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Systematic Review

Systematic Review and Meta-Analysis of Cisplatin Based Neoadjuvant Chemotherapy in Muscle Invasive Bladder Cancer

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Abstract.
BACKGROUND: Cisplatin-based neoadjuvant chemotherapy is the standard of care for muscle invasive bladder cancer (MIBC).
OBJECTIVE: To compare the efficacy and safety of the two most commonly used cisplatin-based regimens; gemcitabine, and cisplatin (GC) vs. accelerated (dose-dense: dd) or conventional methotrexate, vinblastine, adriamycin, and cisplatin (MVAC).
METHODS: We searched MEDLINE, Embase, Scopus and other sources. Outcomes of interest included overall survival, downstaging to pT $\leq$ 1, pathologic complete response (pCR), recurrence, and toxicity. Meta-analysis was conducted using the random-effects model.
RESULTS: We identified 24 studies. Efficacy outcomes were comparable between MVAC and GC for MIBC. dd-MVAC was associated with favorable efficacy compared to GC in terms of downstaging (OR 1.45; 95% CI 1.15–1.82) and all-cause mortality at longest follow-up (OR 0.63; 95% CI 0.44–0.81). However, GC was associated with a better safety profile in terms of febrile neutropenia (OR 0.32; 95% CI 0.13–0.80), anemia (OR 0.32; 95% CI 0.18–0.54), nausea and vomiting (OR 0.27; 95% CI 0.12–0.65) compared to dd-MVAC. Compared to MVAC, patients receiving GC had an increased risk of developing grade 3–4 thrombocytopenia (OR 4.70; 95% CI 1.59–13.89) and a lower risk of nausea and vomiting (OR 0.05; 95% CI 0.01–0.31). Certainty in the estimates was very low for most outcomes.
CONCLUSIONS: Efficacy and safety outcomes were comparable between MVAC and GC for MIBC. Including non-peer-reviewed studies showed higher efficacy with dd-MVAC. A phase III randomized trial comparing the two regimens is needed to guide clinical practice.

Keywords: Bladder cancer, cisplatin

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INTRODUCTION

Bladder cancer remains the a common cancer worldwide with at least half a million new cases annually [1]. While 75% of patients have a non-muscle invasive disease at diagnosis, the rest will present with muscle invasive or advanced disease [2]. Following initial endoscopic removal of bladder tumors, further treatment is often required for muscle-invasive bladder cancer (MIBC) [3], which includes cystectomy (partial or radical), neoadjuvant or adjuvant therapy.

Cisplatin-based neoadjuvant chemotherapy (NAC) has been shown to provide a 5-year disease-free survival (DFS) benefit of close to 10% in patients with MIBC who underwent cystectomy [4–10]. Therefore, it has become a category 1 recommendation for MIBC in patients who are cisplatin-eligible and have operable disease, but there is lack of consensus with regard to the optimal cisplatin regimen [11–13]. Conventional methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) was among the first developed NAC regimens for MIBC with a pathologic complete response (pCR) rate of 38% [7].

Accelerated (or dose-dense: dd) MVAC with pegfilgrastim support was later developed to shorten time to surgery and was shown to be safe and effective [4, 14]. In the metastatic setting, the "newer regimen" gemcitabine and cisplatin (GC) was shown to be effective yet less toxic as compared to MVAC [15–17]. Similar to reasons behind developing dd MVAC, dd GC has been tested as NAC in MIBC and showed comparable pCR rates [6, 18]. Of note, grade 3/4 vascular events occurred in 9% of the first dd GC study [6] and precluded, delayed, or increased the risk of surgery for 23% of patients in the other dd GC study resulting in its early closure [18]. In light of a recent reported clinical trial comparing the dd-MVAC and conventional GC NAC regimens [19], we performed a systematic review and meta-analysis to compare GC with MVAC (including dd-MVAC) in the neoadjuvant setting.

MATERIALS AND METHODS

The reporting of this systematic review follows the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) statement [20]. As a systematic review of the literature, and as no animal or human research was involved, our study is exempt from any requirement for Institutional Review Board approval.

Eligibility criteria

We only included studies that (1) assessed patients with MIBC, (2) directly compared GC with MVAC (including dd MVAC) as neoadjuvant chemotherapy, and (3) reported at least one of the following outcomes: overall and relapse-free survival, pathologic response, and toxicity. We excluded noncomparative studies, studies without original data, mixed population, intervention or comparison not of interest or those that did not provide sufficient data for meta-analysis. Prior systematic reviews were used for cross-referencing. Abstracts without a full text article were included if they met the inclusion criteria.

Data sources and search strategies

A comprehensive search of several databases from inception to March 2, 2020, limited to English language and excluding animal studies, was conducted. The databases included Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily, Ovid Embase, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, and Scopus. The search strategy was designed and conducted by a medical reference librarian with input from the study investigators. Controlled vocabulary supplemented with keywords was used to search for studies of interest. The actual strategy listing all search terms used and how they are combined is available in the appendix (Table s1).

