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Review

Role of gemcitabine and cisplatin as neoadjuvant chemotherapy in muscle invasive bladder cancer: Experience over the last decade

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Abstract *Objective:* Neoadjuvant chemotherapy followed by radical cystectomy is considered the standard of care for patients with muscle invasive bladder cancer. In the last decade, interest in neoadjuvant chemotherapy has slowly shifted from methotrexate, vinblastine, doxorubicin and cisplatin regime to gemcitabine and cisplatin regime. There are many publications on gemcitabine and cisplatin regime in literature which cover different aspects of treatment. This review aims to summarise the findings published so far on gemcitabine and cisplatin regime and present it in a concise manner.
Methods: A systematic literature review was conducted searching the PubMed® database in December 2016 using the medical subject heading (MeSH) with the terms gemcitabine, cisplatin, chemotherapy, muscle invasive bladder cancer, and neoadjuvant. All relevant studies were included and results were analysed.
Results: A total of 13 studies were included which published between 2007 and 2015. These 13 studies comprised of 754 subjects suffering from muscle invasive bladder cancer. The proportion of male patients ranged from 60% to 86.4% and the median age ranged from 54.2 to 77.3 years in various studies. Complete pathological response (pT0) was seen in 30.0% of patients and pathological downstaging (<pT2) was seen in 48.67% of patients.
Conclusion: As per latest guidelines, neoadjuvant chemotherapy is recommended for patients with muscle invasive bladder cancer. There is substantial pathological downstaging with low toxicity in patients of muscle invasive bladder cancer who receive neoadjuvant gemcitabine and cisplatin regime.

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1. Introduction

Muscle invasive bladder cancer (MIBC) is an aggressive malignant disease with early systemic spread. Radical cystectomy (RC) with pelvic lymph node dissection is the standard of care for MIBC [1]. Disease recurrence after RC is relatively common and occurs with greater frequency at distant sites compared to loco-regional recurrence (20%–50% *vs*. 5%–15%) [2]. This is an indirect evidence that systemic treatment modalities may improve outcome of locally advanced bladder cancer. Hence, there is a need for early multimodal therapy to improve prognosis.

There is an emerging trend towards neoadjuvant chemotherapy (NAC) in MIBC. Several randomized controlled trials support the use of platinum-based chemotherapy in MIBC [3,4]. A meta-analysis which included 11 randomized controlled studies suggested that NAC followed by cystectomy compared to cystectomy alone was associated with a 5% improvement in overall survival and 9% improvement in disease-free survival [5].

The role of NAC was first established by SWOG-8710 trial [6]. It randomized MIBC patients to two groups. One group received 3 cycles of MVAC (methotrexate, vinblastine, adriamycin, cisplatin) followed by RC and the other arm directly proceeded to RC. Patients receiving MVAC were noted to have an improved pT0 rate (38% *vs*. 15%, $p < 0.001$) and showed survival of 77 months compared to 46 months in the surgery alone arm ($p = 0.06$). Approximately 73% of patients exposed to MVAC experienced grade 3/4 toxicities. Although the survival rate significantly improved in the neoadjuvant group (MVAC regimen), toxicity (myelosuppression and neutropenia) due to MVAC regimen appears alarming. This has led to search for other chemotherapy regimens which can lead to similar results with lesser toxicity.

A non-randomized study by Dash et al. [7] revealed similar complete pathologic response rate and disease free survival in patients receiving GC (gemcitabine and cisplatin) combination as compared to MVAC with significantly decreased toxicity. Similarly, study by von der Masse [8, 9] showed similar response rate (49% *vs*. 46%), progression-free survival (7.7 months *vs*. 8.3 months), median survival (14.0 months *vs*. 15.2 months) and markedly less toxicity, especially in non-hematologic side effects, when compared with MVAC in locally advanced/metastatic disease.

Hence, the current interest of both medical oncologists and urologists is shifting towards GC. In the last decade, publications have started focusing on the role of GC for NAC in MIBC. In literature, most of the evidences for its use in neoadjuvant setting comes from small single centre retrospective studies or prospective case series [10]. In our manuscript, we have included all studies which have described the role of GC in MIBC patients and summarized the results for better insight.

