Factors associated with not receiving systemic treatment in patients with metastatic urothelial carcinoma: results of a retrospective observational study in Germany

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SCOPE

- **This retrospective study examined factors associated with undertreatment in patients with metastatic urothelial carcinoma (mUC) using 2 German claims databases (AOK PLUS and GWQ)**
- **Multivariable logistic regression and various methods of cluster analysis were used to inform the results[1,2]**

CONCLUSIONS

- **A substantial proportion (58.6%) of patients with mUC in Germany did not receive systemic anticancer treatment within 12 months of their initial metastasis diagnosis, consistent with previous studies[3]**
- **Older patients with mUC who had several comorbidities were most likely to remain untreated, consistent with previous findings from this study[4-6]**
- **Patients who did not receive systemic anticancer treatment were diagnosed more frequently in smaller hospitals than treated patients**
- **Action is needed to educate practitioners across various healthcare delivery settings on the availability of effective and tolerable mUC treatments. This may reduce disparities in treatment outcomes, especially for older patients with comorbidities**
- **Greater patient education may improve treatment rates, adherence, and outcomes**

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SUPPLEMENTARY DATA

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BACKGROUND

- UC constitutes ≈90% of bladder cancer cases and is one of Germany's most observed cancer types[5,7]
- Approximately 30,000 patients in Germany were newly diagnosed with UC in 2018, with ≈11% diagnosed at an advanced or metastatic stage[5]
- Real-world research has shown significant underutilization of systemic anticancer treatment among patients with mUC[3]
- This retrospective real-world study examined factors and outcomes associated with the receipt or nonreceipt of systemic anticancer treatment in patients with mUC

METHODS

Data source and design

- This study used the AOK PLUS and GWQ German health insurance claims databases. The observational period lasted from 2013 to 2020, and patients with an incident mUC diagnosis (*International Statistical Classification of Diseases, Tenth Revision [ICD-10]* codes C65-68 and C77-79) were identified from 2015 to 2019. Those with other malignant tumors were excluded (**Supplementary Figures 1 and 2**)
- Baseline characteristics within 24 months before mUC diagnosis were analyzed. After index diagnosis, patients were followed up for ≥12 months or until death

Statistical analysis

- Patient characteristics were analyzed descriptively. Overall survival (OS) from diagnosis was calculated using Kaplan-Meier estimation, and a multivariable logistic regression using systemic anticancer treatment receipt as the dependent variable was performed to determine variables associated with receiving first-line systemic anticancer treatment
- Analyses were performed separately for each database, with results first combined using meta-analysis methods and then presented in aggregate form

Cluster analysis

- A cluster analysis was used to identify patient characteristics related to nontreatment. After checking the multicollinearity of available variables, their number was reduced so that only 1 expression of each variable with high correlation (r>0.7) was left in the dataset (eg, only 1 hospitalization variable)
- Hierarchical agglomerative clustering* was performed by first identifying outliers in single linkage by looking for clusters with limited data points. Next, the Ward method was conducted with continuous and binary variables to identify the final patient clusters. The Duda–Hart Je(2)/Je(1) index, associated pseudo T-squared value, and Calinski-Harabasz index were used to confirm the number of clusters
- K-means clustering was used to verify the cluster solution. Finally, patient characteristics were illustrated for each cluster in dichotomized (binary) form using mean values as the cutoff for continuous data

*Algorithm starts with considering each observation as a single cluster, followed by merging pairs of clusters one by one until all observations/(in-between) clusters have been joined into 1 overall cluster. The result of the hierarchical agglomerative clustering is a dendrogram (tree-like depiction of the sequences of merges). Patients are homogeneous within a cluster and heterogeneous compared with patients assigned to other clusters.

