World Journal of Urology (2023) 41:1551–1562
https://doi.org/10.1007/s00345-023-04408-w

ORIGINAL ARTICLE

Real-world outcomes of first-line chemotherapy for unresectable stage III and IV bladder cancer

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Received: 9 December 2022 / Accepted: 16 April 2023 / Published online: 5 May 2023

Abstract

Purpose For many malignancies, considerable divergence between the efficacy found in clinical trials and effectiveness in routine practice have been reported (efficacy–effectiveness gap). The purpose of this study was to evaluate the efficacy–effectiveness gap in palliative first-line (1L) chemotherapy treatment (CTx) for urothelial carcinoma of the bladder.

Methods From seven Dutch teaching hospitals, all patients diagnosed with unresectable stage III (cT2-4aN1-3M0) and IV (cT4b and/or cM1) disease, who received 1L-CTx (for both primary as recurrent disease after radical cystectomy) between 2008 and 2016, were captured. Results were compared with data from seven randomised trials that investigated 1L gemcitabine + cisplatin (GemCis) and/or gemcitabine + carboplatin (GemCarbo).

Results Of the 835 included patients, 191 received 1L-CTx. Median overall survival (mOS) of GemCis patients ($N = 88$) was 10.4 months [95% CI 7.9–13.0], which was shorter compared to clinical trial findings (range mOS: 12.7–14.3 months) despite comparable clinical characteristics. The mOS of GemCarbo patients ($N = 92$) was 9.3 months [95% CI 7.5–11.1]. Patients who received GemCarbo had worse prognostic characteristics (higher age, impaired renal function and worse performance status (all P-values < 0.001)) compared to GemCis patients, but were equal in occurrence of dose reductions (24.4% vs. 29.5%, P-value = 0.453), early termination (55.7% vs. 54.1%, P-value = 0.839), clinical best response (P-value = 0.733), and toxicity (68.1% vs. 63.3%, P-value = 0.743). In multivariable regression, GemCis was not superior to GemCarbo (HR 0.90 [95% CI 0.55–1.47], P-value = 0.674).

Conclusion There seems to be an efficacy–effectiveness gap in 1L GemCis treatment, despite patients having similar baseline characteristics. Early termination of treatment occurred more often and dose reduction less often compared to clinical trials, hinting towards abandonment of treatment in case of adverse events. Patients treated with 1L GemCis did not have superior survival compared to GemCarbo patients, even though GemCarbo patients had worse baseline characteristics.

Keywords Bladder cancer · Efficacy · Effectiveness gap · Metastatic · First-line chemotherapy · Real-world outcomes

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Introduction

Before chemotherapy treatment (CTx) was used, patients with metastatic bladder cancer (mBC) had a median overall survival (mOS) of only 3–6 months [1]. Now, standard of care first-line (1L) treatment for mBC is cisplatin-based combination chemotherapy, with the two most frequently used regimens being gemcitabine + cisplatin (GemCis) and methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) [2–4]. The mOS of GemCis is estimated to be 12.7–14.0 months [3–8]. Subsequently, maintenance with avelumab is standard of care for all patients with disease stabilisation on 1L platinum-based chemotherapy.

The major disadvantage of all cisplatin-based chemotherapy regimens is its cumulative renal toxicity. Although the preferred 1L treatment, approximately 28–59% of patients are considered cisplatin-ineligible due to poor performance status (PS), comorbidities, and renal impairment [6, 9–12]. For patients who are unfit for cisplatin, carboplatin can be considered as an alternative [6, 7]. Studied in clinical trial settings, the mOS after treatment with gemcitabine + carboplatin (GemCarbo) is between 9.3 and 9.8 months [5–7], and thus considered less effective [2].

There is potential disconnection between oncological outcomes of an intervention in clinical trial setting and the 'real-world', a phenomenon called the efficacy–effectiveness gap (EEG) [12]. Efficacy is defined as the performance of a treatment modality under ideal, controlled conditions in a selective population such as a randomised-controlled trial (RCT). Effectiveness is the performance of the intervention, in the uncontrolled real world, in a unselected, heterogeneous population [12]. Presumably, an EEG is the result of patients in the real world being dissimilar to those included in the RCTs. Despite RCTs remaining the gold standard to establish efficacy and provide the fundament for evidence-based guidelines, clinicians also need guidance in recommending treatment options to those patients who are outside the characteristics of the RCT-population.

Whether an EEG is present in 1L-CTx for urothelial carcinoma (UC) of the bladder is unknown. The aim of the present study was to describe oncological outcomes in unselected, unresectable stage III and IV bladder cancer (BCa) patients who receive 1L-CTx in the Netherlands and compare outcomes with the results from clinical trials.

Methods

Study design, patient population, and data collection

This retrospective, non-interventional study was performed within Santeon, a network of seven large (non-university) teaching hospitals in the Netherlands responsible for approximately 11% of the Dutch hospital care. The study protocol was reviewed by the local research ethics committee of the St. Antonius Hospital Utrecht/Nieuwegein (W17.087), and approved by each participating hospitals' institutional review board. The study was conducted in accordance with Good Clinical Practice Guidelines and the Declaration of Helsinki.

Patients were identified with help of the Netherlands Cancer Registry (NCR), which tracks all patients with BCa diagnosed in the Netherlands. The study selection period covered patients diagnosed between January 1, 2008 and December 31, 2016, with follow-up through July 2020. Patients with upper tract urinary cancer were excluded from the selection. A consort flowchart can be found in Fig. 1.

A total of 7531 patients with all-stages BCa, diagnosed in the participating hospitals, could be extracted from the NCR-database. From these patients, 2123 (28.2%) were aged ≥ 18 years and labelled with muscle-invasive bladder cancer (MIBC) and/or mBC (i.e. ≥ stage II or cT2-4N0-3M0-1 disease). For this selection, individual patient data were checked and supplemented through manual chart review, resulting in exclusion of 93 patients (4.4%) because of non-retrievable data and 177 patients (8.3%) for a histological variant other than urothelial carcinoma.

