34.4% and 74% for DFS and OS, respectively [11], these findings more or less similar in survival and also little lower as regard CR. Some studies report a CR approximate our results [15-31-36]. Moreover in our series no tissue biopsy confirmation was done after definite treatment as we did not plane to proceed to surgery as selection criteria of our patients.

CMV or MVAC were the most used induction chemotherapy protocol in previous studies, in one study [37] use CMV or GC without comparing of effect, but toxicity profile was better with GC [7% of cases suffered from grade (3/4) neutropenia and thrombocytopenia , cystitis in 26% and enteritis in 18%. The result is comparable to our results as we reported grade 3 haematological toxicities in neutropenia and thrombocytopenia in 5% and 6.6%, respectively. However high incidence of cystitis and enteritis, but most of our cases were in grade 1.CR was high in comparable to us, but in Cobo et al, the patients criteria included patients in stage T2 (21 out of 28 patients) and T3 only. The better results was obtained with stage T2, this was comparable to our results as we reported 100% of 2- year OS and PFS.

Selection of patients with clinically positive lymph node to receive NA chemotherapy before surgery was studies in Hermans et al series [38], they selected 659 patients with cT1-4a N1-3M0 urothelial carcinoma, they reported as statistically significant difference in CR between NA chemotherapy group vs. upfront cystectomy (39% vs. 5%, P < 0.001)) and 27% versus 3% (P < 0.001) for cN2-3 UC, Also survival data was in favor of NA chemotherapy. OS at 3 years were 66% versus 37% (cN1) and 43% versus 22% (cN2-3) (P < 0.001)[39].In another study , CR and PR were 14.5% and 27%, in patients with clinically positive LNs received NA chemotherapy before RC (GC was used in 43%,) [40]. Clinical positive LNs had a significantly lower PFS and OS in relation to negative LNs cases in our study.

The factors affecting survival in this results was grade, tumour stage and LN status. Grade is well stablished as the most important factors affecting the survival of patients of bladder cancer [40]. Patients with Stage T2-T3, grade 2 tumors had a statistically significantly better chance of remaining relapse free than did the others (P = 0.045) [41].

Conclusion

Our study targeted the patients with locally advanced bladder cancer with or without clinically positive LNs and can't be offered by radical cystectomy. They had a chance of treatment with chemoradiotherapy. TURB followed by neoadjuvant chemotherapy based on GC or G-carb for 2 to 3 cycles then radiotherapy concomitant with cisplatin or carboplatin provides acceptable survival results with tolerable toxicity. However our study had several limitations as small number of patients, shorter follows up period and shortage of pathological confirmation after treatment.

Acknowledgments

We are grateful to all colleagues for their help and advice that were granted to us.

Compliance with Ethical standards

The authors declare that they have no conflict of interest. All procedures performed in study were in accordance with ethical standards of our institutional in accordance with ethical standard of deceleration of Helisinki 1964. Informed consent was obtained from all patients before participation in the study.

References

1. Cancer Facts & Figures 2018. American Cancer Society. 2018.

2. Chavan S, Bray F, Lortet-Tieulent J, Goodman M, Jemal A. International variations in bladder cancer incidence and mortality. Eur Urol. 2014;66(1):59-73. doi: 10.1016/j.eururo.2013.10.001

3. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin. 2018;68(1):7-30. doi: 10.3322/caac.21442

4. Clark PE, Agarwal N, Biagioli MC, Eisenberger MA, Greenberg RE, Herr HW, et al. Bladder cancer. J Natl Compr Canc Netw. 2013;11(4):446-475.

5. Gakis G, Efstathiou J, Lerner SP, Cookson MS, Keegan KA, Guru KA, et al. ICUD-EAU International Consultation on Bladder Cancer 2012: radical cystectomy and bladder preservation for muscle-invasive urothelial carcinoma of the bladder. Eur Urol. 2013;63(1):45-57. doi: 10.1016/j.eururo.2012.08.009

6. Grossman HB, Natale RB, Tangen CM, Speights VO, Vogelzang NJ, Trump DL, et al. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. N Engl J Med. 2003;349(9):859-866.

7. Martinez-Pineiro JA, Martinez-Pineiro L. The role of neoadjuvant chemotherapy for invasive bladder cancer. British Journal of Urology. 1998;82:33-42.

8. Advanced Bladder Cancer Meta-analysis Collaboration. Neoadjuvant chemotherapy in invasive bladder cancer: A systematic review and meta-analysis. Lancet. 2003;361(9373):1927-1934.

9. Advanced Bladder Cancer (ABC) Meta-analysis Collaboration. Neoadjuvant chemotherapy in invasive bladder cancer: Update of a systematic review and meta-analysis of individual patient data advanced bladder cancer (ABC) meta-analysis collaboration. Eur Urol. 2005;48(2):202-205; discussion 205-206.