Study selection

Three independent reviewers (RB, TN, SP) screened all the titles and abstracts based on the chosen inclusion and exclusion criteria. Relevant references were retrieved in full text and were further evaluated against the eligibility criteria. Disagreements were resolved by consensus.

Data extraction

Three reviewers (RB, TN, SP) independently extracted data using standardized, pilot-tested forms created in Microsoft Excel. Disagreements were resolved by discussion between the reviewers. We extracted the following variables from each study:

study characteristics, participants' characteristics, intervention details, and outcomes of interest (total sample size and number of events in each group).

Outcomes

Outcomes of interest included overall survival (OS) at 1 year, 2 years, and at the longest follow-up, recurrence, pathologic complete response (pCR), downstaging, and toxicities (neutropenia, febrile neutropenia, anemia, thrombocytopenia, cardiac, nausea/vomiting and mucositis). OS was calculated from therapy start date till death. Patients with no confirmed death date were censored at last contact date. pCR was defined as pT0pN0 or pTispN0 in pathologic assessment. Downstaging was defined as pT $\leq$ 1pN0 in cystectomy pathologic assessment.

Methodologic quality and risk of bias

We used the Newcastle-Ottawa scale [21] to assess risk of bias, in non-randomized studies focusing on cohort selection, outcome ascertainment, controlling for age and sex, and adequacy of follow-up. Cochrane risk-of-bias tool was used to evaluate randomized trials by examining: generation of allocation, concealment of allocation, blinding of participants, caregivers, data collectors, and outcome assessors, incomplete outcome data, selective outcome reporting and any other potential source of bias. Based on these factors, the risk of bias for each study was low, moderate, or high. Three reviewers (RB, TN, SP) independently assessed the risk of bias. Any conflicts were resolved by consensus.

Statistical analysis

For overall survival at 1, 2 years and at the longest follow-up, pCR, downstaging, treatment-related death and toxicity outcomes, we calculated or extracted odds ratio (OR). For overall survival, we also calculated or extracted hazard ratio (HR). The DerSimonian and Laird random effects methods [22] were used to pool outcomes across studies. We conducted the analysis accounting for the intention-to-treat (ITT) principle. We conducted subgroup analyses to explore heterogeneity between studies based on whether the publication is peer-reviewed (i.e., journal article vs conference abstract). Heterogeneity across the included studies was estimated using I^2 statistic, in which $\geq$ 50% suggests substantial heterogeneity. Publication bias was assessed using funnel plots and Egger's test [23]. When Egger's test yielded a statistically significant result, we used Duval & Tweedie's trim-and-fill procedure to adjust for funnel plot asymmetry. The trim-and-fill procedure estimates the effect size of missing small studies and adds them into the funnel plot until symmetry is reached [24]. Statistical analyses were completed using R version 3.6.3 (R Core Team, 2020).

Grading the Certainty of Evidence

We applied the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach to rate the certainty of evidence (CoE). High initial certainty is assigned to the evidence resulting from randomized controlled trials, while evidence from observational studies and nonrandomized clinical trials start at low initial certainty. Then CoE is rated down on outcome bases for risk of bias, inconsistency (i.e., heterogeneity), indirectness, imprecision or publication bias [25].

RESULTS

Study characteristics

A total of 620 titles and abstracts were identified by screening the references retrieved from the electronic search strategy, of which 96 full-text articles were screened for eligibility. Twenty-four studies [19, 26–48] reporting on 3,591 patients were included in the qualitative synthesis (Fig. 1). Of which, 7 were international conference abstracts [19, 34–37, 44, 46] including a phase 3 randomized-controlled clinical trial recently presented by Culine et al. [19] at the annual American Society of Clinical Oncology Genitourinary Symposium 2020, San Francisco, CA.

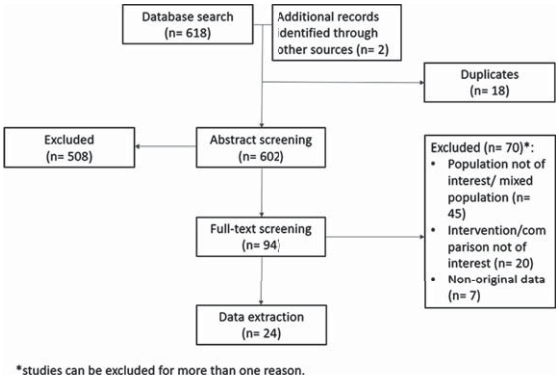

Fig. 1. Flowchart demonstrating the process of study selection.