To align with the study design of the most influential phase III trials on CTx for advanced BCa [3, 4], two groups were considered for the 1L-CTx analyses. The first group was patients with primary ≥ cT2N0M0 disease receiving salvage chemotherapy treatment (sCTx) for recurrent disease after RC. Of the 1853 included patients, 864 patients underwent a RC. Subsequently, 408 patients (47.2%) had recurrent disease (median follow-up time after RC 73.1 months [95% CI 69.8–76.4]).

The second group was patients with primary chemotherapy treatment (pCTx) for unresectable stage III disease (cT2-4aN1-3M0) and stage IV disease (cT4b and/or cM1). A total of 550 patients had cT2-4aN1-3M0 or cT4b and/or cM1 BCa, of which 427 (77.6%) were deemed unresectable (105/216 patients with cT2-4aN1-3M0 and 322/334 patients with cT4b and/or cM1 disease). The 408 patients with recurrent disease after RC and the 427 patients with unresectable stage III and IV disease together form the study population for the present study.

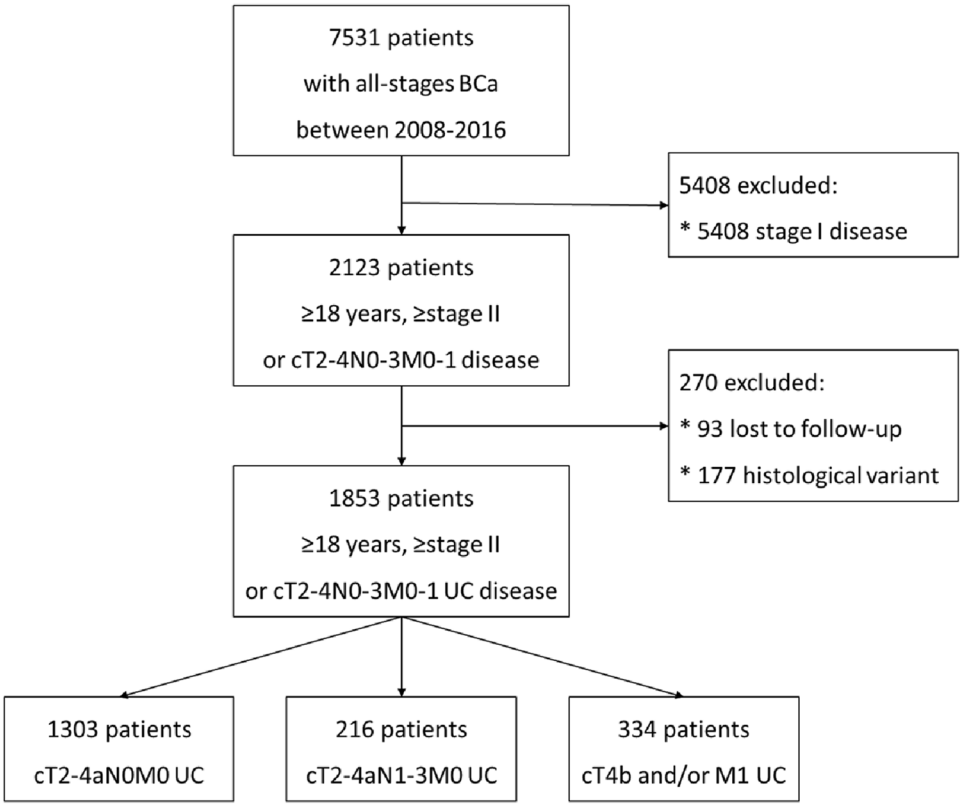

Fig. 1 Consort flowchart of the patient cohort extracted from the Netherlands Cancer Registry (NCR)-database. *BCa* bladder cancer, *UC* urothelial carcinoma

Treatment planning

In the Netherlands, treatment according to the EAU guidelines is standard practice [2], this means for cisplatin-eligible patients: cisplatin 70 mg/m^2 and gemcitabine 1000–1250 mg/m^2 on day 1, and gemcitabine 1000 mg/m^2 on day 8, in a 21-day cycle, and for cisplatin-ineligible patients: an area under the curve (AUC) 5 carboplatin and gemcitabine 1000–1250 mg/m^2 on day 1, and gemcitabine same dose on day 8, also in a 21-day cycle. For both options, the maximum number of cycles is six. Cisplatin-ineligibility is considered a creatinine clearance (CrCl) < 60 mL/min, an Eastern Cooperative Oncology Group performance status (ECOG PS) > 1, and/or a grade ≥ 2 audiometric hearing loss or NYHA class III heart failure [13]. Our study used the CrCl and ECOG PS criteria, since these data were accessible.

Covariates and definitions

During the study years, topography and morphology were classified according to the International Classification of Diseases of Oncology (ICD-O) and tumour stage according to the 7th TNM-classification system [14]. The stages were converted to the 8th TNM-classification system, where N1 and N2-3 are now classified as, respectively, stage III-A and III-B disease.

The patients' performance status was reported in ECOG PS classes. When the Karnofsky performance score (KPS) was reported, it was translated to ECOG PS (KPS 100 = ECOG PS 0; KPS 90–80 = ECOG PS 1; KPS 70–60 = ECOG PS 2; KPS 50–40 = ECOG PS 3; and KPS 30–10 = ECOG PS 4), according to Ma et al. [15]. Evaluation of response to CTx by imaging was performed according to the radiologists' assessment, adhering to the Response Evaluation Criteria in Solid Tumours (RECIST) criteria v1.1 [16]. Best-supportive care was defined as appropriate palliative care without any other anticancer therapies.

Outcomes and definitions

Primary outcome of the study was overall survival (OS). The OS for CTx patients was calculated as the time between date of starting treatment and date of death. A second calculation was done as the time between date of recurrent disease and date of death (to compare sCTx patients with those receiving salvage RTx or BSC) or time between date of diagnosis and date of death (to compare pCTx patients with those receiving primary RTx or BSC).

Secondary outcomes were dose reductions, dose delays, switched treatment, early termination, and clinical response. Dose reduction was defined as receiving a dose < 80% of the initial dose. Early termination of CTx was defined as not receiving the fully, pre-planned amount of cycles. The

definition of dose delay was a delay of the next treatment cycle of > 7 days. A treatment switch was defined as a switch from cisplatin to carboplatin. If patients switched from cisplatin to carboplatin, they were calculated as cisplatin patient. Clinically best response to chemotherapy was defined as response at the end of systemic treatment.

