Guidelines versus real-world data in metastatic bladder cancer: a population-based study on first-line chemotherapy treatment patterns

Slotman, E.; Richters, A.; Fransen, H.P.; Smilde, T.J.; Linden, Y.M. van der; Siesling, S.; ... ; theProBCI Study Grp

ELSEVIER

Urologic Oncology: Seminars and Original Investigations 43 (2025) 328.e17–328.e24

UROLOGIC ONCOLOGY

Clinical-Bladder cancer

Guidelines versus real-world data in metastatic bladder cancer: A population-based study on first-line chemotherapy treatment patterns

Ellis Slotman, M.Sc.[a,b,*], Anke Richters, Ph.D.[a,c], Heidi P. Fransen, Ph.D.[a], Tineke J. Smilde, Ph.D.[d], Yvette M. van der Linden, Ph.D.[e,f], Sabine Siesling, Ph.D.[a,b], Katja K.H. Aben, Ph.D.[a,c], Natasja J.H. Raijmakers, Ph.D.[a], on behalf of theProBCI study group

[a] *Netherlands Comprehensive Cancer Organisation, Department of Research and Development, Utrecht, The Netherlands*
[b] *University of Twente, Technical Medical Centre, Department of Health Technology and Services Research, Enschede, The Netherlands*
[c] *Radboud University Medical Center, Department of IQ Health, Nijmegen, The Netherlands*
[d] *Jeroen Bosch Hospital, Department of Internal Medicine, 's Hertogenbosch, The Netherlands*
[e] *Leiden University Medical Centre, Centre of Expertise in Palliative Care, Leiden, The Netherlands*
[f] *Leiden University Medical Centre, Department of Radiotherapy, Leiden, The Netherlands*

Received 29 May 2024; received in revised form 17 September 2024; accepted 22 October 2024

Abstract

Background: For patients with metastatic bladder cancer (mBC) palliative chemotherapy is one of the main treatment options. Real-world insights into outcomes are available, but a comprehensive overview of specific treatment details like number of chemotherapy cycles received and (reasons for) adjustments is lacking.

Methods: A population-based study was conducted, including all patients diagnosed with mBC in the Netherlands between 2016 and 2021 who started chemotherapy as initial treatment. Data on patient, tumor, and treatment characteristics, including number of cycles, adjustments and reasons for adjustments, and survival were collected from the Netherlands Cancer Registry. Treatment patterns and outcomes were analyzed descriptively. Logistic regression analysis was used to identify factors associated with receiving the full guideline-recommended treatment (4–6 cycles).

Results: A total of 684 patients started first-line chemotherapy, mostly carboplatin-based (54%). Of these patients, 35% did not receive the full course of treatment. Among these patients who received <4 cycles, 24% died within one month of stopping treatment. Male sex and good performance status were independently associated with receiving the full course of treatment. Among patients who did receive a full course of treatment, half still had adjustments to their treatment schedule, which mainly included dose reductions due to side effects.

Conclusions: Among patients with mBC starting first-line chemotherapy, only a small majority received the recommended number of cycles, and treatment adjustments were common. This suggests that adhering to recommended treatment is challenging, emphasizing the importance of integrating insights on treatment discontinuation and modifications into the shared decision-making process and guideline development.

1. Introduction

The survival of patients with metastatic bladder cancer (mBC) remains poor with no distinct improvement over the past decades [1,2]. Treatment of mBC is primarily aimed at prolonging survival, and the administration of platinum-based chemotherapy, specifically cisplatin or carboplatin, is one of the main treatment options for these patients [3].

The decision to start systemic treatment involves trade-offs between quantity and quality of life. Therefore, a shared decision-making process in which the patient, relatives and physician discuss the benefits and risks of a systemic treatment is of utmost importance. Evidence concerning the efficacy of systemic treatment mainly stems from randomized clinical trials, which generally include patients with a more favorable prognostic profile, better

*Corresponding author.
E-mail address: e.slotman@utwente.nl (E. Slotman).

https://doi.org/10.1016/j.urolonc.2024.10.026

performance status and less comorbidities compared to the general patient population [4,5]. As a result, the risks and benefits of treatment may be different for patients in daily clinical practice, which complicates accurately informing patients about the expected risks and benefits of palliative systemic treatment.