2. Material and methods

Institutional review board approval was obtained. A systematic literature review was conducted searching the PubMed database in December 2016 using the medical subject heading (MeSH) with the terms gemcitabine, cisplatin, chemotherapy, muscle invasive bladder cancer, and neoadjuvant. Only articles published in English and studies done on humans were included. Patients with resectable MIBC (cT2–4aN0-N1M0) who underwent NAC with GC regime were included. Patients with pure transitional cell carcinoma on histopathology or mixed with squamous/glandular differentiation were included. Patients with all other variants on histology and cT4b disease were excluded from the analysis.

After extensive search on PubMed, we found 13 relevant articles containing data evaluable specifically for neoadjuvant GC. The quality assessment of the studies is done using New Castle Ottawa Scale (NOS) tool [11]. We looked at the following parameters which were published in the above mentioned research articles: 1) Type of study, 2) number of patients treated with neoadjuvant GC, 3) mean age, 4) male/female ratio, 5) schedule and number of cycles given, 6) toxicity profile, and 7) patients receiving neoadjuvant GC who were pT0 at cystectomy. If available, other data elements were also collected, such as 1) average time between completion of neoadjuvant GC and cystectomy, 2) number of patients with non-muscle invasive disease (*i.e.*, less than pT2 disease) at cystectomy and 3) number of cycles of chemotherapy delivered.

We have assessed pathologic responses to chemotherapy, which was compared amongst different studies. Complete pathological response (pCR) was defined as pT0N0, and pathologic downstaging (pR) was defined as < pT2N0 (including pT0/Ta/Tis/T1). Toxicity profile and completeness of chemotherapy schedule were also assessed.

When available, the chemotherapy dosing schedule was recorded and classified as 1) 70 mg/m^2 cisplatin with 2000 mg/m^2 gemcitabine of a 21-day cycle, 2) 70 mg/m^2 cisplatin with 1000 mg/m^2 gemcitabine of a 21-day cycle, or 3) 75 mg/m^2 cisplatin with 1200 mg/m^2 gemcitabine of a 28-day cycle.

3. Results

3.1. Study identification

Thirteen studies were identified that met the inclusion and exclusion criteria (Fig. 1). The detailed quality assessment is shown in Table 1. In summary, these studies included a total of 754 patients (range: 22 to 150 patients) and were published between 2007 and 2015 (Table 2). Of these studies, 11 were retrospective institutional analyses, one

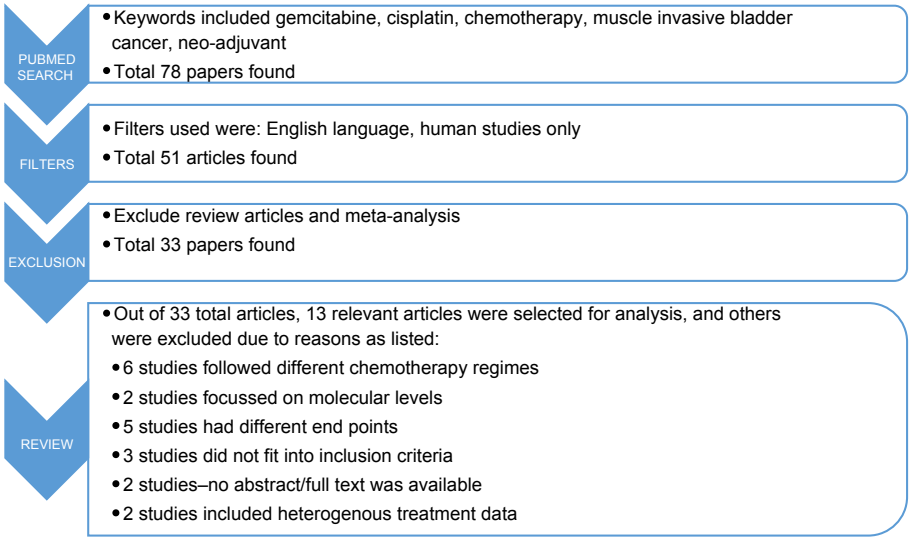

Figure 1 Flowchart of materials and methods.

Table 1 Quality assessment of included studies using NOS tool.