Reference data

A non-systematic PubMed search was conducted to identify all reported randomised clinical trials that investigated either GemCis, GemCarbo or both as study arms. From these publications, data were extracted about all the characteristics and outcomes of interest (see above). Secondary publications about specific subgroups were ignored if the primary publication with full trial results was identified.

Statistical analyses

Descriptive statistics were used to characterise the cohort. Continuous data are presented using mean (± standard deviation (SD)), or when data were skewed, median with interquartile range (IQR). To compare continuous data, t-tests were used. Categorical data are presented as frequencies with percentage, and were compared using the Chi-square tests. The EEG was calculated by dividing survival (mOS) from this study by the average survival (mOS) reported in clinical trials.

The Kaplan–Meier method with 95% confidence intervals [95% CI] was used to determine survival, and survival was compared using the log-rank test. Patients alive at the end of the study were censored at the last available date known to be alive. Kaplan–Meier curves were produced using R (version 4.0.2, R Core Team). The reverse Kaplan–Meier method was used to determine median follow-up.

A Cox proportional-hazards model was constructed to examine the relative effectiveness (OS) of GemCis vs. GemCarbo, taking into account all available patients' characteristics.

All reported *P*-values were two-sided and a *P*-value of < 0.05 was considered statistically significant. Statistical analyses were performed with SPSS (v24.0, IBM). No multiplicity adjustments were made.

Results

Patient characteristics

A Sankey-diagram showing treatment trajectories for all patients diagnosed with MIBC/mBC is provided in Fig. 2.

From a total of 408 patients with recurrence after RC, 88 patients (21.6%) received sCTx, 54 patients (13.2%) received salvage (palliative) local RTx and 242 patients (59.3%) received BSC. From a total of 427 patients with unresectable stage III and IV BCa, 103 (24.1%) received pCTx, 43 (10.1%) received (palliative) primary local RTx, and 236 (55.3%) received BSC. Combining these numbers resulted in a total sample size of 191 for the outcomes analyses for 1L-CTx patients.

Mean age at diagnosis for 1L-CTx was 65.2 (± 8.0) years. The mOS for all types of 1L-CTx was 10.0 months [95% CI 8.5–11.4]. The 6, 12, 24 and 48 months-OS was 71%, 43%, 20% and 11% for all types of 1L-CTx. Female patients less often received 1L-CTx, compared to male patients with similar stage disease (17.4% vs. 28.0%, respectively, *P*-value = 0.009). For comparison, the mean age for RTx and BSC patients was 70.9 (± 11.3) years and 73.0 (± 10.5) years, respectively (*P*-value < 0.001), and the mOS of RTx and BSC patients was 8.0 months [95% CI 5.8–10.2] and 2.0 months [95% CI 1.8–2.3], respectively (*P*-value < 0.001).

Comparing 1L-CTx oncological outcomes with the literature

Of all 191 patients receiving 1L-CTx, 88 (46.1%) were treated with GemCis and 92 (48.2%) with GemCarbo (Table 1). Oncological outcomes of this study were compared to the outcomes of the six major (and only) prospective RCTs on GemCis and/or GemCarbo [3–8, 17, 18] (Table 2).

The mOS for 1L-CTx with GemCis in current study was 10.4 months [95% CI 7.9–13.0], whereas in clinical trials, the mOS ranges from 12.7 to 14.3 months (average 13.5 months). The 6, 12, 24 and 48 months' OS was 70%, 44%, 24% and 12%, whilst in the study of Von der Maase et al., this was 82%, 58%, 25% and 16%. Of all GemCis-treated patients, 26.1% were female (14.5–21.2% in the RCTs), mean age was 63.1 (± 8.0) years (60.5–67.0 years in the RCTs), 89.3% had a CrCl of 60–99 mL/min (100% in the RCTs), 96.4% had an ECOG PS of 0–1 (82.5–100% in the RCTs), and 64.8% of patients were treated in the pCTx setting (62.1–80.4% in the RCTs). Median number of chemotherapy cycles was 5 (4–6 in the RCTs), 66.3% were treated with ≥ 4 cycles, in 24.4% dose reduction occurred (37.0–75.5% in the RCTs), and 55.7% had early termination of treatment (37.0–50.0% in the RCTs). Overall response rates was 44.3% with 12.7% cCR and 31.6% cPR (41.3–65.8% overall response rates of which 12.2–21.7% cCR and 19.6–46.3% cPR in the RCTs).

In current study, the mOS for 1L-CTx with GemCarbo was 9.3 months [95% CI 7.5–11.1], whereas in RCTs, the mOS ranges from 9.3 to 16.3 months. The 6, 12, 24 and 48 months' OS was 71%, 40%, 15% and 9%. Of all GemCarbo-treated patients, 14.1% were female (12.7–24.4% in the RCTs), mean age was 67.8 (± 8.0) years (67.0–70.0 years