Because of this, data on treatment patterns and outcomes in real-world populations of patients with mBC are of added value. Real-world studies showed that the majority of patients with mBC do not start palliative systemic treatment and that there is a disproportionally higher use of carboplatin based chemotherapy in the first line [6]. The observed median survival of patients who received cisplatin-based or carboplatin-based chemotherapy was shown to be 12.9 and 11.1 months, respectively, compared to 2.5 months in patients who did not receive systemic treatment [7]. Although these results contribute to a better understanding of the outcomes of systemic treatment in the real-world patient population, more detailed information on the number of treatment cycles patients with mBC complete in daily clinical practice is lacking, as well as information on what adjustments are made to treatment schedules, and why these adjustments are made. Discontinuation of systemic treatment or adjustments in treatment schedules probably result in suboptimal survival and quality of life outcomes. It can also evoke feelings of disappointment and failure in patients, as they are likely to have high expectations of the treatment [8,9]. In addition, discontinuation of chemotherapy shortly before death is considered an indicator of potentially inappropriate end-of-life care [10], which has been shown to be associated with a reduced quality of life of patients and their relatives [11−13].

To support patients and their treating physicians in making shared decisions about treatments that align with a patient's wishes and needs, real-world insights into treatment patterns and alterations are important. Therefore, the aim of this study was to provide population-based insights into first-line systemic treatment patterns for mBC, including the number of cycles received, adjustments made to treatment schedules, the reasons for these adjustments, and the proportion of patients who died shortly after stopping chemotherapy. In addition, we sought to identify factors associated with receiving the full number of guideline-recommended treatment cycles.

2. Materials and methods

2.1. Study population

All patients aged 18 years or older who were diagnosed with synchronous mBC between 2016 and 2021 and started chemotherapy as initial treatment were selected from the Netherlands Cancer Registry (NCR). The NCR is a population-based cancer registry hosted by the Netherlands Comprehensive Cancer Organisation (IKNL) that contains information on the diagnosis and treatment of all newly diagnosed malignancies in the Netherlands. Patients treated with chemotherapy in combination with radical cystectomy were excluded. Patient, tumor and treatment information as available through the NCR was complemented with more detailed data concerning treatment and follow-up, which was collected as part of ProBCI (Prospective Bladder Cancer Infrastructure) [14]. The study was approved by the Privacy Review Board of the NCR (reference number K23.199) and the ProBCI Steering Committee.

2.2. Data and definitions

Data used in this study included patient and tumor characteristics (age, sex, comorbidities, performance status, renal function, number and localization of metastases), first-line systemic treatment data (type of treatment, start and stop dates, number of cycles, type of adjustments, main reason for adjustments), and vital status.

Comorbidities were grouped into 0, 1, ≥2 or unknown according to the number of categories of the Charlson comorbidity index [15]. Performance status was grouped into ECOG 0, ECOG 1, ECOG ≥2 or unknown. If performance status was documented as Karnofsky Performance Score, it was converted to ECOG (KPS 100 to ECOG 0, KPS 80−90 to ECOG 1, KPS 10−70 to ECOG ≥2). Renal function was measured in mL/min/1.73m2 and grouped into 0−30, 30−60, 60-90, >90 or unknown. The number of metastatic sites was defined as the number of metastases at different sites (e.g., bone metastases and liver metastases count as 2 sites, but two bone metastases count as 1 site).

Type of first-line chemotherapy was grouped into cisplatin-based chemotherapy, carboplatin-based chemotherapy or other. For patients who started cisplatin-based chemotherapy and switched to carboplatin-based chemotherapy (e.g., due to renal insufficiency), the type of chemotherapy was grouped into cisplatin-based chemotherapy and the cumulative number of cycles was calculated. Since 4 to 6 cycles of cisplatin-based or carboplatin-based chemotherapy are recommended in the guidelines [3], receiving ≥4 cycles was considered a full course of treatment in this study (full course group).

Treatment adjustments were grouped into: dose reduction, postponement of a new treatment cycle, discontinuation of one of the chemotherapy agents, a combination of these adjustments or other adjustment. Reason for the adjustment was grouped into: hematological toxicity, gastro-intestinal toxicity, neurological toxicity, other toxicities or patient condition, non-response or progressive disease, wish of the patient and/or family, or other/unknown reason.

Information on vital status in the NCR is available by annual linkage of the NCR to the Dutch Personal Records Database and was updated until February 1, 2023.

2.3. Statistical analyses

The number of patients receiving first-line chemotherapy and the number of cycles received were presented using descriptive statistics. Logistic regression analyses were used to determine which factors were independently associated with receiving a full course of treatment. Univariable and multivariable regression analyses included age, sex, comorbidities, performance status, renal function, and the number and localization of metastatic sites, which reflect patient fitness, cancer burden and treatment eligibility, and were therefore expected to influence treatment tolerability and efficacy [3,16,17]. This analysis was also stratified by type of chemotherapy (cisplatin versus carboplatin-based). Factors independently associated with receiving a full course of treatment without dose reductions were determined using logistic regression analysis in a post hoc analysis of patients who received ≥4 cycles. In the subgroup of patients who completed a full course of treatment, the proportion of treatment adjustments and reasons for these adjustments were described. In addition, insight was provided into the proportion of patients who died within one month of stopping treatment, overall and stratified by patients who received <4 and ≥4 cycles. Statistical analyses were performed using Stata version 17.0 software. A two-tailed p value <0.05 was considered statistically significant.

