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Efficacy of chemotherapy on overall survival in metastatic sarcomatoid bladder cancer patients

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Introduction The role of chemotherapy in metastatic sarcomatoid bladder cancer (mSBC) is unknown. The current work aimed to test the effect of chemotherapy on overall survival (OS) in mSBC patients.

Material and methods Using the Surveillance, Epidemiology and End Results database (2001–2018), we identified 110 mSBC patients of all T and N stages ($T_{any}N_{any}M_1$). Kaplan-Meier plots and Cox regression models were used. Covariates consisted of type of surgical treatment (no treatment vs radical cystectomy vs other), and patient age. The endpoint of interest was OS.

Results In 110 mSBC patients, 46 (41.8%) were exposed to chemotherapy vs 64 (58.2%) who were chemotherapy naive. Chemotherapy exposed patients were younger (median age 66 vs 70, p = 0.005). Median OS was 8 months in chemotherapy exposed vs 2 months in chemotherapy naive patients. In univariable Cox regression models, chemotherapy exposure was associated with a hazard ratio (HR) of 0.58 (p = 0.007). In multivariable Cox regression models adjusted for case mix, chemotherapy exposure was associated with a HR of 0.60 (p = 0.016).

Conclusions To the best of our knowledge, this is the first report of chemotherapy effect on OS in mSBC patients. OS is extremely poor. Nonetheless, it is improved in a statistically significant and clinically meaningful fashion, when chemotherapy is administered.

Key Words: bladder ‹› cancer ‹› metastatic ‹› chemotherapy ‹› sarcomatoid

INTRODUCTION

Chemotherapy represents the mainstay in the treatment of metastatic urothelial cancer of the urinary bladder (mUCUB) [1, 2]. According to randomized clinical trials and retrospective comparative studies, median overall survival (OS) ranges from 12.0 to 14.8 months in chemotherapy exposed patients vs 4.0 to 5.5 months in chemotherapy naive patients [3–8]. However, such data are unavailable for metastatic sarcomatoid bladder cancer (mSBC) patients. In consequence, it is unknown what median OS estimates to expect in either chemotherapy exposed or chemotherapy naïve mSBC patients.

We addressed these knowledge gaps and tested the effect of chemotherapy on OS in mSBC patients. We hypothesized that chemotherapy might be associated with higher OS. We relied on the Surveillance, Epidemiology and End Results [Surveillance, Epidemiology, and End Results (SEER) 2001–2018] database.

MATERIAL AND METHODS

Study population

The SEER database samples 34.6% of the United States population in terms of demographic composition and cancer incidence [9]. Within the SEER database (2001–2018), we identified patients aged ≥18 years, with histologically confirmed bladder cancer (BCa) (International Classification of Disease for Oncology [ICD-O] site code C67.0–67.9), who harbored SBC histology (ICD-O code: 8122-sarcomatoid). According to the 2016 World Health Organization (WHO) classification of bladder tumors, we only included metastatic ($T_{any}N_{any}M_1$) patients (codes: 8120, 8130) [10, 11]. Autopsy or death certificate only cases were excluded.

Statistical analyses

Kaplan-Meier plots and Cox regression models addressed OS. Covariates consisted of type of surgical treatment (no treatment vs radical cystectomy vs other), and patient age (continuous). In all statistical analyses, R software environment for statistical computing and graphics (R version 4.1.2; R Foundation for Statistical Computing, Vienna, Austria) was used [12]. All tests were two sided, with a level of significance set at $p < 0.05$. Owing to the anonymously coded design of the SEER database, study-specific ethics approval was waived by the institutional review board.

RESULTS

Descriptive characteristics of the mSBC patients cohort

Within the SEER database (2001–2018), 110 mSBC patients of all T and N stages ($T_{any}N_{any}M_1$) were identi-

Table 1. *Descriptive characteristics of 110 metastatic sarcomatoid bladder cancer (mSBC) patients, according to chemotherapy exposure status*