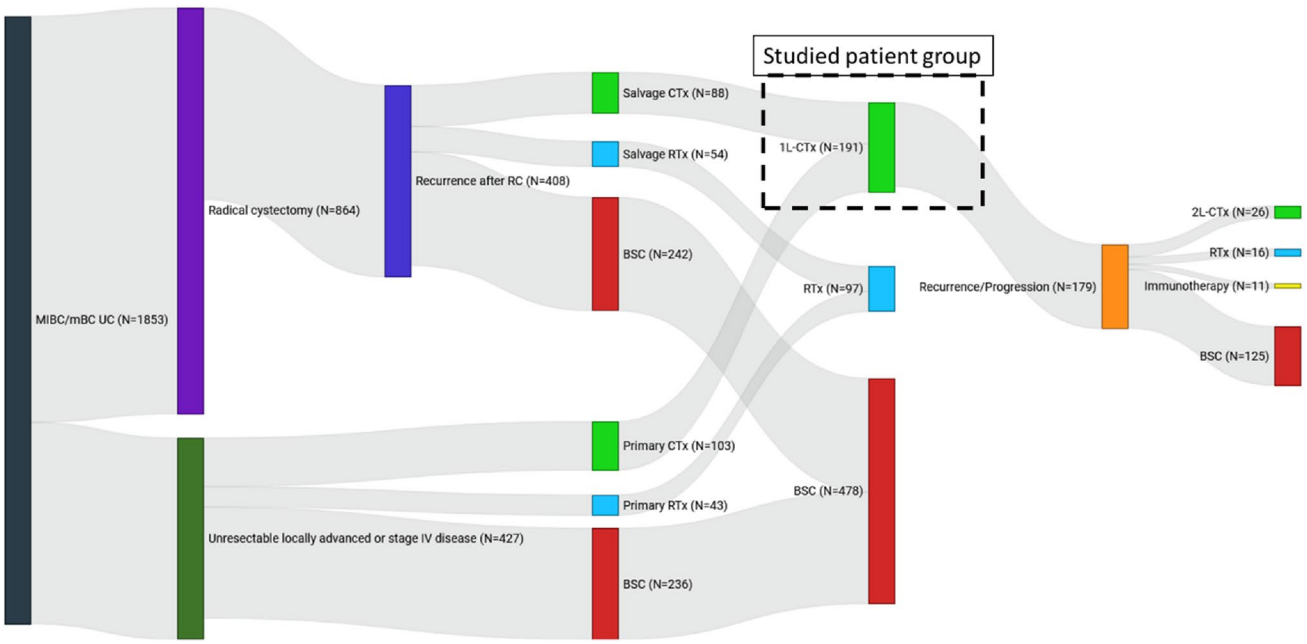

Fig. 2 Sankey diagram of the treatment patterns for the analyses of patients with muscle-invasive bladder cancer (MIBC) or metastatic bladder cancer (mBC) of the bladder (urothelial carcinoma). This study focussed on (1) patients with ≥ cT2N0M0 disease treated with radical cystectomy (RC) and subsequent salvage chemotherapy treatment (CTx) for recurrent disease and (2) patients with unresectable stage III and IV (cT2-4aN1-3M0 and cT4b and/or cM1) disease treated with primary CTx. Frequency of first-line (1L-CTx) (all types), palliative radiotherapy treatment (RTx) and best-supportive care (BSC) are described. * Not all forms of treatment are described. *MIBC* muscle-invasive bladder cancer, *mBC* metastatic bladder cancer, *UC* urothelial carcinoma, *RC* radical cystectomy, *CTx* chemotherapy treatment, *RTx* radiotherapy treatment, *BSC* best-supportive care, *1L* first-line, *2L* second-line

in the RCTs), 44.3% had a CrCl of 60–99 mL/min (various in the RCTs), 40.0% had an ECOG PS of 0–1 (55.5–86.7% in the RCTs), and 44.6% of patients were treated in the pCTx setting (60.0% in the RCTs). Median number of chemotherapy cycles was 4 (4–6 in the RCTs), 59.4% were treated with ≥ 4 cycles (43.2–53.3% in the RCTs), in 29.5% dose reduction occurred (72.9% in RCTs), and 54.1% had early termination of treatment (21.0–46.7% in the RCTs). Overall response rates was 41.4%, with 9.2% cCR and 32.2% cPR (38.4–56.4% overall response rates of which 2.6–11.7% cCR and 26.7–53.8% cPR in the RCTs).

Results for the separate analyses for sCTx and pCTx can be found in Online Resource 1 and Online Resource 2.

Of the 180 patients receiving 1L-CTx GemCis or GemCarbo, only 83 patients (46.1%) were deemed eligible for cisplatin-based chemotherapy (CrCl ≥ 60 mL/min, ECOG PS 0–1). The mOS for cisplatin-eligible patients receiving GemCis was 11.4 months [95% CI 8.6–14.2], whilst the mOS for cisplatin-eligible patients receiving GemCarbo was 12.1 months [95% CI 10.3–13.8]. For cisplatin-ineligible patients receiving GemCis or GemCarbo, the mOS was 9.0 months [95% CI 7.0–11.1] and 8.1 months [95% CI 6.5–9.6], respectively (Table 3). Of the 19 ineligible patients, 14 had a CrCl between 46 and 59, and 5 had a ECOG PS of 2–3.

Comparing GemCis vs. GemCarbo patients

The mOS between 1L GemCis and GemCarbo patients did not differ (P-value = 0.184). Kaplan–Meier OS-curves for GemCis vs. GemCarbo patients and 1L-CTx vs. RTx vs. BSC patients are shown in Fig. 3a, b. Kaplan–Meier curves for the separate analyses for sCTx and pCTx can be found in Online Resource 3 and Online Resource 4.

Baseline characteristics of 1L GemCis- and GemCarbo-treated patients can be found in Table 1. The GemCarbo-treated patients had worse baseline characteristics compared to GemCis-treated patients (age, CrCl and ECOG PS (all P-values < 0.001)). Between GemCis- and GemCarbo-treated patients, there was no difference in frequency of dose reduction (24.4% vs. 29.5%, P-value = 0.453), early termination (55.7% vs. 54.1%, P-value = 0.839) or clinical best response (P-value = 0.733). Grade ≥ 3 complications occurred equally in GemCis- and GemCarbo-treated patients (68.1% vs. 63.3%, P-value = 0.743).

The survival outcomes of the subgroups cisplatin-eligible and cisplatin-ineligible patients treated with GemCis vs. GemCarbo was not statistical significant different (Table 3).