Table 1
Baseline characteristics of included patients; * median

Author last name, year (country)	Number of patients			Age (mean ± SD, years)			Males *n* (%)			Clinical staging *n* (%)		
	MVAC	GC	dd-MVAC	MVAC	GC	dd-MVAC	MVAC	GC	dd-MVAC	MVAC	GC	dd-MVAC
Conference abstracts												
Mitra, 2011 (USA)	NR	23	15	NR	NR	NR	NR	NR	NR	NR	T2-4 23(100)	T2-4 15(100)
Wright, 2013 (USA)	32	46	NR	NR	NR	NR	NR	NR	NR	T2-4 32(100)	T2-4 46 (100)	NR
Yokomizo, 2013 (Japan)	55	46	NR	NR	NR	NR	NR	NR	NR	T2- T4 55(100)	T2- T4 46(100)	NR
Matulay, 2019 (USA)	NR	88	265	NR	NR	NR	NR	NR	NR	NR	NR	NR
Lee, 2019 (South Korea)	NR	176	41	NR	NR	NR	NR	NR	NR	NR	T2-4 176(100)	T2-4 41(100)
Miron, 2019 (USA)	NR	24	34	NR	NR	NR	NR	NR	NR	NR	T2-4 24(100)	T2-4 34(100)
Culine, 2020 (France)	NR	245	248	NR	63*	63*	NR	206(84)	201(81)	NR	T2 210(85.7) >T2 34(13.9)	T2 200(80.6) >T2 47(19)
Peer-review journal articles												
Dash, 2008 (USA)	54	42	NR	63*	64*	NR	43(79.6)	32(76.2)	NR	T2 32(59.3) T3 15(27.7) T3 7(13)	T2 19(45.2) T3 19(45.2) T4 4 (9.6)	NR
Weight, 2009 (USA)	4	20	NR	NR	NR	NR	NR	NR	NR	T2-4 4(100)	T2-4 20(100)	NR
Kaneko, 2011 (Japan)	9	22	NR	62	69	NR	8(88.9)	16(72.7)	NR	T1 1(11.1) T2 4(44.4) T3 1(11.1) T4 3(33.3)	T2 15(68.2) T3 6(27.3) T4 1(4.5)	NR
Alva, 2011 (USA)	12	20	NR	NR	NR	NR	NR	NR	NR	T2 -4 12(100)	T2-4 20(100)	NR
Pal, 2012 (USA)	22	24	NR	60*	68.6*	NR	20(90.9)	19(79.2)	NR	T2 18(81.8) T3 1(4.5) T4 2(9.1)	T2 22(91.7) T3 2(8.3) T4 0(0)	NR
Yeshchina, 2012 (USA)	45	16	NR	NR	NR	NR	NR	NR	NR	T2-T4a 45(100)	T2-T4a 16(100)	NR
Shindo, 2012 (Japan)	17	10	NR	64*	61.5*	NR	16(94)	8(80)	NR	T2-4 17 (100)	T2-4 10 (100)	NR
Fairey, 2013 (USA)	58	58	NR	63	67	NR	45(77.6)	44(75.9)	NR	T2 28(48.3) T3 14(24.1) T4 16(27.6)	T2 28(48.3) T3 18(31) T4 12(20.7)	NR
Lee, 2013 (USA)	31	41	NR	NR	NR	NR	28(90.3)	31(75.6)	NR	T2 14(45.2) T3 9(29) T4 8(25.8)	T2 23(56.1) T3 11(26.8) T4 7(17.1)	NR
Kawamura, 2013 (Japan)	44	14	NR	64 ± 10.25	68 ± 8.75	NR	37(84.1)	10 (71.4)	NR	T2a/b 11 (25) T3a 6 (13.6) T3b 21 (47.7) T4a 5 (11.4), T4b 1 (2.3)	T2a/b 6 (42.9) T3a 0 (0), T3b 7 (50) T4a 0 (0), T4b 1 (7.1)	NR

Table 1
(*Continued*)

Zargar, 2015 (International)	183	602	NR	62 ± 8.9	65 ± 10.4	NR	145(79.2)	472(78.4)	NR	T2-4 183(100)	T2-4 602(100)	NR
Van De Putte, 2015 (Netherlands)	35	51	80	59 ± 9	63 ± 8	57 ± 8	26(74.3)	36(70.6)	60(75)	T2 15(42.9) T3 6(17.1) T4 14(40)	T2 11(21.6) T3 25(49) T4 15(29.4)	T2 25(31.3) T3 30(37.4) T4 25(31.3)
Galsky, 2015 (International)	66	146	NR	63*	63*	NR	NR	NR	NR	T2 41(62.1) T3 17(25.8) T4 8(12.1)	T2 90(61.6) T3 40(27.4) T4 16(11)	NR
Fukui, 2016 (Japan)	21	37	NR	NR	NR	NR	NR	NR	NR	T2-4 21(100)	T2-4 37	NR
Zargar, 2018 (International)	NR	219	100	NR	67 ± 10.4	61 ± 7.4	NR	171(78.1)	74(74)	NR	T2-4 219(100)	T2-4 100(100)
Nguyen, 2018 (France)	23	4	NR	62*	70*	NR	20(87)	3(75)	NR	T1 2(8.7) T2 20(87) T3 1(4.3) T4 0(0)	T2 3(75) T3 1(25)	NR
Okabe, 2018 (Japan)	74	58	NR	59.4 ± 9	68 ± 8.6	NR	65(87.8)	51(87.9)	NR	T2 24(32.4) T3 36(48.6) T4 14(19)	T2 22(37.9) T3 29(50) T4 7(12.1)	NR

Eighteen studies [26–33, 38–47] evaluated GC versus MVAC. One study [42] was found to have three arms comparing GC versus MVAC versus dd-MVAC. The rest [19, 34–37, 42, 48] were comparing GC versus dd-MVAC. All of the included peer-reviewed studies [26–33, 38–43, 45, 47, 48] had a retrospective cohort design. We were not able to assess risk of bias for the international conference abstracts due to the unavailability of the required information. Baseline characteristics and quality of all included studies are fully detailed in Table 1 and Tables s2-s3 in the appendix.