3. Results

3.1. Cohort

A total of 684 patients diagnosed with synchronous mBC and treated with first-line chemotherapy between 2016 and 2021 were identified from the NCR (Table 1). The majority of patients were aged 70−79 years (39%), male (71%), and had ECOG performance status 0 or 1 (67%). Most patients had one metastatic site (61%), with the most common sites being the lymph nodes (58%), followed by bone (33%) and lung (29%).

3.2. Treatment patterns

Of the 684 patients receiving first-line chemotherapy, 297 (43%) received cisplatin-based chemotherapy, 370 (54%) received carboplatin-based chemotherapy and 17 (3%) received other chemotherapy. In the overall group, 35% of patients received <4 cycles of chemotherapy and 57% received a full course of treatment (>4 cycles) (Fig. 1). There were slight differences between cisplatin-based and carboplatin-based chemotherapy (<4 cycles: 31% vs. 40%; > 4 cycles: 59% vs. 57%). Among patients receiving <4 cycles (n=241), 80 patients (13%) stopped treatment after 1 cycle, 64 (10%) after 2 cycles, and 97 (15%) after 3 cycles (Fig. 2). In the overall group, 11% of patients died within one month of stopping their chemotherapy treatment (Table 2). This was 24% in those who received <4 cycles of chemotherapy and 3% in those who received ≥4 cycles.

3.3. Factors associated with receiving a full course of treatment

Age, number of comorbidities, renal function and the number of metastatic sites were comparable between patients receiving a full course of treatment and patients receiving <4 cycles (Table 1). Patients who received a full course of treatment were more often male (74% vs. 66%, $P = 0.02$), had a better performance status (ECOG 0: 47% vs. 26%, $p \leq 0.001$) and slightly less often liver metastases (16% vs. 22%, $P = 0.04$) or lung metastases (27% vs. 35%, $P = 0.03$). The proportion of patients with lymph node metastases was higher in the full course group (61% vs. 52%, $P = 0.02$).

Multivariable regression analysis showed that sex and performance status were independently associated with receiving a full course of treatment (≥4 cycles) (Table 3). Female patients were less likely to receive a full course of treatment compared to male patients. Patients with a poorer performance status at diagnosis (ECOG ≥1) were also less likely to receive a full course of treatment compared to patients with a better performance status (ECOG 0). Stratified analyses by type of chemotherapy showed that sex was still associated with receiving a full course of treatment of cisplatin-based chemotherapy, whereas performance status remained associated with receiving a full course of treatment of carboplatin-based chemotherapy (supplementary tables 1 and 2). Among patients who received a full course of treatment, older age was independently associated with lower odds of receiving a full course of treatment without dose reductions (supplementary table 3).

3.4. Adjustments in treatment schedules

Among patients who received a full course of treatment (≥4 cycles, n=396), 50% were required to have their treatment schedule adjusted. The most commonly reported adjustment was dose reduction (52%), followed by postponement of a new treatment cycle (21%) and a combination of dose reduction and postponement of a new treatment cycle (23%). Hematological toxicity was the most commonly reported reason for these adjustments (47%), followed by other toxicities or impairments in the patient's condition (33%). Gastro-intestinal or neurological toxicity were each reported to be the main reason for adjustment in 4% of patients.

4. Discussion

This study provides insight into first-line palliative chemotherapy treatment patterns, including the number of cycles received, treatment adjustments and reasons for

Table 1
Characteristics of patients with synchronous metastatic bladder cancer receiving first-line chemotherapy for the total cohort and stratified by <4 and ≥4 cycles of chemotherapy