Characteristic	Overall, n = 110[1]	Chemotherapy naive, n = 64[1] (58.2%)	Chemotherapy exposed, n = 46[1] (41.8%)	p-value[2]
Age	69 (60, 77)	70 (64, 80)	66 (56, 74)	0.005
Sex				>0.9
Female	34 (30.9%)	20 (31.3%)	14 (30.4%)	
Male	76 (69.1%)	44 (68.7%)	32 (69.6%)	
T stage				0.4
T1	9 (8.2%)	8 (12.5%)	1 (2.2%)	
T2	34 (30.9%)	19 (29.7%)	15 (32.6%)	
T3	21 (19.1%)	12 (18.8%)	9 (19.6%)	
T4	29 (26.4%)	15 (23.4%)	14 (30.4%)	
TX	17 (15.4%)	10 (15.6%)	7 (15.2%)	
N stage				0.2
N0	54 (49.1%)	28 (43.7%)	26 (56.5%)	
N1	10 (9.1%)	9 (14.1%)	1 (2.2%)	
N2	23 (20.9%)	14 (21.8%)	9 (19.6%)	
N3	1 (0.9%)	1 (1.6%)	0	
NX	22 (20.0%)	12 (18.8%)	10 (21.7%)	
Surgical treatment				0.8
None	10 (9.1%)	7 (10.9%)	3 (6.5%)	
Partial cystectomy or TURBT	72 (65.4%)	41 (64.1%)	31 (67.4%)	
Radical cystectomy	28 (25.5%)	16 (25.0%)	12 (26.1%)	

N – number of patients; TURBT – transurethral resection of bladder tumor
[1]Median (IQR – interquartile range)
[2]Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test

Table 2. *Univariable and multivariable Cox regression analyses predicting overall survival (OS) in 110 metastatic sarcomatoid bladder cancer patients (mSBC)*

Characteristic	Univariable			Multivariable		
	HR	95% CI	p-value	HR	95% CI	p-value
Age	1.01	1.00, 1.03	0.14	1.008	0.990, 1.027	0.359
Chemotherapy exposure (vs no chemotherapy)	0.58	0.39, 0.86	0.007	0.603	0.399, 0.911	0.016
Surgical treatment (radical cystectomy vs none)	0.77	0.36, 1.66	0.51	0.954	0.435, 2.094	0.907
Surgical treatment (other[1] vs none)	0.84	0.41, 1.69	0.62	0.918	0.447, 1.886	0.816

HR – hazard ratio; CI – confidence interval
[1]Other – partial cystectomy or transurethral resection of the bladder tumor

fied (Table 1). Of those, 46 (41.8%) patients received chemotherapy vs 64 (58.2%) patients who did not. Chemotherapy exposed patients were younger (median age 66 vs 70, p = 0.005). No differences were recorded in sex, T and N stages, as well as surgical treatment.

Effect of chemotherapy on over survival

Median OS was 8.0 months (interquartile range [IQR]: 6–10) for chemotherapy exposed vs 2.0 months (IQR: 2.0–4.0) for chemotherapy naive patients, respectively (Figure 1). These median OS values corresponded to an univariable hazard ratio (HR) of 0.58 (CI 0.39–0.86, p = 0.007). In multivariable Cox regression models (Table 2), the association between chemotherapy vs no chemotherapy resulted in a HR of 0.60 (CI 0.39–0.91, p = 0.016).

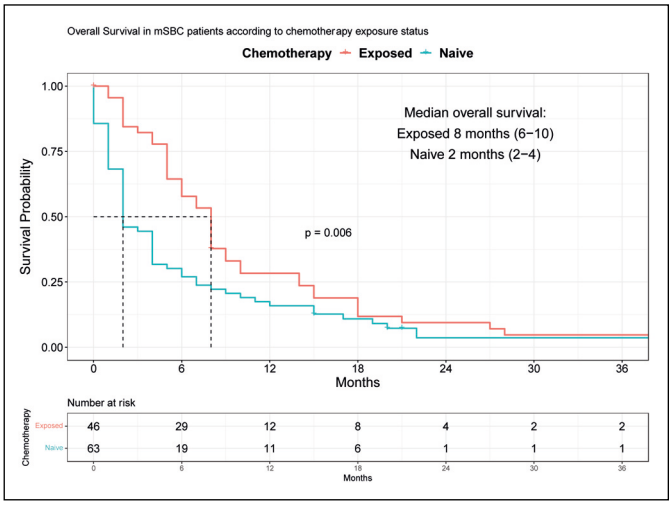

Figure 1. *Kaplan-Meyer curves of overall survival (OS) according to chemotherapy exposure status in metastatic sarcomatoid bladder cancer patients (mSBC).*

DISCUSSION

No data exist regarding chemotherapy exposure rates, as well as chemotherapy efficacy in mSBC patients. We addressed this knowledge gap and tested the effect of chemotherapy on OS in mSBC patients. We hypothesized that chemotherapy might be associated with higher OS. We made several noteworthy observations.

First, mSBC represents an orphan entity. Within the SEER database (2001–2018), we identified only 110 mSBC patients. To the best of our knowledge this is the largest ever reported population-based cohort of mSBC. Despite its largest sample size, the relatively limited numbers of observations attest to the rarity of this mUCUB variant. Other existing studies addressing mSBC relied on substantially smaller sample sizes (from 4 to 55 patients) [13–16]. Specifically, two large-scale population-based studies by Diamantopoulos et al. [15] and Sui et al. [16] described the second and the third ever reported mSBC cohorts, that respectively included 55 and 40 patients. However, neither addressed chemotherapy rates or chemotherapy efficacy.