10. Griffiths G, Hall R, Sylvester R, Raghavan D, Parmar MK .International phase III trial assessing neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: long-term results of the BA06 30894 trial. J Clin Oncol. 2011;29(16):2171-2177. doi: 10.1200/JCO.2010.32.3139

11. Byun SJ, Kim JH, Oh YK, Kim BH. Concurrent chemoradiotherapy improves survival outcome in muscle-invasive bladder cancer. Radiation oncology journal. 2015;33:294–300.

12. Mak RH, Hunt D, Shipley WU, Efstathiou JA, Tester WJ, Hagan MP, et al. Long-term outcomes in patients with muscle-invasive bladder cancer after selective bladder-preserving combined-modality therapy: a pooled analysis of Radiation Therapy Oncology Group protocols 8802, 8903, 9506, 9706, 9906, and 0233. J Clin Oncol. 2014;32(34):3801-3809. doi: 10.1200/JCO.2014.57.5548

13. Efstathiou JA, Spiegel DY, Shipley WU, Heney NM, Kaufman DS, Niemierko A, et al. Long-term outcomes of selective bladder preservation by combined-modality therapy for invasive bladder cancer: the MGH experience. Eur Urol. 2012;61(4):705-711. doi: 10.1016/j.eururo.2011.11.010

14. Hermans TJN, Voskuilen CS, van der Heijden MS, Schmitz-Dräger BJ, Kassouf W, Seiler R, et al. Neoadjuvant treatment for muscle-invasive bladder cancer: The past, the present, and the future. Urol Oncol. 2018;36(9):413-422. doi: 10.1016/j.urolonc.2017.10.014

15. Zargar H, Espiritu PN, Fairey AS, Mertens LS, Dinney CP, Mir MC, et al. Multicenter assessment of neoadjuvant chemotherapy for muscle-invasive bladder cancer. Eur Urol. 2015;67(2):241-249. doi: 10.1016/j.eururo.2014.09.007

16. von der Maase H, Sengelov L, Roberts JT, Ricci S, Dogliotti L, Oliver T, et al. Long-term survival results of a randomized trial comparing gemcitabine plus cisplatin, with methotrexate, vinblastine, doxorubicin, plus cisplatin in patients with bladder cancer. J Clin Oncol. 2005;23(21):4602-4608.

17. Porter MP, Kerrigan MC, Donato BM, Ramsey SD. Patterns of use of systemic chemotherapy for Medicare beneficiaries with urothelial bladder cancer. Urol Oncol. 2011;29(3):252-258. doi: 10.1016/j.urolonc.2009.03.021

18. Yin M, Joshi M, Meijer RP, Glantz M, Holder S, Harvey HA, et al. Neoadjuvant Chemotherapy for Muscle-Invasive Bladder Cancer: A Systematic Review and Two-Step Meta-Analysis. Oncologist. 2016;21(6):708-715. doi: 10.1634/theoncologist.2015-0440

19. Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0. Published: 2009: evs.nci.nih.gov/ftp1/ CTCAE/ CTCAE_4.03_2010-06-22. Accessed: 2016.

20. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228-247. doi: 10.1016/j.ejca.2008.10.026

21. Ismaili N. Neoadjuvant Chemotherapy: A New Standard for Muscle Invasive Bladder Cancer?. Gulf J Oncolog. 2017;1(23):82-85.

22. Chang SS, Bochner BH, Chou R, Dreicer R, Kamat AM, Lerner SP, et al. Treatment of non-metastatic muscle-invasive bladder cancer: AUA/ASCO/ASTRO/SUO Guideline. J Urol. 2017;198(3):552-559. doi: 10.1016/j.juro.2017.04.086

23. George W Moran, Gen Li, Dennis J Robins, Justin T Matulay, James M McKiernan, Christopher B Andersonc. Systematic Review and Meta-Analysis on the Efficacy of Chemotherapy with Transurethral Resection of Bladder Tumors as Definitive Therapy for Muscle Invasive Bladder Cancer. Bladder Cancer. 2017;3(4):245–258.

24. Dogliotti L, Cartenì G, Siena S, Bertetto O, Martoni A, Bono A, et al. Gemcitabine plus cisplatin versus gemcitabine plus carboplatin as first-line chemotherapy in advanced transitional cell carcinoma of the urothelium: Results of a randomized phase 2 trial. Eur Urol. 2007;52(1):134-141.

25. Marta GN, Hanna SA, Gadia R, Correa SF, Silva JL, Carvalho Hde A. The role of radiotherapy in urinary bladder cancer: current status. Int Braz J Urol. 2012;38(2):144-153; discussion 153-154.

26. Stenzl A, Sherif H, Kuczyk M. Radical cystectomy with orthotopic neobladder for invasive bladder cancer: a critical analysis of long term oncological, functional and quality of life results. Int Braz J Urol. 2010;36(5):537-547.