Table 1 Baseline characteristics and oncological outcomes of patients with urothelial carcinoma of the bladder, treated with first-line chemotherapy (1L-CTx)

	All types of chemotherapy *(N = 191)*	Gemcitabine + cisplatin *(N = 88)*	Gemcitabine + carboplatin *(N = 92)*	*P*-value*
Female sex, no. (%)	39 (20.4)	23 (26.1)	13 (14.1)	**0.044**
Age at diagnosis, mean years (SD)	65.2 (± 8.0)	63.1 (± 7.5)	67.8 (± 8.0)	**< 0.001**
Age at diagnosis, no. (%)				**0.002**
< 65 years	96 (50.3)	54 (61.4)	33 (35.9)	
65–69	38 (19.9)	16 (18.2)	20 (21.7)	
70–74	33 (17.3)	14 (15.9)	19 (20.7)	
75–79	18 (9.4)	3 (3.4)	15 (16.3)	
80–84	6 (3.1)	1 (1.1)	5 (5.4)	
85 +	0 (0.0)	0 (0.0)	0 (0.0)	
Creatinine clearance (CrCl), mL/min, no. (%)				**< 0.001**
60–99	120 (66.7)	75 (89.3)	39 (44.3)	
50–59	43 (23.9)	7 (8.3)	34 (38.6)	
30–49	17 (9.4)	2 (2.4)	15 (17.0)	
Unknown	11	4	4	
ECOG PS, no. (%)				
0–1	117 (70.5)	81 (96.4)	30 (40.0)	
2	48 (28.9)	2 (2.4)	45 (60.0)	
3	1 (0.6)	1 (1.2)	0 (0.0)	
Unknown	25	4	17	
Setting chemotherapy, no. (%)				**0.007**
Salvage chemotherapy treatment (sCTx)	88 (46.1)	31 (35.2)	51 (55.4)	
Primary chemotherapy treatment (pCTx)	103 (53.9)	57 (64.8)	41 (44.6)	
Number of chemotherapy cycles, median (IQR)	4.0 (3.0–6.0)	5.0 (3.0–6.0)	4.0 (3.0–6.0)	0.679
Treated with ≥ 4 cycles, no. (%)	113 (64.6)	53 (66.3)	41 (59.4)	
Dose reduction, no. (%)	46 (26.4)	19 (24.4)	26 (29.5)	0.453
Switch cisplatin to carboplatin, no. (%)	–	8 (9.5)	–	–
Early termination, no. (%)	92 (53.5)	44 (55.7)	46 (54.1)	0.839
Clinical best response, no. (%)				0.733
Complete response (cCR)	18 (10.3)	10 (12.7)	8 (9.2)	
Partial response (cPR)	56 (32.0)	25 (31.6)	28 (32.2)	
Stable disease (cSD)	17 (9.7)	7 (8.9)	9 (10.3)	
Progressive disease (cPD)	84 (48.0)	37 (46.8)	42 (48.3)	
Unknown	16	9	5	
CTCAE complications, no. (%)				0.743
Grade 3	74 (43.0)	35 (50.7)	36 (45.6)	
Grade 4	22 (12.8)	10 (14.5)	12 (15.2)	
Grade 5	4 (2.3)	2 (2.9)	2 (2.5)	
OS from start chemotherapy, median months [95% CI]	10.0 [8.5–11.4]	10.4 [7.9–13.0]	9.3 [7.5–11.1]	0.184
OS from diagnosis (of recurrence), median months [95% CI]	12.1 [10.8–13.5]	12.7 [9.9–15.4]	11.8 [9.0–14.7]	0.291
Subsequent treatment with systemic therapy, no. (%)	38 (21.1)	16 (19.5)	19 (21.8)	0.772

Bold values denote statistical significance at *P*-value < 0.05

ECOG Eastern Cooperative Oncology Group, *PS* performance score, *CTCAE* common terminology criteria for adverse events, *OS* overall survival, *SD* standard deviation, 95% *CI* 95% confidence interval

**P*-value is calculated for the difference between gemcitabine + cisplatin and gemcitabine + carboplatin

Cox-regression analyses

Cox proportional-hazards regression analyses are shown in Table 4. In the univariable analyses, only an ECOG PS 0–1 vs. > 1 was associated with improved survival. In multivariable analyses, treatment with GemCis was not associated

Table 2 Literature on clinical trials reporting on survival outcomes of patients receiving first-line chemotherapy treatment (1L-CTx) in the form of gemcitabine + cisplatin or gemcitabine + carboplatin

	GEMCIS				GEMCARBO		
	Kaufman [16]	Von der Maase [3, 4]	Dogliotti [5]	Bellmunt [8]	Bamias [17]	Dogliotti [5]	Desantis [6, 7]
Study years	N.M	1996–1998	2000–2002	2001–2004	2002–2003	2000–2002	2001–2005
Phase study	Phase II	Phase III	Phase II	Phase III	Non-RCT, Phase II	Phase II	Phase II/III
Included stage [a]	Stage III–IV	Stage III–IV locally advanced [cT4bN(any) or cT(any)N2-3 or cM1]	Locally advanced [stage III cT3b-T4a or stage IV cT4b] or metastatic [cT(any) N2-3 or M1], not suitable for RC]	Stage III-IV locally advanced [cT4bN(any) or cT(any)N2-3 or cM1]	Recurrent disease after RC or inoperable locally advanced or metastatic	Stage III-IV locally advanced [cT3b-T4a or cT4bN(any) or cT(any)N2-3 or cM1, not suitable for RC]	[cT3-4 unresectable or N1-3 or cM1]
Follow-up duration	Until death or lost to follow-up	> 60 months	Median = 7.2 months	> 36 months	Median (range) = 18.4 months (0.2–21.3)	Median = 6.9 months	Median = 54 months
Patients, no. (%)	46	203	55	314	60	55	119
Female sex, no. (%)	8 (17.4)	43 (21.2)	8 (14.5)	59 (19.0)	11 (18.3)	7 (12.7)	29 (24.4)
Age at diagnosis, mean years	60.5	63.0	67.0	61.0	69.0	67.0	70.0
Disease stage, no. (%)	Local = 13 (28.3)	cM0 = 60 (29.5)	Stage III (cT3b-T4a) = 5 (9.1)	cM0 = 38 (12.1)	Locoregional = 29 (48.3)	Stage III (cT3b-T4a) = 5 (9.1)	cM0 = 18 (20.5)
	cN1-3 = 13 (28.3)	cM1 = 141 (69.5)	Stage III-B (cN2-3) or VI (cT4b) = 50 (90.1) [c]	cM1 = 276 (87.9)	Metastatic = 31 (51.7)	Stage III-B or VI (cT4b) = 50 (90.1)	cM1 = 68 (77.3)
	Both = 5 (10.9)	cMx = 2 (1.0)					cMx = 2 (2.3)
	cM1 = 15 (32.6)						
CrCl, mL/min, no. (%)	≥ 60 = 46 (100)	≥ 60 = 203 (100)	≥ 60 = 55 (100)	≥ 60 = 314 (100)	≥ 50 = 47 (78.3)	≥ 60 = 55 (100)	Median (range) 50 (31–128) [d]
ECOG PS, no. (%)							
0	12 (26.1)	165 (82.5)	29 (52.7)	171 (54.5)	52 (86.7)	23 (41.8)	20 (16.8)
1	28 (60.8)		23 (41.8)	143 (45.5)		24 (43.6)	46 (38.7)
2	6 (13.1)	38 (17.5)	3 (5.5)	0 (0)	8 (13.3)	8 (14.6)	53 (44.5)
Setting CTx, no (%)							
Salvage CTx	9 (19.6)	77 (37.9)	N.M	N.M	24 (40.0)	N.M	N.M
Primary CTx	37 (80.4)	126 (62.1)	N.M	N.M	36 (60.0)	N.M	N.M
Chemotherapy cycles	N.M	Median = 6	Median (range) = 4 (1–6)	≥ 4 = 230 (75.4)	Median (range) = 6 (1–9) ≥ 6 = 32 (53.3)	Median (range) = 4 (1–6)	Median (range) = 4 (1–23) ≥ 6 = 51 (43.2)
Dose reduction, no. (%)	N.M	(37.0)	N.M	231 (75.7)	N.M	N.M	86 (72.9)
Early termination, no. (%)	23 (50.0)	N.M	25 (45.4)	113 (37.0)	28 (46.7)	25 (45.4)	25 (21.0)