Study	Selection domain (max of 4 points)	Comparability domain (max of 2 points)	Outcome domain (max of 3 points)	Quality rating
Kim et al. [12]	****	*-	*-*	Fair
van de Putte et al. [13]	****	*-	*-*	Fair
Galsky et al. [14]	*-**	**	*--	Poor
Gandhi et al. [15]	****	**	**-	Good
Chau et al. [16]	****	**	*--	Poor
Khaled et al. [17]	NA	NA	NA	NA
Fairey et al. [18]	****	*-	*-*	Fair
Pal et al. [19]	****	**	*-*	Good
Matsubara et al. [20]	****	*-	*-*	Fair
Scosyrev et al. [21]	****	--	*-*	Poor
Kaneko et al. [22]	****	--	*-*	Poor
Dash et al. [7]	****	**	*-*	Good
Herchenhorn et al. [23]	NA	NA	NA	NA

*, Each single symbol represents 1 point assigned for the domain; NA, not applicable; -, each single symbol represents no point scored; NOS, New Castle Ottawa Scale.

was prospective and other one was a randomized controlled trial. Most of the studies were conducted in western hemisphere, with only three studies from Asia and one from Egypt. The proportion of male patients ranged from 60% to 86.4% and the median age ranged from 54.2 to 77.3 years in various studies.

3.2. Chemotherapy regimen

Details related to chemotherapy regimen were studied across the 13 studies included in our analysis as shown in Table 3. The National Comprehensive Cancer Network (NCCN) guidelines suggest 3 to 4 cycles of NAC for survival benefit [24]. Regimen across the studies varied from 3 to 4 weekly cycles with number of cycles ranging from 3 to 4 except for Kaneko et al. [22] and Scosyrev et al. [21] where only 2 cycles were given. The most frequently administered regimen was 70 mg/m^2 cisplatin on Day 1 with 1000 mg/m^2 gemcitabine on Days 1 and 8 of a 21-day cycle. Drug intensity (DI) was calculated in three studies ranging from 83.8% to 93.0% for gemcitabine and 91.0%–95.4% for cisplatin.

A relative DI (RDI) was first calculated for each agent administered to each patient by dividing the target dose by the actual dose rendered. The target dose was generated using the expectation that patients would receive a total of 3 months of NAC (*i.e.*, 4 cycles of a 3-weekly regimen, or 3 cycles of a 4-weekly regimen). An average DI for each patient was calculated by averaging the RDI for each agent rendered to the patient.

3.3. Clinical and pathological outcome

The clinical stage of patients before treatment is shown in Table 4. All these studies assessed the response of GC regime by calculating the complete pathological response (pCR defined as pT0N0) and pathologic downstaging (<pR

Table 2 Demographic characteristics of the studies.

Study	Year	Country	Type of study	Length of study	Sample size, *n*	Males, *n* (%)	Age (year, median)
Kim et al. [12]	2015	Korea	Retrospective	2003–2013	47	38 (80.9)	–
van de Putte et al. [13]	2015	–	Retrospective	1990–2014	51	36 (70.6)	63
Galsky et al. [14]	2015	USA	Retrospective	2005–2012	146	115 (78.8)	63
Gandhi et al. [15]	2015	USA	Retrospective	2000–2013	150	123 (82)	62.5
Chau et al. [16]	2015	UK	Retrospective	2005–2011	83	60 (72.3)	68
Khaled et al. [17]	2014	Egypt	RCT	2000–2002	59	44 (74.6)	54.2
Fairey et al. [18]	2013	USA	Retrospective	1985–2011	58	44 (75.9)	67
Pal et al. [19]	2012	USA	Retrospective	1995–2012	24	19 (79.2)	77.3
Matsubara et al. [20]	2012	Japan	Retrospective	2005–2010	25	15 (60)	67
Scosyrev et al. [21]	2012	USA	Retrospective	1999–2009	25	18 (72)	65
Kaneko et al. [22]	2011	Japan	Retrospective	2007–2011	22	16 (72.7)	69
Dash et al. [7]	2008	USA	Retrospective	2000–2006	42	32 (76.2)	64
Herchenhorn et al. [23]	2007	Brazil	Prospective	2002–2005	22	19 (86.4)	63

RCT, randomized control trial; –, not available.

Table 3 Variation in chemotherapy regimen among various studies.