Second, nowadays no specific standard of care has been established relative to mSBC, reasonably due to the extreme paucity of evidence about the best management of such a rare entity [17]. Chemotherapy exposure rate in the current study was 41.8% (n = 46). This chemotherapy exposure rate could not be compared to other mSBC studies, since such studies did not explicitly report chemotherapy rates [13–16]. With the due caution, a suitable mean of comparison for mSBC may be represented by mUCUB, whose standard treatment is platinum-based systemic therapy [2, 4]. Chemotherapy rates in retrospective mUCUB studies ranged from 46.2 to 47.0% [6, 18, 19]. The discrepancy between 41.8% chemotherapy rate in mSBC patients observed in the current study vs 46.2 to 47.0% in studies addressing mUCUB is consistent with less established role and efficacy of chemotherapy in mSBC setting [1]. In consequence, it is not surprising to note somewhat lower rate than in mUCUB.

Finally, we addressed the effect of chemotherapy on OS in mSBC patients. The recorded median OS

values of 8.0 vs 2.0 months in, respectively, chemotherapy exposed vs chemotherapy naive patients, resulted in univariable and multivariable HRs of 0.58 (p = 0.007) and 0.60 (p = 0.016). These HRs reflect a clinically meaningful and statistically significant protective effect of chemotherapy in mSBC patients. However, this protective effect cannot be directly compared to other mSBC studies since such studies do not exist. Conversely, within the bounds of the above-mentioned word of caution, it may be compared to the effect of chemotherapy in mUCUB studies. The observed HR of 0.60 is less favorable than HRs recorded for chemotherapy in mUCUB studies. Specifically, Sorce et al. and Shou et al. reported respective HRs of 0.43 and 0.46 in mUCUB patients [6, 7]. Less protective HR of 0.60 recorded in the current study addressing mSBC vs lower and more protective HRs recorded for mUCUB are consistent with more aggressive nature of mSBC relative to mUCUB [17, 20].

Our study has several limitations. First, our database did not have the benefit of central review to validate histological subgroup assignment. Second, the population-based nature of the study does not allow a detailed analysis of the number, duration, and type of systemic therapy that was administered. Third, lack of information about laboratory values and comorbidities, which could affect treatment characteristics, are unavailable in the SEER database. Finally, the SEER database only includes patients from the United States and our findings may not be generalized to patients with mSBC from other parts of the world. These, as well as all other limitations related to the retrospective, population-based nature of the SEER database, apply to this study, as well as to other similar analyses that were based on other similar large-scale data repositories.

CONCLUSIONS

To the best of our knowledge, this is the first report of chemotherapy effect on OS in mSBC patients. OS is extremely poor. Nonetheless, it is improved in a statistically significant and clinically meaningful fashion when chemotherapy is administered.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

All data generated for this analysis were from the Surveillance, Epidemiology, and End Results Research Plus (SEER) database. The code for the analyses will be made available upon request.

ETHICS CONSENT STATEMENT

All analyses and their reporting followed the SEER reporting guidelines. Due to the anonymously coded design of the SEER database, study-specific Institutional Review Board ethics approval was not required.

AUTHORS' CONTRIBUTIONS

Stefano Tappero: concept and design; draft of manuscript; statistical analysis; analysis and interpretation of the data; draft of the manuscript

Gabriele Sorce: acquisition of data; analysis and interpretation of the data; statistical analysis

Andrea Panunzio: acquisition of data; statistical analysis; analysis and interpretation of the data; draft of the manuscript

Lukas Hohenhorst: acquisition of data; analysis and interpretation of the data analysis and interpretation of the data

Cristina Cano Garcia: analysis and interpretation of the data

Mattia Piccinelli: analysis and interpretation of the data

Zhe Tian: concept and design; acquisition of data; statistical analysis

Stefano Parodi: acquisition of data; analysis and interpretation of the data

Felix K. H. Chun: critical revision of the manuscript; important intellectual content

Markus Graefen: critical revision of the manuscript; important intellectual content

Alessandro Antonelli: supervision; critical revision of the manuscript; important intellectual content

Ottavio De Cobelli: supervision; critical revision of the manuscript; important intellectual content

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Francesco Montorsi: supervision; critical revision of the manuscript; important intellectual content

Nazareno R. Suardi: critical revision of the manuscript; important intellectual content

Marco Borghesi: critical revision of the manuscript; important intellectual content