Results of all performed analyses are summarized in Table 2. Forest plots of the remaining outcomes including subgroup analyses can be found in Figures s1-22 in the appendix. Tables s4-s5 in the appendix contain details of CoE of all reported outcomes.

Findings

GC vs MVAC

Overall Survival. Six retrospective peer reviewed studies [26, 28, 30, 32, 39, 40] compared overall survival at different time points between GC and MVAC. The analysis showed that neither of the two regimens was significantly associated with reduction in mortality at one year, at two years and at the longest follow up. The CoE was very low due to study design and severe imprecision.

Pathological complete response (pCR). Fifteen retrospective cohort studies [27, 28, 30–33, 39–47] compared pCR between GC and MVAC. The analysis showed no significant difference in achieving pCR between the two groups. The analysis was consistent when comparing the results of the thirteen peer-[27, 28, 30–33, 39–43, 45, 47] and two non-peer reviewed studies [44, 46] (Fig. 2).

We assessed the publication bias using funnel plot and Egger's test. The funnel plot (Figure s23) showed asymmetry suggesting the presence of publication bias which was confirmed when Egger's test yielded a statistically significant result (p-value < 0.02). We ran Duval & Tweedie's trim-and-fill procedure to estimate the effect size of the missing small studies. The trim-and-fill procedure added 6 studies to the funnel plot (Figure s24) to achieve symmetry and the overall effect size became less prominent with the same statistical insignificance OR (1.03; 95% CI 0.79–1.36; very low CoE due to study design, methodological limitations, imprecision and publication bias).

Downstaging. Thirteen retrospective cohort studies [27, 28, 31–33, 38–42, 45–47) compared downstaging between GC and MVAC. The analysis showed no significant difference between the two groups. The analysis was consistent when comparing the results of the twelve peer-[27, 28, 31–33, 38–42, 45, 47] and one non-peer reviewed studies [46] (Fig. 3).

We assessed the publication bias using funnel plot and Egger's test. The funnel plot (Figure s25) was symmetric excluding the presence of publication bias which was confirmed when Egger's test yielded a statistically insignificant result (p-value > 0.05).

The CoE was very low due to study design, methodological limitations and imprecision.

Recurrence probability. Three retrospective peer reviewed studies [27, 28, 39] compared the probability of recurrence at different timepoints between GC and MVAC. The analysis did not show any significant difference between the two groups at one year, at two-year intervals as well as at the longest follow-up. The CoE was very low due to study design, methodological limitations and severe imprecision.

Grade 3–4 toxicity analysis. Grade 3–4 neutropenia, febrile neutropenia, anemia, thrombocytopenia, nausea/vomiting, mucositis, and cardiac toxicity were assessed in six retrospective peer reviewed studies [19, 31, 32, 39, 41, 42].

The analysis showed that receiving GC significantly increased the risk of developing grade 3–4 thrombocytopenia (OR 4.70; 95% CI 1.59–13.89) but decreased the risk of nausea and vomiting (OR 0.05; 95% 0.01–0.31) when compared to MVAC. There was no statistical difference between the two regimens in developing mucositis, neutropenia, febrile neutropenia and anemia. The CoE is very low due to study design, methodological limitations and imprecision.

GC vs dd-MVAC

Overall Survival. Four retrospective cohort studies [34–36, 48] compared overall survival between GC and dd-MVAC at the longest follow-up. Compared with GC, dd-MVAC was associated with reduction in mortality (OR 0.63; 95% CI 0.44–0.81). The analysis was consistent when comparing the results of the one peer-[48] and the three non-peer reviewed studies [34–36] (Fig. 4).The CoE was very low due to study design and methodological limitations.