Study	No. of cycles	Schedule (3/4 weekly)	Dose of gemcitabine	Dose of cisplatin	DI for gemcitabine (%)	DI for cisplatin (%)
Kim et al. [12]	3.2	–	–	–	–	–
van de Putte et al. [13]	3	3	1000 mg/m^2	70 mg/m^2	–	–
Galsky et al. [14]	3	–	–	–	–	–
Gandhi et al. [15]	3,4	3,4	1000 mg/m^2	70/35 mg/m^2	–	–
Chau et al. [16]	3,4	3	1000 mg/m^2	70 mg/m^2	–	–
Khaled et al. [17]	3	3	1250 mg/m^2	70 mg/m^2	–	–
Fairey et al. [18]	4	3	–	–	–	–
Pal et al. [19]	3,4	4,3	–	–	93	93
Matsubara et al. [20]	4	4	1000 mg/m^2	70 mg/m^2	–	–
Scosyrev et al. [21]	2,3,4	3	2000 mg/m^2	70 mg/m^2	–	–
Kaneko et al. [22]	2	4	1000 mg/m^2	70 mg/m^2	83.8	95.4
Dash et al. [7]	4	3	615 mg/m^2 weekly	21 mg/m^2 weekly	90	91
Herchenhorn et al. [23]	3	3	1200 mg/m^2	75 mg/m^2	–	–

DI, drug intensity; –, not available.

defined as <pT2N0 including pT0/Ta/Tis/T1) after cystectomy as shown in Table 5. Overall, pCR was achieved in 20%–63% patients except Kim et al. [12] where only 12.5% patients achieved complete response. Also, pR was achieved in 36%–63.6% patients.

3.4. Survival analysis

The survival data reported in the studies were analysed. The detailed survival data are enumerated in Table 6. A few studies have calculated overall survival while others have focussed on disease free survival.

3.5. Toxicity

Although the general tolerability of the treatment regimen was satisfactory, only five studies provided an analysis of specific toxicities related to neoadjuvant GC. Only grade 3/4 toxicity was analysed across all the studies as it leads to dose modification and discontinuation of treatment. All these are as shown in Table 7.

4. Discussion

Bladder cancer accounts for a significant proportion of hospital occupancy and is an important cause of morbidity and mortality amongst elderly men. Approximately 70% of bladder cancers are non-muscle invasive at presentation. The remaining 30% of bladder cancers are muscle invasive/metastatic at the time of presentation [2].

Overall 5-year survival after RC with pelvic lymph node dissection is 50% for organ confined disease, which decreases to 30% with extra-vesical extension and lymph node involvement [2]. Since a significant proportion of these patients have micro-metastases at the time of surgery, early multimodal therapy in the form of systemic chemotherapy is expected to improve prognosis. Now, there is an emerging trend towards NAC in MIBC, as also recommended

Table 4 Distribution of patients based on pre-chemotherapy staging (T stage).

Study	T2 *n* (%)	T3 *n* (%)	T4 *n* (%)
Kim et al. [12]	–	–	–
van de Putte et al. [13]	11 (21.5)	25 (49)	15 (29.4)
Galsky et al. [14]	90 (62)	40 (27)	16 (11)
Gandhi et al. [15]	97 (65)	38 (25)	15 (10)
Chau et al. [16]	43 (51.8)	33 (39.8)	7 (8.4)
Khaled et al. [17]	1 (2)	45 (76)	13 (22)
Fairey et al. [18]	28 (49)	18 (31)	12 (20)
Pal et al. [19]	19 (91.7)	2 (8.3)	0 (0)
Matsubara et al. [20]	9 (36)	16 (64)	
Scosyrev et al. [21]	6 (24)	19 (76)	
Kaneko et al. [22]	15 (68.2)	6 (27.3)	1 (4.5)
Dash et al. [7]	19 (45)	19 (45)	4 (10)
Herchenhorn et al. [23]	11 (52.4)	2 (9.5)	8 (38.1)

–, not available.

Table 5 Pathological response after neo-adjuvant chemotherapy and definitive surgery.

Study	pT0 (%)	<pT2 (%)
Kim et al. [12]	12.5	–
van de Putte et al. [13]	31.4	43.2
Galsky et al. [14]	31	–
Gandhi et al. [15]	35–63	–
Chau et al. [16]	36.9	–
Khaled et al. [17]	25.6	–
Fairey et al. [18]	27.3	45.5
Pal et al. [19]	25	58
Matsubara et al. [20]	40	44
Scosyrev et al. [21]	20	44
Kaneko et al. [22]	50	63.6
Dash et al. [7]	26	36
Herchenhorn et al. [23]	26.7	–

–, not available; pT0, complete pathological response (pCR); <pT2, pathologic downstaging (pR).

by European Association of Urology (EAU) [25]. According to EAU guidelines, patients with T2–T4a, cN0Mo bladder cancer are offered cisplatin based NAC.