RESULTS

Patient demographics

- Of the 3,226 patients with mUC, 70.8% were male, mean (SD) age was 73.8 (10.8) years, mean (SD) Charlson Comorbidity Index (CCI) score was 6.3 (3.8), and mean (SD) Elixhauser Comorbidity Index score was 17.6 (11.4) (**Table 1**)

Treatment patterns and outcomes

- A total of 1,286 patients (39.9%) received systemic anticancer treatment (**Supplementary Figure 2**)
- A total of 1,892 patients (58.6%) with mUC did not receive systemic treatment within 12 months of diagnosis (**Supplementary Figure 2**)

Clinical outcomes

- Median OS from diagnosis was notably shorter in untreated vs treated patients (AOK PLUS, 3.0 vs 13.7 months; GWQ, 3.6 vs 13.8 months, respectively; **Table 1**)
- Untreated patients were substantially older, had more comorbidities, and a higher German care level vs treated patients (aged ≥80 years, 48.2% vs 13.5%; mean [SD] CCI score, 6.8 [3.9] vs 5.5 [3.5]; care level,* 37.5% vs 11.0%, respectively; **Table 1**)
- Multivariable regression analysis revealed that a higher likelihood of not receiving treatment was associated with older age, a higher CCI score, no prior UC-related surgery, systemic or nonsystemic treatment, inpatient† mUC diagnosis, more hospitalizations at baseline, female sex, and being diagnosed in 2015 vs 2019 (**Table 2**)
- Potential contraindications to the administration of systemic anticancer treatment at baseline are presented in **Table 3**
- Nonsystemic UC-related treatments at baseline are summarized in **Table 4**

*The German care level determines the disability grade of a patient and decides which subsidies that insured patients receive from their care insurance fund. The higher the level of care, the higher the level of monetary and material benefits. Data on care level were only available for patients insured with AOK PLUS.

†First diagnosis of mUC during a hospital stay.

Table 1. Patient characteristics and comorbidities at baseline

	Main cohort N=3,226	Untreated cohort n=1,892	Treated cohort n=1,286
Observational period, mean (SD), months	13.8 (16.1)	10.6 (15.9)	17.9 (15.3)
Deaths, n (%)	2,533 (78.5)	1,576 (83.3)	926 (72.0)
Time to death from mUC diagnosis, median (IQR), months			
AOK PLUS	5.9 (1.8-19.1)	3.0 (1.2-10.8)	13.7 (6.8-32.9)
GWQ	9.1 (2.5-31.2)	3.6 (1.2-18.8)	13.8 (7.1-41.7)
Age at mUC diagnosis, mean (SD), years	73.8 (10.8)	77.3 (9.8)	68.8 (10.4)
Age group, n (%)			
<60 years	356 (11.0)	114 (6.0)	239 (18.6)
60-79 years	1,775 (55.0)	866 (45.8)	873 (67.9)
≥80 years	1,095 (33.9)	912 (48.2)	174 (13.5)
Male, %	70.8	68.7	74.0
Female, %	29.2	31.3	26.0
Index year, n (%)			
2015	600 (18.6)	380 (20.1)	212 (16.5)
2016	649 (20.1)	383 (20.2)	260 (20.2)
2017	695 (21.5)	406 (21.5)	272 (21.2)
2018	595 (18.4)	352 (18.6)	230 (17.9)
2019	687 (21.3)	371 (19.6)	312 (24.3)
Outpatient index diagnosis, n (%)	694 (21.5)	370 (19.6)	312 (24.3)
Charlson Comorbidity Index score (24-month baseline)			
Mean (SD)	6.3 (3.8)	6.8 (3.9)	5.5 (3.5)
Median (min-max)	6 (0-19)	6 (0-19)	5 (0-18)
Elixhauser Comorbidity Index score (24-month baseline)			
Mean (SD)	17.6 (11.4)	19.3 (11.6)	15.2 (10.7)
Median (min-max)	16 (−7 to 66)	18 (−7 to 66)	14 (−3 to 53)
AOK PLUS only	n=1,852 (57.4)	n=1,188 (62.8)	n=637 (49.5)
Presence of a care level (24-month baseline), n (%)*	522 (28.2)	446 (37.5)	70 (11.0)

IQR, interquartile range; **max.**, maximum; **min.** minimum; **mUC**, metastatic urothelial carcinoma.