Pathological complete response (pCR). Six studies [19, 34, 35, 37, 42, 48] compared pCR between GC and dd-MVAC. The analysis showed no significant difference between the two regimens. The analysis was consistent when comparing the results of the two

Table 2
Results of analyses on all studied outcomes

Outcome	subgroup	Comparison	Number of studies	Number of patients	Effect measure (95% Cl)	Heterogeneity (P; I^2(%))
All- cause mortality	At 1 year	GC vs MVAC	3 (28, 39, 40)	140 vs 154	OR 0.84 (0.43–1.67)	0.25; 28
	At 2 years	GC vs MVAC	3 (28, 39, 40)	140 vs 154	OR 0.80 (0.50–1.30)	0.57; 0
	Longest follow up	GC vs MVAC	6(26, 28, 30, 32, 39, 40)	320 vs 276	OR 0.67 (0.35–1.32)	0.02; 63
		GC vs dd-MVAC	4(34–36, 48)	507 vs 440	OR 1.68 (1.23–2.28)	0.53; 0
	Overall survival	GC vs MVAC	5(26, 28, 38, 45, 47)	700 vs 321	HR 0.97 (0.43–2.19)	0.87; 0
Recurrence	At 1 year	GC vs MVAC	3(27, 28, 39)	158 vs 186	OR 1.13 (0.62–2.03)	0.30; 16
	At 2 years		3(27, 28, 39)	158 vs 186	OR 0.92 (0.57–1.46)	0.41; 0
	Longest follow up		3(27, 28, 39)	158 vs 186	OR 0.75 (0.32–1.74)	0.09; 58
pCR		GC vs MVAC	15(27, 28, 30–33, 39–47)	1196 vs 729	OR 1.20 (0.95–1.51)	0.58; 0
		GC vs dd-MVAC	6(19, 34, 35, 37, 42, 48)	802 vs 749	OR 0.81 (0.59–1.12)	0.19; 33
Downstaging		GC vs MVAC	13(27, 28, 31–33, 38–42, 45–47)	988 vs 650	OR 1.24 (0.90–1.71)	0.12; 32
		GC vs dd-MVAC	6(19, 34, 35, 37, 42, 48)	803 vs 749	OR 0.69 (0.55–0.87)	0.87; 0
Febrile Neutropenia		GC vs MVAC	4(31, 32, 41, 42)	97 vs 105	OR 0.35 (0.07–1.75)	0.29; 21
		GC vs dd-MVAC	2(19, 42)	296 vs 328	OR 0.32 (0.13–0.80)	0.44; 0
Neutropenia		GC vs MVAC	3(31, 32, 41)	46 vs 70	OR 1.31 (0.43–3.98)	0.28; 21
		GC vs dd-MVAC	1(19)	245 vs 248	OR 1.33 (0.93–1.91)	–
Anemia		GC vs MVAC	4(31, 32, 41, 42)	97 vs 105	OR 0.81 (0.20–3.22)	0.39; 1
		GC vs dd-MVAC	2(19, 42)	296 vs 328	OR 0.32 (0.18–0.54)	0.46; 0
Thrombocytopenia		GC vs MVAC	4(31, 32, 41, 42)	97 vs 105	OR 4.70 (1.59–13.89)	0.66; 0
		GC vs dd-MVAC	2(19, 42)	296 vs 328	OR 0.80 (0.51–1.26)	0.53; 0
Cardiac Toxicity		GC vs dd-MVAC	1(19)	245 vs 248	OR 1.08 (0.53–2.19)	–
Nausea/Vomiting		GC vs MVAC	2(31, 32)	36 vs 53	OR 0.05 (0.01–0.31)	0.28; 13
		GC vs dd-MVAC	1(19)	245 vs 248	OR 0.27 (0.12–0.65)	–
Mucositis		GC vs MVAC	2(31, 32)	36 vs 53	OR 0.24 (0.02–2.50)	0.71; 0