	Total cohort	Characteristics by number of cycles received	
	N (%)	< 4 cycles N (%)	≥4 cycles N (%)
Total number of patients	684	241	396
Characteristics at diagnosis			
Age			
<60	142 (21)	50 (21)	80 (20)
60-69	237 (35)	83 (34)	136 (34)
70-79	271 (39)	99 (41)	155 (39)
80+	34 (5)	9 (4)	25 (6)
Sex			
Male	486 (71)	158 (66)	293 (74)
Female	198 (29)	83 (34)	103 (26)
Number of comorbidities			
0	307 (45)	111 (46)	186 (47)
1	196 (29)	74 (31)	115 (29)
≥2	111 (16)	47 (20)	62 (16)
Unknown	70 (10)	9 (4)	33 (8)
Performance status			
ECOG 0	258 (38)	63 (26)	186 (47)
ECOG 1	195 (29)	89 (37)	103 (26)
ECOG ≥2	38 (6)	23 (10)	15 (4)
Unknown	193 (28)	66 (27)	92 (23)
Renal function (mL/min/1.73m2)			
0-30	27 (4)	11 (5)	15 (4)
30-60	203 (30)	82 (34)	118 (30)
60-90	275 (40)	97 (40)	170 (43)
90+	85 (12)	31 (13)	53 (13)
Unknown	94 (14)	20 (8)	40 (10)
Number of metastatic sites			
1	418 (61)	140 (58)	253 (64)
2	161 (24)	57 (24)	89 (23)
≥3	105 (15)	44 (18)	54 (14)
Localization of metastases[a]			
Liver	123 (18)	53 (22)	62 (16)
Lung	201 (29)	84 (35)	107 (27)
Bone	223 (33)	87 (36)	123 (31)
Lymph nodes	395 (58)	124 (52)	242 (61)
Other	128 (19)	49 (20)	67 (17)

[a] Percentages do not add to 100% because patients may have metastases at multiple localizations.

these adjustments in a population-based cohort of 684 patients with synchronous mBC. A substantial proportion of patients who started chemotherapy did not complete a full course of treatment cycles as recommended by guidelines. Male sex and good performance status were independently associated with receiving the full course of treatment. In approximately half of the patients with a full course of treatment, treatment adjustments, mainly dose reductions due to side effects, were made.

Among patients starting first-line palliative chemotherapy, approximately 4 in 10 patients completed fewer than the 4 to 6 cycles recommended by guidelines. Not completing the full guideline-recommended treatment schedule was independently associated with a worse performance status, probably because patients with poorer physical condition prior to treatment are likely to have more difficulty tolerating the treatment. Female patients were also less likely to complete 4 or more cycles. Several factors may contribute to this. First, women are at greater risk for toxicity and adverse drug reactions from systemic therapies [18], which may contribute to women discontinuing treatment earlier. In addition, the patient's living situation and level of social support may play a role. Women are less likely to be married than men in the Dutch elderly population. [19] Living alone and therefore a lack of spousal support in female patients may contribute to different treatment choices and earlier treatment discontinuation. Previous studies suggest that patients living alone receive less or less intensive chemotherapy, and that oncologists are more reluctant to treat patients living alone with chemotherapy because of concerns about managing toxicities. [20−23] In addition, physician adherence to guidelines may also play a

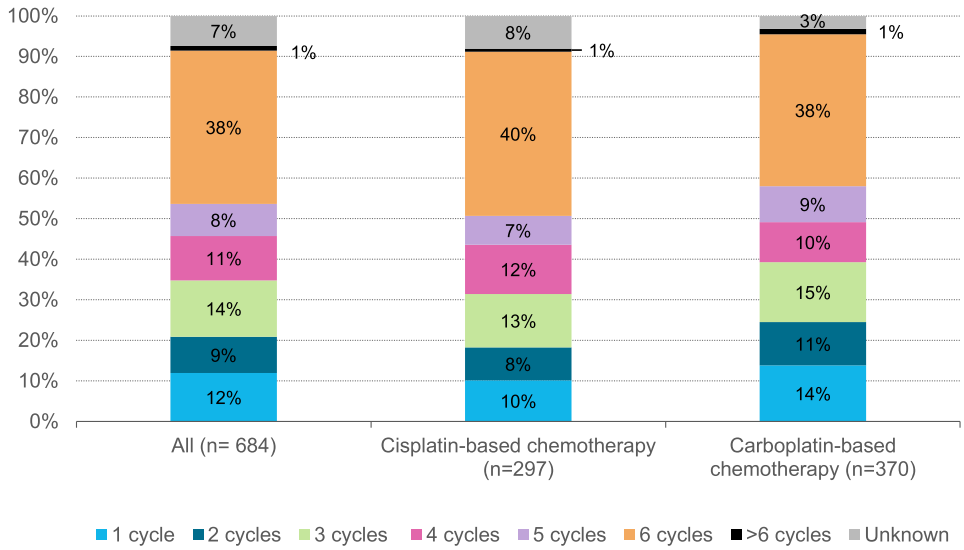

Fig. 1. Number of treatment cycles received among patients with synchronous metastatic bladder cancer who received first-line chemotherapy for the total group of patients and stratified by type of chemotherapy.

role in guideline deviation, with barriers to guideline adherence including physician awareness of guidelines, guidelines perceived as too generic, concerns about the evidence supporting guideline recommendations, limited access to treatment resources, and limited or negative experience with the recommended treatment [24].