27. Fahmy O, Khairul-Asri MG, Schubert T, Renninger M, Malek R, Kübler H, et al. A systematic review and meta-analysis on the oncological long-term outcomes after trimodality therapy and radical cystectomy with or without neoadjuvant chemotherapy for muscle-invasive bladder cancer. Urol Oncol. 2018;36(2):43-53. doi: 10.1016/j.urolonc.2017.10.002

28. Kim YJ, Byun SJ, Ahn H, Kim CS, Hong BS, Yoo S, et al. Comparison of outcomes between trimodal therapy and radical cystectomy in muscle-invasive bladder cancer: a propensity score matching analysis. Oncotarget. 2017;8(40):68996-69004. doi: 10.18632/oncotarget.16576

29. Giacalone NJ, Shipley WU, Clayman RH, Niemierko A, Drumm M, Heney NM, et al. Long-term Outcomes After Bladder-preserving Tri-modality Therapy for Patients with Muscle-invasive Bladder Cancer: An Updated Analysis of the Massachusetts General Hospital Experience. Eur Urol. 2017;71(6):952-960. doi: 10.1016/j.eururo.2016.12.020

30. Taghian AG, Abi-Raad R, Assaad SI, Casty A, Ancukiewicz M, Yeh E, et al. Paclitaxel decreases the interstitial fluid pressure and improves oxygenation in breast cancers in patients treated with neoadjuvant chemotherapy: clinical implications. J Clin Oncol. 2005;23(9):1951-1961.

31. Mertens LS, Meijer RP, Kerst JM, Bergman AM, van Tinteren H, van Rhijn BW, et al. Carboplatin based induction chemotherapy for nonorgan confined bladder cancer--a reasonable alternative for cisplatin unfit patients?. J Urol. 2012;188(4):1108-1113. doi: 10.1016/j.juro.2012.06.018

32. Ohyama C, Hatakeyama S, Yoneyama T, Koie T. Neoadjuvant chemotherapy with gemcitabine plus carboplatin followed by immediate radical cystectomy for muscle-invasive bladder cancer. Int J Urol. 2014;21(1):3-4. doi: 10.1111/iju.12230

33. Neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: a randomized controlled trial. International collaboration of trialists. Lancet. 1999;354(9178):533-540.

34. Griffiths G, Hall R, Sylvester R, Raghavan D, Parmar MK. International phase III trial assessing neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: long-term results of the BA06 30894 trial. J Clin Oncol. 2011;29(16):2171-2177. doi: 10.1200/JCO.2010.32.3139

35. Langsenlehner T, Döller C, Quehenberger F, Stranzl-Lawatsch H, Langsenlehner U, Pummer K, et al.: Treatment results of radiation therapy for muscle-invasive bladder cancer. Strahlenther Onkol. 2010;186(4):203-209. doi: 10.1007/s00066-010-2053-1

36. Galsky MD, Pal SK, Chowdhury S, Harshman LC, Crabb SJ, Wong YN, et al. Comparative effectiveness of gemcitabine plus cisplatin versus methotrexate, vinblastine, doxorubicin, plus cisplatin as neoadjuvant therapy for muscle-invasive bladder cancer. Cancer. 2015;121(15):2586-2593. doi: 10.1002/cncr.29387

37. Cobo M, Delgado R, Gil S, Herruzo I, Baena V, Carabante F, et al. Conservative treatment with transurethral resection, neoadjuvant chemotherapy followed by radiochemotherapy in stage T2-3 transitional bladder cancer. Clin Transl Oncol. 2006;8(12):903-911.

38. Hermans TJ, Fransen van de Putte EE, Horenblas S, Meijer RP, Boormans JL, Aben KK, et al. Pathological downstaging and survival after induction chemotherapy and radical cystectomy for clinically node-positive bladder cancer-Results of a nationwide population-based study. Eur J Cancer. 2016;69:1-8. doi: 10.1016/j.ejca.2016.09.015

39. Zargar-Shoshtari K, Zargar H, Lotan Y, Shah JB, van Rhijn BW, Daneshmand S, et al. A Multi-Institutional Analysis of Outcomes of Patients with Clinically Node Positive Urothelial Bladder Cancer Treated with Induction Chemotherapy and Radical Cystectomy. J Urol. 2016;195(1):53-59. doi: 10.1016/j.juro.2015.07.085

40. George L, Bladou F, Bardou VJ, Gravis G, Tallet A, Alzieu C, et al. Clinical outcome in patients with locally advanced bladder carcinoma treated with conservative multimodality therapy. Urology. 2004;64(3):488-493.

41. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol. 2010;17(6):1471-1474. doi: 10.1245/s10434-010-0985-4