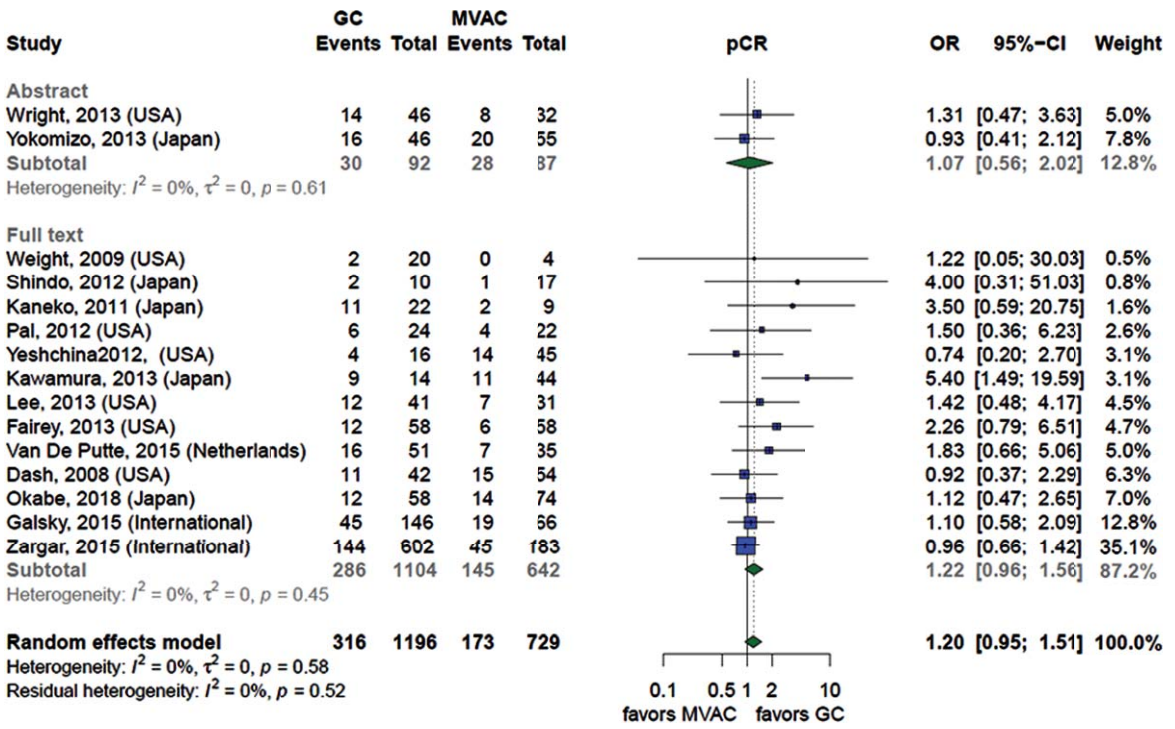

Fig. 2. Forest plot comparing the rates of achieving pathological complete response between patients receiving GC and MVAC stratified by the type of publication.

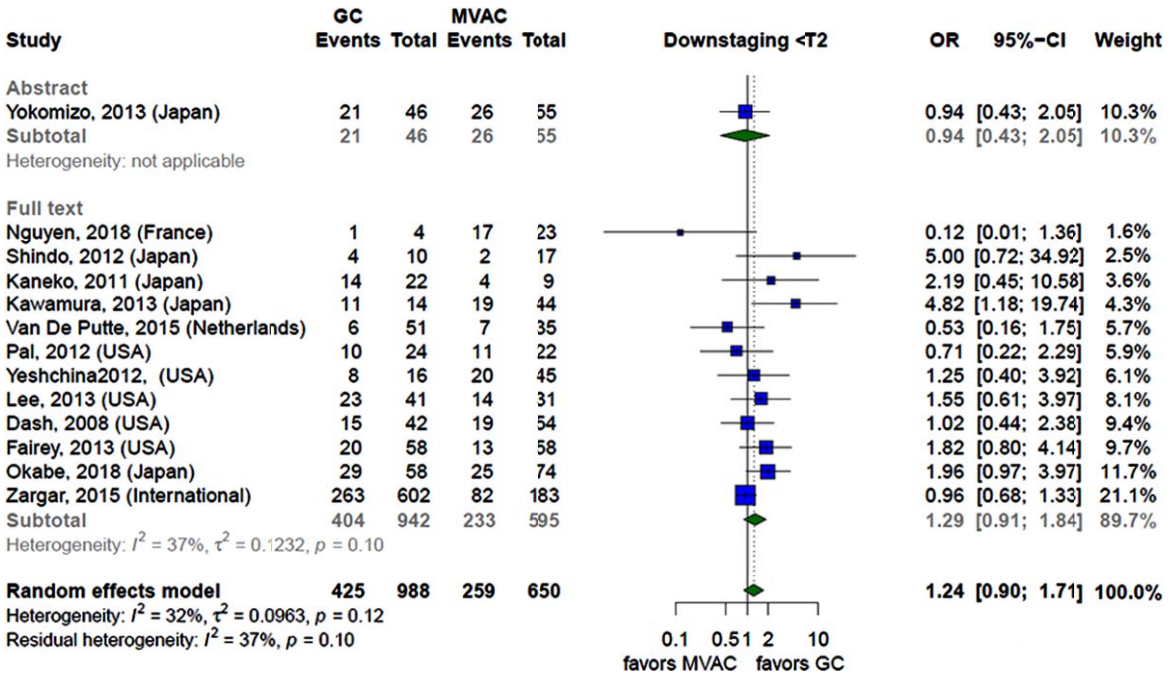

Fig. 3. Forest plot comparing the rates of achieving a pT $\leq$ 1 stage of between patients receiving GC and MVAC stratified by the type of publication.