This study shows that even in case of a full course of chemotherapy, in nearly half of the patients their treatment schedule had to be adjusted, most commonly by reducing the dose or postponing a new cycle of treatment. This is consistent with studies in advanced breast, lung and ovarian cancer, which showed that approximately 50% of patients required dose reduction or dose delay [25,26]. Dose reductions were the most commonly reported adjustment in this study and probably result in suboptimal disease control and treatment benefits. This is confirmed by the results of a systematic review and meta-analysis that showed that patients with advanced cancer who received less than 80 percent of the standard dose of chemotherapy had worse survival than patients who received more than 80 percent of the standard dose [27].

Overall, patients were more often treated with carboplatin-based chemotherapy compared to cisplatin-based

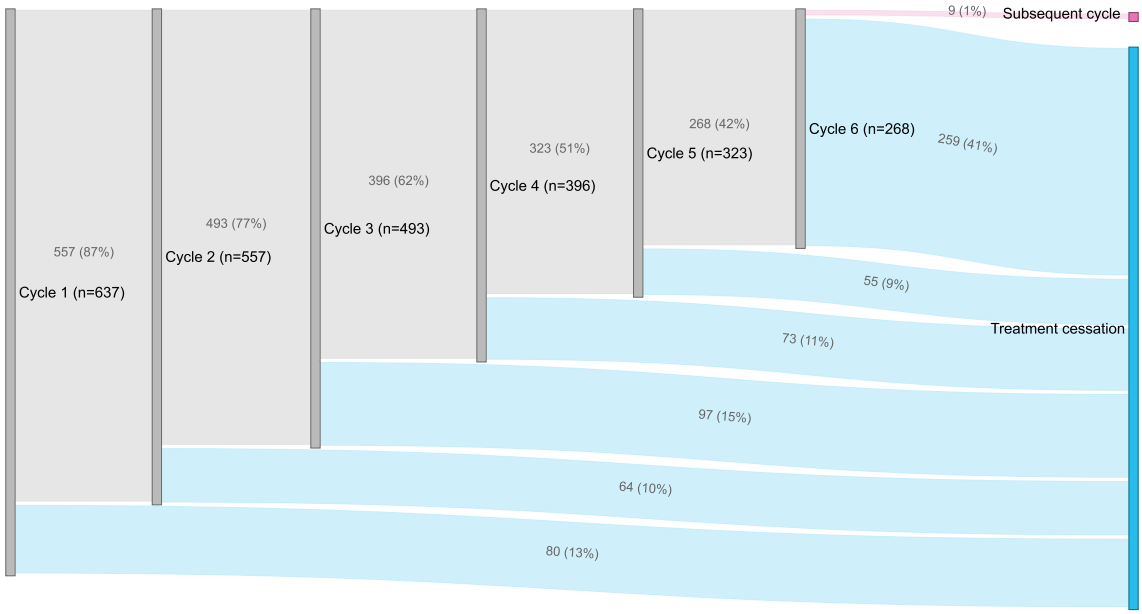

Fig. 2. Timing of treatment cessation in patients receiving first-line chemotherapy for synchronous metastatic bladder cancer. Data shown only for patients with known number of cycles.

Table 2
Proportion of patients dying within one month of treatment cessation among all patients receiving first-line chemotherapy for synchronous metastatic bladder cancer and stratified by <4 and ≥4 cycles of chemotherapy.

	Total number of patients	Death <31 days of stopping treatment
	N	N (%)
All patients receiving first-line chemotherapy	684	74 (11)
<4 cycles	241	59 (24)
≥4 cycles	396	12 (3)

Table 3
Unadjusted and adjusted odds ratios for the probability of receiving ≥4 cycles of first-line chemotherapy in patients with synchronous metastatic bladder cancer