There is level of evidence 1a (LE 1a) and grade of recommendation A (GR A) from several randomized controlled trials that supports the use of platinum-based chemotherapy in MIBC [3,4,25] (LE 1a—Evidence obtained from meta-analysis of randomised trials. GR A—Based on clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomised trial). In the advanced bladder cancer meta-analysis [5], platinum based chemotherapy showed a 5% improvement in overall survival at 5 years. Although cisplatin based NAC followed by RC is the standard treatment for MIBC [26], it has been underused. In surveillance, epidemiology and end results analysis by Gore and colleagues [26], it was demonstrated that only 21% of patients underwent RC out of 3262 MIBC patients. This could be attributed to treatment related morbidity and mortality. A report from National Cancer Database published in the year 2007 revealed that only 1.2% of patients received NAC and 10.4% received adjuvant chemotherapy in a subset of 7000 patients with MIBC. Trend towards NAC is increasing, and National Cancer Database in 2014 showed that 16.9% of patients with MIBC received NAC [27].

There are several arguments in favour of cisplatin-based NAC for patients with MIBC.

i. Systemic chemotherapy is often better tolerated before surgery, rather than after surgery. Patients are able to tolerate higher doses and a greater number of cycles before surgery than post-operatively [28].
ii. Patients who present with micro-metastatic disease will receive chemotherapy in a more timely manner, when their burden of disease is potentially low.
iii. NAC has the potential to downstage bulky and locally advanced tumors, allowing for a higher likelihood for negative surgical margins that are a known predictor of local recurrence following cystectomy. A study reported that 31.2% of patients who received NAC were downstaged as compared to 7.6% who immediately underwent RC [29].

Table 6 Survival analysis.

Study	Overall survival (%)	Disease free survival (%)
Galsky et al. [14]	26.8 months	–
Gandhi et al. [15]	–	58% (5-year)
Chau et al. [16]	65.8% (3-year) (age≥70 years) 63.2% (3-year) (age <70 years)	–
Khaled et al. [17]	51.9% (3-year)	31.8% (3-year)
Fairey et al. [18]	24.8 months	–
Pal et al. [19]	104.3 months	–
Matsubara et al. [20]	–	66.7%
Scosyrev et al. [21]	68%	–
Dash et al. [7]	–	67.5%
Herchenhorn et al. [23]	36 months	57.2%

–, not available.

Table 7 Toxicity profile.

Study	Toxicity profile (Grade 3/4)				
	Anemia, *n* (%)	Neutropenia, *n* (%)	Thrombocyto-penia, *n* (%)	Nausea/Vomiting, *n* (%)	Diarrhea, *n* (%)
Van de Putte et al. [13]	1 (2.6)	2 (5.1)	0 (0.0)	1 (2.6)	—
Khaled et al. [17]	2 (3.4)	3 (5.2)	3 (5.2)	22 (40)	1 (1.7)
Matsubara et al. [20]	8 (32)	10 (40)	10 (40)	—	—
Kaneko et al. [22]	1 (2.4)	6 (14.3)	9 (21.4)	0 (0)	0 (0)
Herchenhorn et al. [23]	0 (0)	7 (33.3)	1 (4.76)	6 (28.6)	—

—, not available.

iv. NAC allows the clinician to assess each individual's response to therapy, and it thus helps in guiding the adjuvant treatment strategy by identifying ineffective agents that should be avoided postoperatively [29].

There are concerns regarding delay in RC in patients who receive NAC that can result in worse pathological outcomes, but the report from National Cancer Database demonstrated similar mean time from diagnosis to RC (3.3 months *vs.* 3.8 months) between those who did not or did receive NAC [27]. Moreover, a study reported that use of NAC is not correlated with increased risk of complications, reoperations, wound infection or wound dehiscence [30].

Considering the above facts, there are now several drugs available for NAC. The most commonly employed chemotherapy regimens include: GC, Classic MVAC, ddMVAC (dose dense methotrexate + vinblastine + adriamycin + cisplatin) and CMV (cisplatin + methotrexate + vinblastine). The different neoadjuvant regimens have not been compared in randomized trials; retrospective evidence has not identified substantial difference between the various regimens [14].