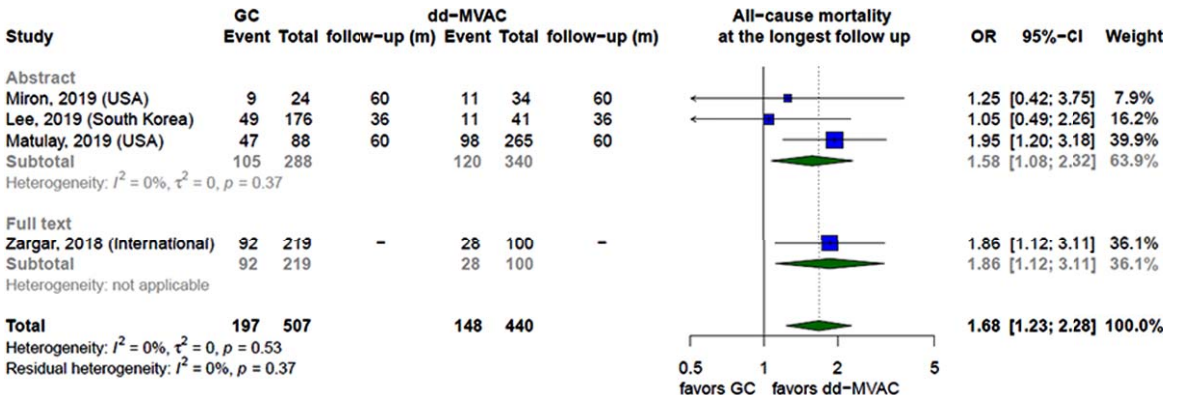

Fig. 4. Forest plot comparing all-cause mortality rates at the longest follow up between patients receiving GC and dd-MVAC stratified by the type of publication.

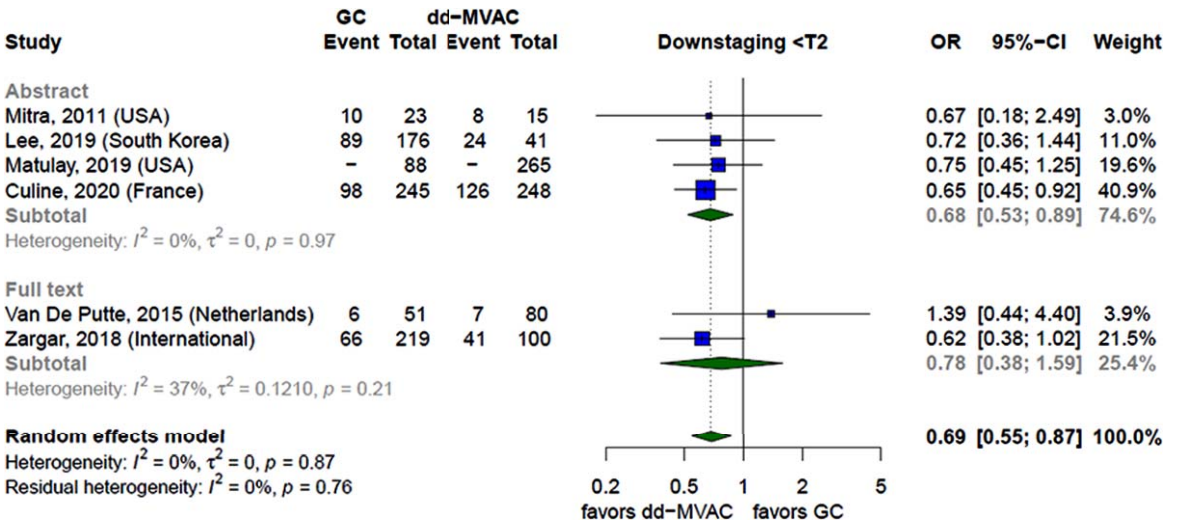

Fig. 5. Forest plot comparing the rates of achieving a pT≤1 stage between patients receiving GC and dd-MVAC stratified by the type of publication.

peer-[42, 48] and the four non-peer reviewed studies [19, 34, 35, 37]. Of the included studies, only one RCT [19] was found to report the outcome of interest, the results of which were consistent with those of the remaining five retrospective cohort studies [34, 35, 37, 42, 48]. The CoE was very low due to study design, methodological limitations and imprecision.

Downstaging. Six studies [19, 34, 35, 37, 42, 48] compared downstaging between GC and dd-MVAC. The analysis favored dd-MVAC over GC for this outcome (OR 0.69; 95% CI 0.55–0.87; very low CoE due to study design and methodological limitations) (Fig. 5). The analysis showed different results when assessing the outcome based on the type of publication. Four of the included studies [19, 34, 35, 37] were non-peer reviewed and reported consistent findings, also favoring dd-MVAC over GC (OR 0.68; 95% CI 0.53–0.89). The analysis of the remaining two peer reviewed studies [42, 48] showed no significant difference between the two regimens. The results were significant and consistent when assessing the outcome based on study design. Only one RCT [19] was found to report on downstaging and favored dd-MVAC over GC (OR 0.65; 95% CI 0.45–0.92; moderate CoE due to methodological limitations). The remaining five retrospective cohort studies [34, 35, 37, 42, 48] yielded similar results, also favoring dd- MVAC (OR 0.72; 95% CI 0.54–0.97; very low CoE due to study design and methodological limitations).