	Probability of receiving ≥4 cycles	
	Univariable OR (95% CI)	Multivariable OR (95% CI)
Characteristics at diagnosis		
Age		
<60	Ref	Ref
60−69	1.02 (0.66−1.59)	1.02 (0.63−1.66)
70−79	0.97 (0.63−1.51)	0.98 (0.60−1.61)
80+	1.73 (0.74−4.02)	2.01 (0.81−4.95)
Sex		
Male	Ref	Ref
Female	0.66 (0.47−0.94) [a]	0.64 (0.44−0.94) [a]
Number of comorbidities		
0	Ref	Ref
1	0.93 (0.63−1.34)	0.88 (0.58−1.32)
≥2	0.78 (0.50−1.22)	0.74 (0.46−1.21)
Unknown	2.18 (1.00−4.74) [a]	2.43 (1.08−5.47) [a]
Performance status		
ECOG 0	Ref	Ref
ECOG 1	0.39 (0.26−0.59) [a]	0.40 (0.36−0.60) [a]
ECOG ≥2	0.22 (0.11−0.45) [a]	0.23 (0.10−0.49) [a]
Unknown	0.47 (0.30−0.72) [a]	0.47 (0.30−0.73) [a]
Renal function (mL/min/1.73m2)		
0−30	Ref	Ref
30−60	1.05 (0.46−2.41)	1.07 (0.45−2.56)
60−90	1.28 (0.56−2.90)	1.26 (0.53−2.99)
90+	1.25 (0.51−3.06)	1.28 (0.49−3.32)
Unknown	1.46 (0.56−3.77)	1.39 (0.51−3.79)
Number of metastatic sites±		
1	Ref	Ref
2	0.86 (0.58−1.27)	1.18 (0.52−2.66)
≥3	0.67 (0.43−1.06)	1.19 (0.24−5.75)
Localization of metastases		
Liver	0.65 (0.43−0.98) [a]	0.60 (0.27−1.31)
Lung	0.69 (0.48−0.97) [a]	0.62 (0.28−1.35)
Bone	0.79 (0.56−1.11)	0.74 (0.34−1.63)
Lymph nodes	1.48 (1.07−2.04) [a]	1.07 (0.50−2.32)
Other	0.79 (0.53−1.20)	0.78 (0.34−1.76)

[a] indicates a significant result ($P < 0.05$).

chemotherapy, only a small minority received the guideline-recommended number of treatment cycles, and even these latter patients often required treatment adjustments. These results indicate that it is difficult to adhere to guideline-recommended treatment for a large proportion of patients, likely resulting in poorer outcomes than expected based on the results of randomized trials. Among patients who received less than the recommended number of treatment cycles, one-fifth died within one month of stopping treatment. This suggests that starting chemotherapy may not have been the most appropriate care for these patients [10] and underscores the importance of providing patients with a realistic understanding of both the likely benefits and burdens of chemotherapy. In this way they can make informed decisions about whether the proposed treatment is in line with their expectations, wishes and preferences. Therefore, in addition to informing patients with mBC about the expected toxicities and survival benefits, it is important to discuss scenarios that may occur after initiation of chemotherapy, including early discontinuation and adjustments to treatment schedules, as this occurs in a significant proportion of patients. This can help to manage the patient's expectations and may reduce feelings of disappointment and failure during the treatment process. Moreover, information regarding treatment patterns from real-world data can inform guideline development.

This study showed that adhering to guideline-recommended treatment is challenging, which clearly highlights the importance of more effective and less toxic first-line treatment options. Recently, studies using combinations of chemotherapy and checkpoint inhibitors, or a combination of checkpoint inhibitors, have shown promising results in previously untreated patients with mBC [28,29]. These new treatments will probably change the treatment landscape for mBC. However, due to factors such as patient condition and disparities in access to cancer medicines between high-income and low- and middle-income countries [30], it is likely that there will still be patients who are ineligible for these new treatments. Therefore, the treatment of metastatic bladder cancer will most likely continue to involve first-line chemotherapy. Besides, also for these new treatment options, effectiveness and adherence in everyday clinical practice are likely to differ from those observed in the randomized controlled trials. Therefore, it remains important to evaluate the effects and tolerance of these treatments in real-world populations and to incorporate these findings into the shared decision-making process.

5. Strengths and limitations

The main strength of this study is the use of population-based data of all patients diagnosed with synchronous mBC in the Netherlands, thereby reflecting daily clinical practice. However, there are some limitations. First, no data were available on the reasons why patients discontinued their chemotherapy regimen, making it impossible to assess

whether patients stopped because of treatment toxicity, disease progression, or at their own request. Second, there was no complete data on the exact dose of chemotherapy received, nor on the weight of the patients, so the relative dose intensity of the chemotherapy received could not be calculated. This information would have been helpful in providing a more accurate assessment of the extent of dose reductions in this population. Third, patients with metachronous metastases were not included in this study. Because these patients have received prior treatment, unlike patients with synchronous disease, this may affect their eligibility for and tolerability of systemic treatment for their metastatic disease. Therefore, treatment patterns and treatment alterations may be different in these patients.

6. Conclusion

This population-based study showed that among patients with metastatic bladder cancer receiving first-line chemotherapy, only a small majority received the guideline recommended number of treatment cycles. Adjustments to treatment schedules and dose reductions were common. These results highlight the importance of incorporating evidence about treatment discontinuation and adjustments into the shared decision-making process and guideline development.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Ellis Slotman: Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Anke Richters:** Writing – review & editing, Methodology, Conceptualization. **Heidi P. Fransen:** Writing – review & editing, Conceptualization. **Tineke J. Smilde:** Writing – review & editing. **Yvette M. van der Linden:** Writing – review & editing, Supervision. **Sabine Siesling:** Writing – review & editing, Supervision. **Katja K.H. Aben:** Writing – review & editing. **Natasja J. H. Raijmakers:** Writing – review & editing, Supervision, Conceptualization.