Paradigm has now shifted from using MVAC regime to GC regime as there is less toxicity in patients given GC regime with similar pathological outcomes as outlined in introduction section. Here, we would like to mention the regime of ddMVAC, as studies have shown that ddMVAC has a safer toxicity profile, shorter time to surgery, and a similar complete pathologic response compared to historical MVAC [31,32]. Only a randomized trial comparing ddMVAC and GC could answer the question in terms of better response and survival along with lower toxicity profile, and such a trial is ongoing in France. Due to a lack of study giving a concise detail of all the studies using GC regime in MIBC patients, we chose to do research on this topic.

In our review, out of 754 patients with MIBC, we reported pCR in 30.8% patients and pR in 40.86% patients. Prospective analysis of MVAC in SWOG-8710 analysis showed pCR rate in 38% of patients [3] compared to 30.8% with GC exhibited in our present analysis. On applying intention to treat analysis, pT0 rate was 32% as per SWOG-8710 data. Other retrospective studies on neoadjuvant MVAC done in past have shown pT0 ranging between 19% and 31% [7,33,34].

Earlier, overall survival was taken as primary end point to assess the effect of NAC. Although overall survival still remains the gold standard to assess end point, recently, various studies have tried examining other clinical parameters that can be analysed in a shorter time period. Hence, pathological down staging is now being used as a surrogate indicator for long-term oncologic control and survival [35,36].

The pathological response rate varies widely amongst various studies. This heterogeneity in response arises from different inclusion criteria, varying schedule and dosing of GC regime, and lack of randomized controlled trials. In a pooled analysis of seven studies incorporating 164 patients receiving GC, Yuh et al. [10] reported a pCR rate of 25.6%. Some studies have analysed the factors predicting pCR following NAC; cT stage has been found to be a predictor for overall survival and disease free recurrence in patients receiving NAC [18].

Five out of 13 studies showed toxicity data for neoadjuvant GC regime, of which three studies were retrospective in nature. The most common side effects reported in literature are anemia, leukopenia, thrombocytopenia, vomiting and diarrhea [13,17,20,22,23]. Frequency of Grade 3/4 anemia was reported in range of 0—32%. The frequency of vomiting was 2.6%—40.0% of patients in literature. Thrombocytopenia was seen in up to 40% of patients in previous studies. The varying frequency of adverse effects between various studies is probably due to different patient profile, dosage forms and number cycles of chemotherapy. Although the rate of adverse events with GC regime appears lower than with studies done on MVAC earlier [7—9], further randomized studies between MVAC and GC will substantiate the opinion that neoadjuvant GC has a more favourable toxicity profile.

There are a few limitations in our study. Although appropriate MeSH terms were used, the heterogeneity in treatments administered in terms of dosage and schedule, varying indications for NAC and patients not undergoing cystectomy following NAC affected the results. Due to lack of data, we could not assess NAC dose adjustment, growth factor support, morbidity, mortality, performance status, renal function and the presence of hydronephrosis.

5. Conclusion

As per latest guidelines, NAC is recommended for patients with MIBC. NAC is underutilized all over the world. There is substantial pathological response rate with low toxicity in patients of MIBC who receive neoadjuvant cisplatin and gemcitabine.

Author contribution

Study concept and design: Sunny Goel, Rahul J. Sinha, Ruchir Aeron, Ashish Sharma, Ved Bhaskar, Vishwajeet Singh.
Data acquisition: Sunny Goel, Rahul J. Sinha, Ruchir Aeron.
Data analysis: Sunny Goel, Ruchir Aeron, Ved Bhaskar, Ashish Sharma, Rahul J. Sinha.
Drafting of manuscript: Sunny Goel, Ruchir Aeron, Rahul J. Sinha.
Critical revision of the manuscript: Sunny Goel, Rahul J. Sinha, Vishwajeet Singh.

Conflicts of interest

The authors declare no conflict of interest.