Grade 3–4 toxicity analysis. Overall, two studies [19, 42] evaluated the risk of developing grade 3–4

toxicities between GC and dd-MVAC. The analysis showed that receiving GC significantly reduced the risk of developing febrile neutropenia (OR 0.32; 95% CI 0.13–0.80), anemia (OR 0.32; 95% CI 0.18–0.54) and nausea and vomiting (OR 0.27; 95% CI 0.12–0.65) compared to dd-MVAC. CoE was low due to methodological limitations and imprecision. Even after the addition of prophylactic Granulocyte Colony-Stimulating Factor (G-CSF) to dd-MVAC, the incidence of febrile neutropenia remained significantly lower in the group of patients who received GC ($p = 0.004$) [34]. No regimen demonstrated a favorable safety profile over the other in terms of developing neutropenia, thrombocytopenia or cardiac toxicity. CoE was very low due to methodological limitations and severe imprecision. Of the included studies, one non-peer reviewed RCT [19] reported significant and consistent results favoring GC over dd-MVAC in terms of developing febrile neutropenia (OR 0.36; 95% CI 0.14–0.80), anemia (OR 0.30; 95% CI 0.17–0.54) and nausea and vomiting (OR 0.27; 95% CI 0.12–0.65). Neither of the two regimens demonstrated a favorable safety profile over the other in terms of developing neutropenia, thrombocytopenia or cardiac toxicity. The other one was a peer reviewed retrospective cohort study [42], the results of which were insignificant and inconsistent with the results of the included RCT [19].

DISCUSSION

In this systematic review and meta-analysis of patients with MIBC treated with the two most common cisplatin-based neoadjuvant chemotherapies, we demonstrate that MVAC and GC may have comparable efficacy and safety outcomes. Non-peer-reviewed studies showed higher downstaging rates with dd-MVAC at the expense of febrile neutropenia, anemia, nausea and vomiting. Higher downstaging rates have been linked to survival advantage [8], and this is consistent with our findings that showed favorable survival outcomes with dd-MVAC when we analyzed non-peer-reviewed studies.

Our study included 24 studies that met the eligibility criteria with a total patient population of 3591. In 2016, Yin et al. [49] assessed a total of 1,766 patients from 13 retrospective studies and found no significant difference in pCR between MVAC and GC. On the other hand, a later meta-analysis done by Yu et al. [50], which included 2174 patients from 13 retrospective studies found that pCR rates were higher among patients receiving GC as compared to those receiving MVAC. Our review included a higher number of studies and patients; however, we did not find a significant difference between MVAC and GC in terms of pCR. Additionally, our review shed light on studies comparing dd-MVAC to GC which has not been published previously.

Our study faces several limitations, the most important of which is the lack of randomized comparisons. Therefore, the results are subject to confounding and selection bias. Some studies were not peer reviewed and were only available as abstracts, with minimal details about risk of bias. In addition, the included studies had some differences in their chemotherapy protocols (dd-MVAC vs conventional MVAC), patient selection and follow up time. Moreover, evidence on the addition of G-CSF was lacking. Lee et al. [34] was the only study that addressed this question. And finally, the CoE of most of the outcomes was very low, hence caution is advised when interpreting the results.

The phase III CETUG/AFU V05 VESPER trial (NCT01812369) compares dd-MVAC to GC with the primary outcome of progression-free survival (PFS) at 3 years, and the secondary outcomes of pCR and safety. Preliminary results from this trial showed higher pCR and downstaging rates in the dd-MVAC arm, which was at the expense of higher gastrointestinal grade ≥ 3 toxicities in this arm. PFS data was not mature at this interim analysis. Findings from our study agree with the preliminary results from this trial; however, our findings remain based on retrospective data. Therefore, awaiting the final analysis of NCT01812369 is essential to help guide clinical practice.

CONCLUSION

The available literature comparing MVAC and GC neoadjuvant therapy is retrospective in nature. Efficacy and safety outcomes may be comparable between the two regimens for MIBC. Analysis of non-peer-reviewed studies suggested higher efficacy with dd-MVAC but increased toxicity. A Large randomized trial comparing dd-MVAC to GC is ongoing and will help provide more definitive evidence to guide clinical practice. Future research should explore post NAC cystectomy completion rates and the possible association between the different components of NAC (number of completed chemotherapy

cycles, dosages, co-administered medications, etc.) and the outcomes of interest.

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AUTHOR CONTRIBUTIONS

Raed Benkhadra, MD: conception; performance of work; interpretation of data; writing the article.

Tarek Nayfeh, MD: conception; performance of work; interpretation of data; writing the article.

Sai Krishna Patibandla, MD: conception; performance of work; interpretation of data; writing the article.

Chelsea Peterson, DO: conception; performance of work; interpretation of data; writing the article

Larry Prokop, MLS: conception; performance of work; interpretation of data; writing the article

Omar Alhalabi, MD: conception; performance of work; interpretation of data; writing the article

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Shifeng S Mao, MD, PhD: conception; performance of work; interpretation of data; writing the article

ETHICAL CONSIDERATIONS

As a systematic review of the literature, and as no animal or human research was involved, our study is exempt from any requirement for Institutional Review Board approval.

CONFLICT OF INTEREST

Raed Benkhadra, Tarek Nayfeh, Sai Krishna Patibandla, Chelsea Peterson, Larry Prokop, Omar Alhalabi, M. Hassan Murad and Shifeng S. Mao declare that they have no conflict of interest.

SUPPLEMENTARY MATERIAL

The supplementary files are available from https://dx.doi.org/10.3233/BLC-201511.

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