Funding

This study was carried out with data from the Prospective Bladder Cancer Infrastructure (ProBCI). ProBCI received funding for the set-up and maintenance of the infrastructure from Astellas, AstraZeneca, BMS, and Merck, paid to the Netherlands Comprehensive Cancer Organisation. The funding parties played no role in the conception, execution, or reporting of research reported in the manuscript.

Acknowledgments

The authors thank the registration team of the Netherlands Comprehensive Cancer Organisation (IKNL) for the collection of data for the Netherlands Cancer Registry.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urolonc.2024.10.026.

References

[1] Zang Y, Li X, Cheng Y, Qi F, Yang N. An overview of patients with urothelial bladder cancer over the past two decades: a surveillance, epidemiology, and end results (SEER) study. Ann Transl Med 2020;8 (23):1587. https://doi.org/10.21037/atm-20-2108.

[2] Netherlands Comprehensive Cancer Organisation (IKNL). Survival by years after diagnosis, Relative Survival, Bladder, Stage IV. Accessed February 7, 2024. https://nkr-cijfers.iknl.nl/viewer/relatieve-overleving-per-jaren-na-diagnose?language=en_GB&viewerId=59bcb054-567d-46a0-8f64-3a75ec640b77.

[3] Alfred Witjes J, Max Bruins H, Carrión R, et al. European association of urology guidelines on muscle-invasive and metastatic bladder cancer: summary of the 2023 guidelines. Eur Urol 2024;85(1):17–31. https://doi.org/10.1016/j.eururo.2023.08.016.

[4] Elting LS, Cooksley C, Bekele BN, et al. Generalizability of cancer clinical trial results: prognostic differences between participants and nonparticipants. Cancer 2006;106(11):2452–8.

[5] Kennedy-Martin T, Curtis S, Faries D, Robinson S, Johnston J. A literature review on the representativeness of randomized controlled trial samples and implications for the external validity of trial results. Trials 2015;16:1–14.

[6] Swami U, Grivas P, Pal SK, Agarwal N. Utilization of systemic therapy for treatment of advanced urothelial carcinoma: lessons from real world experience. Cancer Treat Res Commun 2021;27:100325. https://doi.org/10.1016/j.ctarc.2021.100325.

[7] Richters A, Mehra N, Meijer RP, et al. Utilization of systemic treatment for metastatic bladder cancer in everyday practice: results of a nation-wide population-based cohort study. Cancer Treat Res Commun 2020;25:100266. https://doi.org/10.1016/j.ctarc.2020.100266.

[8] Lindhardt CL, Winther SB, Pfeiffer P, Ryg J. Information provision to older patients receiving palliative chemotherapy: a quality study. BMJ Support Palliat Care 30 2021. https://doi.org/10.1136/bmjspcare-2021-003074.

[9] Grunfeld EA, Maher EJ, Browne S, et al. Advanced breast cancer patients' perceptions of decision making for palliative chemotherapy. J Clin Oncol 2006;24(7):1090–8. https://doi.org/10.1200/jco.2005.01.9208.

[10] Earle CC, Park ER, Lai B, Weeks JC, Ayanian JZ, Block S. Identifying potential indicators of the quality of end-of-life cancer care from administrative data. J Clin Oncol 2003;21(6):1133–8. https://doi.org/10.1200/JCO.2003.03.059:2003/03/15.

[11] Bolt EE, Pasman HR, Willems D, Onwuteaka-Philipsen BD. Appropriate and inappropriate care in the last phase of life: an explorative study among patients and relatives. BMC Health Serv Res 2016;16 (1):655. https://doi.org/10.1186/s12913-016-1879-3.

[12] Zhang B, Nilsson ME, Prigerson HG. Factors important to patients' quality of life at the end of life. Arch Intern Med 2012;172 (15):1133–42. https://doi.org/10.1001/archinternmed.2012.2364.

[13] Ham L, Slotman E, Burghout C, et al. Potentially inappropriate end-of-life care and its association with relatives' well-being: a systematic review. Support Care Cancer 2023;31(12):731. https://doi.org/10.1007/s00520-023-08198-0.

[14] Richters A, Meijer RP, Mehra N, et al. Prospective bladder cancer infrastructure for experimental and observational research on bladder cancer: study protocol for the 'trials within cohorts' study ProBCI. BMJ Open 2021;11(5):e047256. https://doi.org/10.1136/bmjopen-2020-047256.