Table 2 (continued)

	GEMCIS				GEMCARBO		
	Kaufman [16]	Von der Maase [3, 4]	Dogliotti [5]	Bellmunt [8]	Bamias [17]	Dogliotti [5]	Desantis [6, 7]
Clinical best response, no. (%)							
Complete response (cCR)	10/46 (21.7)	20/164 (12.2)	8/41 (19.5)	35/281 (12.5)	7/60 (11.7)	1/39 (2.6)	4/106 (3.8)
Partial response (cPR)	9/46 (19.6)	61/164 (37.2)	19/41 (46.3)	102/281 (36.3)	16/60 (26.7)	21/39 (53.8)	45/106 (42.5)
Stable disease (cSD)	18/46 (39.1)	55/164 (33.5)	12/41 (29.3)	97/281 (34.5)	15/60 (25.0)	14/39 (35.9)	39/106 (36.8)
Progressive disease (cPD)	9/46 (19.6)	28/164 (17.1) [b]	2/41 (4.9)	47/281 (16.7)	10 + 11/60 (16.7)	3/39 (7.7)	18/106 (17.0)
Unknown	0 (-)	N.M	14 (-)	33 (-)	0 (-)	16 (-)	13 (-)
CTCAE complications, no. (%)							
Grade 5	N.M	(1.0)	1 (1.8)	7 (2.2)	3 (5.0)	0 (0.0)	2 (1.7)
OS, median months [95% CI]	14.3 [9.7–21.3]	14.0 [12.3–15.5]	12.8 [-]	12.7 [11.0–14.4]	16.3 [12.0–20.6]	9.8 [-]	9.3 [-]

1L first line, *CTx* chemotherapy treatment, *GemCis* gemcitabine + cisplatin, *GemCarbo* gemcitabine + carboplatin, *RCT* randomised controlled trial, *CrCl* creatinine clearance, *ECOG* Eastern Cooperative Oncology Group, *PS* performance score, *CTCAE* common terminology criteria for adverse events, *OS* overall survival, *RC* radical cystectomy, *95% CI* 95% confidence interval, *N.M.* not mentioned

[a]If the 7th TNM-classification was used, it was updated to the 8th TNM-classification

[b]Percentage was estimated based on the other percentages

[c]Study did not mention percentage of patients with metastatic [cT(any)N2-3 or M1] disease

[d]Study included only patients with poor creatinine clearance (< 60 mL/min)

Table 3 Kaplan–Meier analyses of survival for patients receiving first-line chemotherapy treatment (1L-CTx) for unresectable stage III and IV (cT2-4aN1-3M0 and cT4b and/or cM1) urothelial carcinoma of the bladder

	N	Overall survival (date of treatment)			Overall survival (date of diagnosis)		
		(Median months)	[95% CI]	*P-value*	(Median months)	[95% CI]	*P-value*
All patients	180	9.8	[8.3–11.4]		12.1	[10.8–13.5]	
GemCis	*88*	10.4	[7.9–13.0]	0.184	12.7	[9.9–15.4]	0.291
GemCarbo	*92*	9.3	[7.5–11.1]		11.8	[9.0–14.7]	
Cisplatin-eligible	83	11.6	[9.4–13.7]		14.0	[12.0–15.9]	
GemCis	*69*	11.4	[8.6–14.2]	0.790	14.0	[11.6–16.3]	0.755
GemCarbo	*14*	12.1	[10.3–13.8]		13.8	[10.7–17.1]	
Cisplatin-ineligible	97	8.6	[7.1–10.1]		10.3	[8.8–11.7]	
GemCis	*19*	9.0	[7.0–11.1]	0.520	10.8	[9.0–12.7]	0.713
GemCarbo	*78*	8.1	[6.5–9.6]		10.0	[7.7–12.2]	

GemCis gemcitabine + cisplatin, *GemCarbo* gemcitabine + carboplatin, *95% CI* 95% confidence interval

Patients were stratified based on cisplatin-(in)eligibility and type of chemotherapy received