References

[1] Stenzl A, Cowan NC, De Santis M, Kuczyk MA, Merseburger AS, Ribal MJ, et al. Treatment of muscle-invasive and metastatic bladder cancer: update of the EAU guidelines. Eur Urol 2011; 59:1009—18.
[2] Stein JP, Lieskovsky G, Cote R, Groshen S, Feng AC, Boyd S, et al. Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1,054 patients. J Clin Oncol 2001; 19:666—75.
[3] 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;349:859—66.
[4] Griffiths G, Hall R, Sylvester R, Raghavan D, Parmar MK, International collaboration of trialists, Medical Research Council Advanced Bladder Cancer Working Party, European Organization for Research and Treatment of Cancer Genito-Urinary Tract Cancer Group, et al. 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: 2171—7.
[5] 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;48:202—6.
[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;349:859.
[7] Dash A, Pettus JA, Herr HW, Bochner BH, Dalbagni G, Donat SM, et al. A role for neoadjuvant gemcitabine plus cisplatin in muscle-invasive urothelial carcinoma of the bladder: a retrospective experience. Cancer 2008;113:2471—7.
[8] Von der Maase H, Hansen SW, Roberts JT, Dogliotti L, Oliver T, Moore MJ, et al. Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study. J Clin Oncol 2000; 18:3068—77.
[9] 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;23:4602.
[10] Yuh BE, Ruel N, Wilson TG, Vogelzang N, Pal SK. Pooled analysis of clinical outcomes with neoadjuvant cisplatin and gemcitabine chemotherapy for muscle invasive bladder cancer. J Urol 2013;189:1682—6.
[11] Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analysis. [Accessed August 2011]. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp
[12] Kim SH, Seo HK, Shin HC, Chang SJ, Yun S, Joo J, et al. Trends in the use of chemotherapy before and after radical cystectomy in patients with muscle-invasive bladder cancer in Korea. J Kor Med Sci 2015;30:1150—6.
[13] van de Putte EE, Mertens LS, Meijer RP, van der Heijden MS, Bex A, van der Poel HG, et al. Neoadjuvant induction dose-dense MVAC for muscle invasive bladder cancer: efficacy and safety compared with classic MVAC and gemcitabine/cisplatin. World J Urol 2016;34:157—62.
[14] Galsky MD, Pal SK, Chowdhury S, Harshman LC, Crabb SJ, Wong YN, et al. Retrospective International Study of Cancers of the Urothelial Tract (RISC) Investigators. Comparative effectiveness of gemcitabine plus cisplatin versus methotrexate, vinblastine, doxorubicin, plus cisplatin as neoadjuvant therapy for muscle-invasive bladder cancer. Cancer 2015;121:2586—93.
[15] Gandhi NM, Baras A, Munari E, Faraj S, Reis LO, Liu JJ, et al. Gemcitabine and cisplatin neoadjuvant chemotherapy for muscle-invasive urothelial carcinoma: predicting response and assessing outcomes. Urol Oncol 2015;33:e1—7.
[16] Chau C, Whether M, Geldart T, Crabb SJ. Clinical outcomes following neoadjuvant cisplatin-based chemotherapy for bladder cancer in elderly compared with younger patients. Eur J Canc Care 2015;24:155—62.
[17] Khaled HM, Shafik HE, Zabhloul MS, Ghoneim M, Saber RA, Manie M, et al. Gemcitabine and cisplatin as neoadjuvant chemotherapy for invasive transitional and squamous cell carcinoma of the bladder: effect on survival and bladder preservation. Clin Genitourin Cancer 2014;12:e233—40.
[18] Fairey AS, Daneshmand S, Quinn D, Dorff T, Dorin R, Lieskovsky G, et al. Neoadjuvant chemotherapy with gemcitabine/cisplatin *vs.* methotrexate/vinblastine/doxorubicin/cisplatin for muscle-invasive urothelial carcinoma of the bladder: a retrospective analysis from the University of Southern California. Urol Oncol 2013;31:1737—43.
[19] Pal SK, Ruel NH, Wilson TG, Yuh BE. Retrospective analysis of clinical outcomes with neoadjuvant cisplatin-based regimens for muscle-invasive bladder cancer. Clin Genitourin Cancer 2012;10:246—50.
[20] Matsubara N, Mukai H, Naito Y, Nezu M, Itoh K. Comparison between neoadjuvant and adjuvant gemcitabine plus cisplatin chemotherapy for muscle-invasive bladder cancer. Asia Pac J Clin Oncol 2013;9:310—7.
[21] Scosyrev E, Messing EM, van Wijngaarden E, Peterson DR, Sahasrabudhe D, Golijanin D, et al. Neoadjuvant gemcitabine and cisplatin chemotherapy for locally advanced urothelial cancer of the bladder. Cancer 2012;118:72—81.
[22] Kaneko G, Kikuchi E, Matsumoto K, Obata J, Nakamura S, Miyajima A, et al. Neoadjuvant gemcitabine plus cisplatin for muscle-invasive bladder cancer. Jpn J Clin Oncol 2011;41: 908—14.
[23] Herchenhorn D, Dienstmann R, Peixoto FA, de Campos FS, Santos VO, Moreira DM, et al. Phase II trial of neoadjuvant gemcitabine and cisplatin in patients with resectable bladder caracinoma. Int Braz J Urol 2007;33:630—8.