[15] Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. J Chronic Dis 1987;40(5):373–83. https://doi.org/10.1016/0021-9681(87) 90171-8:1987/01/01/.

[16] Shou J, Zhang Q, Zhang D. The prognostic effect of metastasis patterns on overall survival in patients with distant metastatic bladder cancer: a SEER population-based analysis. World J Urol 2021;39 (11):4151–8. https://doi.org/10.1007/s00345-021-03721-6.

[17] Bellmunt J, Albanell J, Paz-Ares L, et al. Pretreatment prognostic factors for survival in patients with advanced urothelial tumors treated in a phase I/II trial with paclitaxel, cisplatin, and gemcitabine. Cancer 2002;95(4):751–7. https://doi.org/10.1002/cncr.10762.

[18] Unger JM, Vaidya R, Albain KS, et al. Sex differences in risk of severe adverse events in patients receiving immunotherapy, targeted therapy, or chemotherapy in cancer clinical trials. J Clin Oncol 2022;40(13):1474–86. https://doi.org/10.1200/jco.21.02377.

[19] Centraal Bureau voor de Statistiek (CBS). Bevolking; geslacht, leeftijd en burgerlijke staat. Accessed January 19, 2024. https://opendata.cbs.nl/#/CBS/nl/dataset/7461bev/table?ts=1705659221242</bib>

[20] Cavalli-Björkman N, Qvortrup C, Sebjørnsen S, et al. Lower treatment intensity and poorer survival in metastatic colorectal cancer patients who live alone. Br J Cancer 2012;107(1):189–94. https://doi.org/10.1038/bjc.2012.186.

[21] Ahmed S, Baig T, Iqbal N, et al. Effects of social and contextual factors including marital status and children on the use of palliative chemotherapy in metastatic colorectal cancer. Am J Clin Oncol 2019;42 (4):363–6. https://doi.org/10.1097/coc.0000000000000530.

[22] Randén M, Helde-Frankling M, Runesdotter S, Strang P. Treatment decisions and discontinuation of palliative chemotherapy near the end-of-life, in relation to socioeconomic variables. Acta Oncol 2013;52(6):1062–6. https://doi.org/10.3109/0284186x.2012.758872.

[23] Cavalli-Björkman N, Glimelius B, Strang P. Equal cancer treatment regardless of education level and family support? A qualitative study of oncologists' decision-making. BMJ Open 2012;2(4). https://doi.org/10.1136/bmjopen-2012-001248.

[24] Bierbaum M, Rapport F, Arnolda G, et al. Clinicians' attitudes and perceived barriers and facilitators to cancer treatment clinical practice guideline adherence: a systematic review of qualitative and quantitative literature. Implement Sci 2020;15(1):39. https://doi.org/10.1186/s13012-020-00991-3.

[25] Crawford J, Denduluri N, Patt D, et al. Relative dose intensity of first-line chemotherapy and overall survival in patients with advanced non-small-cell lung cancer. Support Care Cancer 2020;28(2):925–32. https://doi.org/10.1007/s00520-019-04875-1.

[26] Denduluri N, Lyman GH, Wang Y, et al. Chemotherapy Dose Intensity and Overall Survival Among Patients With Advanced Breast or Ovarian Cancer. Clin Breast Cancer 2018;18(5):380–6. https://doi.org/10.1016/j.clbc.2018.02.003.

[27] Nielson CM, Bylsma LC, Fryzek JP, Saad HA, Crawford J. Relative dose intensity of chemotherapy and survival in patients with advanced stage solid tumor cancer: a systematic review and meta-analysis. Oncologist 2021;26(9):e1609–18. https://doi.org/10.1002/onco.13822.

[28] Powles T, Valderrama BP, Gupta S, et al. LBA6 EV-302/KEYNOTE-A39: open-label, randomized phase III study of enfortumab vedotin in combination with pembrolizumab (EV+ P) vs chemotherapy (Chemo) in previously untreated locally advanced metastatic urothelial carcinoma (la/mUC). Ann Oncol 2023;34:S1340.

[29] van der Heijden M, Sonpavde G, Powles T, et al. LBA7 Nivolumab plus gemcitabine-cisplatin versus gemcitabine-cisplatin alone for previously untreated unresectable or metastatic urothelial carcinoma: Results from the phase III CheckMate 901 trial. Ann Oncol 2023;34:S1341.

[30] Mayor S. Differences in availability of cancer drugs across Europe. Lancet Oncol 2016;17(9):1196. https://doi.org/10.1016/s1470-2045(16)30378-3.