Carlo Terrone: concept and design; supervision; critical revision of the manuscript; important intellectual content

Pierre I. Karakiewicz: concept and design; acquisition of data; draft of manuscript; statistical analysis; supervision; critical revision of the manuscript; important intellectual content

References

1. Witjes JA, Babjuk M, Bellmunt J, et al. EAU-ESMO Consensus Statements on the Management of Advanced and Variant Bladder Cancer- An International Collaborative Multistakeholder Effort Formula presented: Under the Auspices of the EAU-ESMO Guidelines Committees. Eur Urol. 2020; 77: 223-250.
2. Witjes J, Bruins H, Carrión A, et al. Muscle-invasive and Metastatic Bladder Cancer EAU Guidelines on Muscle-invasive and Metastatic Bladder Cancer. EAU Guidelines 2022.
3. Rosenberg JE, Carroll PR, Small EJ. Update on chemotherapy for advanced bladder cancer. J Urol. 2005; 174: 14-20.
4. Bellmunt J, Petrylak DP. New therapeutic challenges in advanced bladder cancer. Semin Oncol. 2012; 39: 598-607.
5. von der Maase H, Hansen SW, Roberts JT, et al. Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study. J Clin Oncol. 2000; 18: 3068-3077. https://doi.org/10.1200/JCO.2000.18.17.3068.
6. Sorce G, Chierigo F, Flammia RS, et al. Survival trends in chemotherapy exposed metastatic bladder cancer patients and chemotherapy effect across different age, sex, and race/ethnicity. Urol Oncol. 2022; 40: 380.e19-380.e27.
7. 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: 4151-4158.
8. von der Maase H, Sengelov L, Roberts JT, et al. Long-term survival results of a randomized trial comparing gemcitabine plus cisplatin, with methotrexate, vinblastine, doxorubicin, plus cisplatin in patients with bladder cancer. J Clin Oncol. 2005; 23: 4602-4608.
9. Howlader N, Noone A, Krapcho M, Miller D, Brest A, Cronin K. Cancer Statistics Review, 1975-2018- SEER Statistics n.d. https://seer.cancer.gov/csr/1975_2018/ (accessed April 13, 2022).
10. Humphrey PA, Moch H, Cubilla AL, Ulbright TM, Reuter VE. The 2016 WHO Classification of Tumours of the Urinary System and Male Genital Organs- Part B: Prostate and Bladder Tumours. Eur Urol. 2016; 70: 106-119.
11. Brierley J, Gospodarowicz MD, Wittekind CT. TNM Classification of Malignant Tumors International Union Against Cancer. 8th. Oxford, England: Wiley; 2017. Wiley 2017; pp. 57-62.
12. The R Project for Statistical Computing n.d. https://www.r-project.org/ (accessed April 13, 2022).
13. Lopez-Beltran A, Pacelli A, Rothenberg HJ, et al. Carcinosarcoma and sarcomatoid carcinoma of the bladder: clinicopathological study of 41 cases. J Urol. 1998; 159: 1497-1503.
14. Wright JL, Black PC, Brown GA, et al. Differences in Survival Among Patients With Sarcomatoid Carcinoma, Carcinosarcoma and Urothelial Carcinoma of the Bladder. J Urol. 2007; 178: 2302-2306.
15. Diamantopoulos LN, Korentzelos D, Alevizakos M, Wright JL, Grivas P, Appleman LJ. Sarcomatoid Urothelial Carcinoma: A Population-Based Study of Clinicopathologic Characteristics and Survival Outcomes. Clin Genitourin Cancer. 2022; 20: 139-147.
16. Sui W, Matulay JT, Onyeji IC, et al. Contemporary treatment patterns and outcomes of sarcomatoid bladder cancer. World J Urol. 2017; 35: 1055-1061.
17. Moschini M, D'Andrea D, Korn S, et al. Characteristics and clinical significance of histological variants of bladder cancer. Nat Rev Urol. 2017; 14: 651-668.
18. Mazzone E, Preisser F, Nazzani S, et al. More Extensive Lymph Node Dissection Improves Survival Benefit of Radical Cystectomy in Metastatic Urothelial Carcinoma of the Bladder. Clin Genitourin Cancer. 2019; 17: 105-113.e2.
19. Klapheke A, Yap SA, Pan K, Cress RD. Sociodemographic disparities in chemotherapy treatment and impact on survival among patients with metastatic bladder cancer. Urol Oncol. 2018; 36: 308.e19-308.e25.
20. Malla M, Wang JF, Trepeta R, Feng A, Wang J. Sarcomatoid Carcinoma of the Urinary Bladder. Clin Genitourin Cancer. 2016; 14: 366-372.