[24] Clark PE, Spiess PE, Agarwal N, Bangs R, Boorjian SA, Buyyounouski MK, et al. NCCN guidelines insights: bladder cancer, version 2. 2016. J Natl Compr Canc Netw 2016;14:1213—24.
[25] Witjes JA, Compérat E, Cowan NC, De Santis M, Gakis G, Lebret T, et al. EAU guidelines on muscle-invasive and metastatic bladder cancer: summary of the 2013 guidelines. Eur Urol 2014;65:778—92.
[26] Gore JL, Litwin MS, Lai J, Yano EM, Madison R, Setodji C, et al. Use of radical cystectomy for patients with invasive bladder cancer. J Natl Cancer Inst 2010;102:802—11.
[27] Zaid HB, Patel SG, Stimson CJ, Resnick MJ, Cookson MS, Barocas DA, et al. Trends in the utilization of neoadjuvant chemotherapy in muscle-invasive bladder cancer: results from the National Cancer Database. Urology 2014;83:75—80.
[28] Millikan R, Dinney C, Swanson D, Sweeney P, Ro JY, Smith TL, et al. Integrated therapy for locally advanced bladder cancer: final report of a randomized trial of cystectomy plus adjuvant M-VAC versus cystectomy with both preoperative and postoperative M-VAC. J Clin Oncol 2001;19:4005—13.
[29] Milowsky MI, Stadler WM, Bajorin DF. Integration of neoadjuvant and adjuvant chemotherapy and cystectomy in the treatment of muscle-invasive bladder cancer. BJU Int 2008;102:1339—44.
[30] Johnson DC, Nielsen ME, Matthews J, Woods ME, Wallen EM, Pruthi RS, et al. Neoadjuvant chemotherapy for bladder cancer does not increase risk of perioperative morbidity. BJU Int 2014;114:221—8.
[31] Choueiri TK, Jacobus S, Bellmunt J, Qu A, Appleman LJ, Tretter C, et al. Neoadjuvant dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin with pegfilgrastim support in muscle-invasive urothelial cancer: pathologic, radiologic, and biomarker correlates. J Clin Oncol 2014;32:1889—94.
[32] Plimack ER, Hoffman-Censits JH, Viterbo R, Trabulsi EJ, Ross EA, Greenberg RE, et al. Accelerated methotrexate, vinblastine, doxorubicin, and cisplatin is safe, effective, and efficient neoadjuvant treatment for muscle-invasive bladder cancer: results of a multicenter phase II study with molecular correlates of response and toxicity. J Clin Oncol 2014;32:1895—901.
[33] Yeshchina O, Badalato GM, Wosnitzer MS, Hruby G, RoyChoudhury A, Benson MC, et al. Relative efficacy of perioperative gemcitabine and cisplatin versus methotrexate, vinblastine, adriamycin, and cisplatin in the management of locally advanced urothelial carcinoma of the bladder. Urology 2012;79:384—90.
[34] Matsui Y, Nishiyama H, Watanabe J, Teramukai S, Ono Y, Ohshima S, et al. The current status of perioperative chemotherapy for invasive bladder cancer: a multi institutional retrospective study in Japan. Int J Clin Oncol 2005;10:133—8.
[35] Splinter TA, Scher HI, Denis L, Bukowski R, Simon S, Klimberg I, et al. The prognostic value of the pathological response to combination chemotherapy before cystectomy in patients with invasive bladder cancer. European Organization for Research on Treatment of Cancer—Genitourinary Group. J Urol 1992;147:606—8.
[36] Rosenblatt R, Sherif A, Rintala E, Wahlqvist R, Ullén A, Nilsson S, et al. Pathologic downstaging is a surrogate marker for efficacy and increased survival following neoadjuvant chemotherapy and radical cystectomy for muscle invasive urothelial bladder cancer. Eur Urol 2012;61:1229—38.