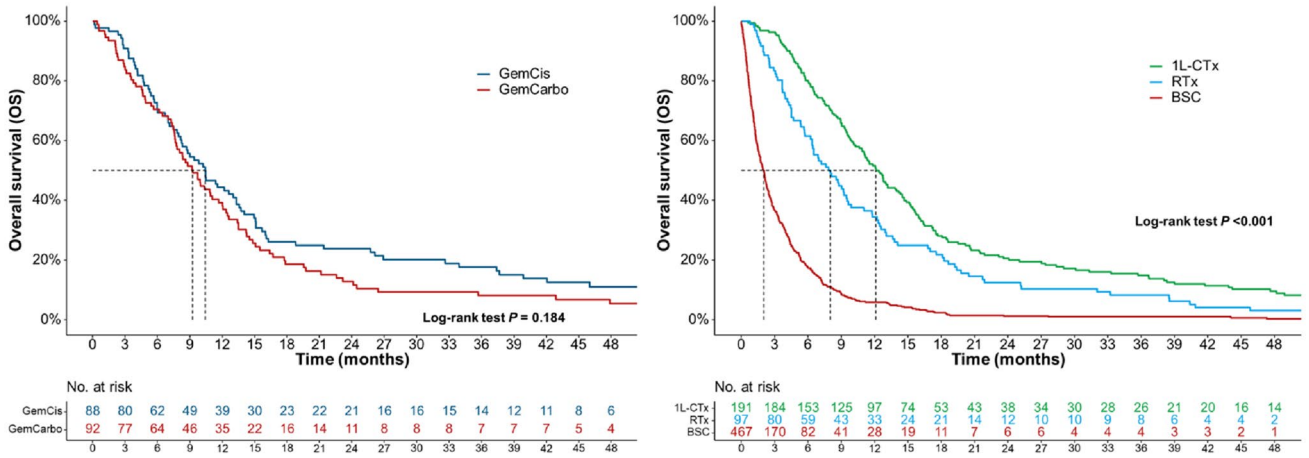

Fig. 3 a, b Kaplan–Meier analyses of overall survival for patients receiving first-line chemotherapy treatment (1L-CTx) for urothelial carcinoma of the bladder. **a** The difference between 1L gemcitabine + cisplatin (GemCis) and gemcitabine + carboplatin (GemCarbo) (10.4 months [95% CI 7.9–13.0] vs. 9.3 months [95% CI 7.5–11.1], respectively), and **b** the difference between 1L-CTx (all types), palliative radiotherapy treatment (RTx) and best-supportive care (BSC) (10.0 months [95% CI 8.5–11.4] vs. 8.0 months [95% CI 5.8–10.2] vs. 2.0 months [95% CI 1.8–2.3], respectively)*. *Survival of (**b**) was calculated from date of recurrence after radical cystectomy or date of diagnosis and date of death

Table 4 Univariable and multivariable Cox proportional-hazards analyses for 180 patients receiving first-line chemotherapy treatment (1L-CTx) for unresectable stage III and IV (cT2-4aN1-3M0 and cT4b and/or cM1) urothelial carcinoma of the bladder, for the association between patient factors and overall survival

Chemotherapy type (GemCis* vs. GemCarbo)	Univariable HR [95% CI]		*P*-value	Multivariable HR [95% CI]		*P*-value
	1.23	[0.91–1.68]	0.185	0.90	[0.55–1.47]	0.674
Age	0.99	[0.97–1.00]	0.256	0.98	[0.96–0.99]	**0.043**
Creatinine clearance (CrCl) (≥ 60 mL/min* vs. < 60)	1.31	[0.94–1.82]	0.111	1.47	[0.97–2.21]	0.067
ECOG PS (0–1* vs. > 1)	1.65	[1.16–2.35]	**0.006**	1.69	[1.04–2.75]	**0.035**
Setting chemotherapy (sCTx* vs. pCTx)	1.08	[0.79–1.47]	0.641			

Bold values denote statistical significance at P-value < 0.05

GemCis gemcitabine + cisplatin, *GemCarbo* gemcitabine + carboplatin, *ECOG* Eastern Cooperative Oncology Group, *PS* performance score, *sCTx* salvage chemotherapy treatment, *pCTx* primary chemotherapy treatment, *HR* hazard ratio, *95% CI* 95% confidence interval

* Groups marked *are the reference category in case of categorical variables

with increased survival, after adjusting for age, CrCl and ECOG PS (HR 0.90 [95% CI 0.55–1.47], *P*-value = 0.674).

Discussion

This retrospective, observational, multi-centre cohort study describes the oncological outcomes in unselected patients who receive palliative 1L-CTx for urothelial carcinoma of the bladder, in the Netherlands. The aim of this study was to evaluate the effectiveness of 1L-CTx treatment in real-world cohort, and compare outcomes with the efficacy found in clinical trials, to examine the existence of an efficacy–efficiency gap (EEG) [12].

The survival of patients treated with GemCis in this study was inferior to the efficacy from RCTs, and an EEG seems present. The EEG of 1L GemCis treatment is 77%. It has been proposed that the explanation of an EEG can be described as a difference in behaviour [19]. The first behavioural explanation is that patients presenting with BCa in the real world are dissimilar to those enrolled in clinical trials, yet physicians still may offer treatment, including to those patients who are considered ineligible considering the criteria of clinical trials. In other words, the EEG is caused by a difference between the characteristics of the highly selected patients in clinical trials (according to strict inclusion and exclusion criteria) and the unselected patients in daily practice. However, baseline characteristics such as percentage of female patients, age, CrCl, and ECOG PS of the current study were all similar to patients in the clinical trials, including the percentage of patients in sCTx and pCTx setting, and the cTNM-stage [3–5, 8, 17]. There were some patients ($N = 19$) considered cisplatin-ineligible, in who GemCis was used. But even when these patients were excluded from analysis, the survival only slightly increased (10.4 months to 11.4 months), and an EEG was still present (84% effectiveness). Only a fraction of the EEG can be explained by physicians also treating patients who are considered ineligible. Other, unknown, unmeasured baseline, diagnostic workup or treatment variables must be responsible for the decreased effectiveness of GemCis in routine practice.

Despite similar baseline characteristics, the oncological outcomes did show a divergence. Compared to clinical trials, patients in current study experienced more often early termination of treatment. In contrary, dose reductions occurred less often. There is another possible explanation encompassing the behaviour of physicians and patients adherence to treatment [19]. Increased early termination may be the cause of scepticism about the clinical benefit of the treatment for the patient, which may lead to early termination. Otherwise, the behaviour of physicians might be different compared to the behaviour of physicians in clinical trials, when the real-world physician offers the patient different CTx protectants or support, such as hydration regimens, nausea and vomiting support [19]. Possibly, when treatment complications occurred, treatment was terminated, instead of the patient and physician trying to continue albeit with dose reduction. In concordance, patients were less often staged cCR and cPR compared to some trials, and subsequently, survival outcomes were shorter. Thus, treatment adherence despite occurring complications could result in better oncological outcomes, which could explain a portion of the observed EEG.

In contrast with GemCis patients, for the GemCarbo regimen survival was more equal to the outcomes of clinical trials. The survival after 1L GemCarbo treatment varies widely in clinical trials [5–7, 18] and as a result the calculated EEG was still 78%. However, the best designed and powered study of DeSantis et al. had an equal survival to the current study. Although the patients' baseline characteristics resembled the data from the three prospective RCTs, dose reductions also occurred less often compared to the literature, yet patients received less treatment cycles and had more often early termination of treatment. This resulted to a lesser extent into worse survival outcomes. Thus, the 'persistence in continuing chemotherapy cycles despite complications will result in increased survival' theory, suggested in GemCis patients, seems not applicable for GemCarbo patients. The large variety in survival outcomes after 1L GemCarbo treatment warrants future studies on survival in both clinical trial as the real-world setting.

Due to the lower than expected survival in GemCis patients, the survival between GemCis- and GemCarbo-treated patients in current study did not differ, despite patients treated with GemCarbo having worse baseline characteristics known to be linked to poor prognosis. In addition, other oncological outcomes such as therapy completion, response rates and toxicity were similar in GemCis- and GemCarbo-treated patients. The EAU-guidelines state that CTx with carboplatin is not equivalent to cisplatin, and should not be considered interchangeable or standard [2]. This is based on four phase II-III trials showing lower complete response and shorter OS rates in patients treated with carboplatin-based regimens compared to cisplatin-based regimens [20]. Of these four studies, only Dogliotti et al. studied GemCis vs. GemCarbo patients [5]. However, the study had major flaws such as a small sample size of only 55 patients in both arms, resulting in limited statistical power, and the short median follow-up of only 7 months, with the GemCis arm never reaching 50% deceased. It is unknown why long-term follow-up data have not been published. The question is whether there is enough evidence to suggest GemCarbo is inferior to GemCis.

The debate of cisplatin vs. carboplatin is not limited to BCa alone. In non-small cell lung cancer (NSCLC), a phase

III trial on 1L GemCarbo vs. GemCis treatment did not show inferiority of GemCarbo compared to GemCis in terms of survival [21]. In addition, a meta-analysis of 12 RCTs on 1L carboplatin-based and cisplatin-based chemotherapy for NSCLC showed no difference in OS, despite a slight benefit in ORR for cisplatin [22]. It is not inconceivable that a lack of a relevant difference in effectiveness does also extend to BCa treatment (as observed in present study) but it is unlikely that another randomised trial on the subject will be conducted in the future.

In this study, the proportion of patients not undergoing 1L-CTx is higher compared to other studies. A study by Flannery et al. from the USA on cN1-3, cT4b, and cM1 patients showed that 34% of patients received primary, palliative 1L-CTx. This number was already lower compared to earlier US studies which had frequencies ranging from 52 to 76% [23]. In the population of this study group, only 19% of cT2-4aN1-3M0 and cT4b and/or cM1 patients were treated with palliative 1L-CTx. Patients with cT2-4aN1-3M0 disease still have a considerable chance of curation. This is reflected in the treatment patterns in our study group. Curative radical cystectomy was performed in 51% of these patients. Only 15% of cT2-4aN1-3M0 disease patients received palliative 1L-CTx, and 20% BSC. Curation in the cT4b and/or M1 group is considered much harder to achieve. In the current study population, these patients received palliative 1L-CTx in 21% of cases, whereas 58% received BSC. For the cT2-4aN1-3M0 disease patients, it can be concluded that the frequency of palliative 1L-CTx used is low because a substantial part of the group is still considered for curative treatment. For the cT4b and/or cM1 disease stage, it seems that when curation cannot be achieved, patients refrain from life-prolonging treatment. These substantial differences in treatment patterns must be placed in perspective, when interpreting the oncological outcomes including survival of a study population.

Strengths of this study are the transparent selection of the study population from an unselected baseline population of all incident BCa diagnoses from a period of 9 years. Medical records of all patients were manually checked, resulting in high-resolution data on treatment patterns and outcomes. In addition, the study has a minimum follow-up duration of 4 years, resulting in only a few censored patients in the survival analyses. This study is relevant, because patients are counselled by their physician on their prognosis based on oncological outcomes reported in clinical trials. As the current study shows, these outcomes (including survival, treatment tolerability, clinical response and toxicity) in the real world are less favourable. With data from this study, patients can be counselled on the actual expected outcomes which matches their characteristics.

In addition, the current study has several limitations. Several, potential confounding, baseline characteristics could not be included in comparative analyses due to absence of uniform reporting, such as comorbidities, laboratory values and smoking status. Finally, the total number of patients ($N = 191$) prevented assessment of different subgroups, due to low numbers.

Conclusion

The present study shows that there seems to be an efficacy–effectiveness gap in 1L GemCis for BCa treatment. This is despite patients having similar baseline characteristics compared to clinical trials. Early termination of treatment occurred more often and dose reduction less often compared to clinical trials, hinting towards abandonment of treatment in case of adverse events. Patients treated with 1L GemCis did not have statistically significant superior survival compared to GemCarbo-treated patients, even though patients treated with GemCarbo had worse baseline characteristics known to be linked to poor prognosis.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00345-023-04408-w.

Acknowledgements The authors thank the registration team of the Netherlands Comprehensive Cancer Organisation (IKNL) for the collection of data for the Netherlands Cancer Registry as well as IKNL staff for scientific advice. The authors thank Roche Nederland B.V. for funding for this research project.

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Funding This research received a grant from Roche Nederland B.V. to perform this study (Grant number: ML40374).

Availability of data and materials Anonymised data available upon request.

Code availability Not applicable.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval The study has been approved by the local research ethics committee of the St. Antonius Hospital Utrecht/Nieuwegein (W17.087) and was conducted in accordance with Good Clinical Practice Guidelines.

Consent to participate Not applicable.

Consent for publication Not applicable.

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