Table 2. Factors associated with receiving mUC treatment within 12 months of mUC diagnosis

	Odds ratio	p value	Standard error	95% CI
Age at mUC diagnosis (continuous)	0.93	**<0.001**	0.01	0.92-0.94
Previous UC-related treatments, surgeries, and interventions (24-month baseline; binary)	1.65	**<0.001**	0.12	1.37-2.00
Charlson Comorbidity Index score (24-month baseline: continuous)	0.97	**0.011**	0.01	0.93-1.00
Outpatient diagnosis setting (binary)	1.28	**0.013**	0.11	1.05-1.54
Number of all-cause hospitalizations (24-month baseline: continuous)	0.97	**0.027**	0.02	0.94-1.00
Female sex (binary)	0.83	**0.032**	0.16	0.69-0.98
Diagnosis year (reference year, 2015; categorical)				
2016	1.26	0.117	0.17	0.97-1.62
2017	1.16	0.288	0.15	0.90-1.49
2018	1.24	0.148	0.17	0.96-1.61
2019	1.66	**0.002**	0.21	1.29-2.13

mUC, metastatic urothelial carcinoma; **UC**, urothelial carcinoma.

Table 3. Potential contraindications to treatment at baseline

Contraindications, n (%)	Main cohort N=3,226	Untreated cohort n=1,892	Treated cohort n=1,286
Ischemic heart disease	1,032 (32.0)	714 (37.7)	302 (23.5)
Dementia in Alzheimer disease	64 (2.0)	56 (3.0)	7 (0.5)
Stroke	223 (6.9)	142 (7.5)	78 (6.1)
Parkinson disease	56 (1.7)	47 (2.5)	9 (0.7)
Heart failure	826 (25.6)	621 (32.8)	194 (15.1)
Renal tubulointerstitial disease	1,318 (40.9)	788 (41.7)	517 (40.2)
Renal failure	1,472 (45.6)	984 (52.0)	465 (36.2)
Hyperuricemia without signs of inflammatory arthritis and tophaceous disease	738 (22.9)	475 (25.1)	251 (19.5)
Glomerular diseases	444 (13.8)	287 (15.2)	151 (11.7)
Type 2 diabetes	1,155 (35.8)	770 (40.7)	367 (28.5)
Hearing loss	794 (24.6)	539 (28.5)	245 (19.1)
Neuropathies	533 (16.5)	371 (19.6)	155 (12.1)
Undesirable side effects during therapeutic use of medicines and drugs	125 (3.9)	86 (4.6)	36 (2.8)
Essential (primary) hypertension	2,518 (78.1)	1,562 (82.6)	916 (71.2)

Table 4. Nonsystemic UC-related treatments at baseline

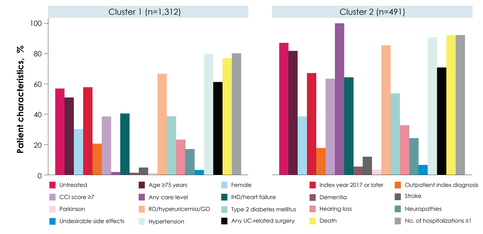
	Main cohort N=3,226	Untreated cohort n=1,892	Treated cohort n=1,286
Any UC-related nonsystemic treatment/ intervention, n (%)	2,126 (65.9)	1,205 (63.7)	891 (69.3)
Cystectomy	430 (13.3)	214 (11.3)	211 (16.4)
Radical cystectomy	426 (13.2)	210 (11.1)	210 (16.3)
Nephroureterectomy	147 (4.6)	69 (3.6)	75 (5.8)
Radical nephroureterectomy	78 (2.4)	38 (2.0)	38 (3.0)
Ureteroreno scopy	255 (7.9)	137 (7.2)	113 (8.8)
Cystoscopy	723 (22.4)	416 (22.0)	296 (23.0)
Lymph node dissection	163 (5.1)	79 (4.2)	84 (6.5)
Nephrectomy	204 (6.3)	96 (5.1)	105 (8.2)
Percutaneous nephrostomy	378 (11.7)	237 (12.5)	134 (10.4)
Cutaneous urinary drainage	394 (12.2)	213 (11.3)	177 (13.8)
Surgical evacuation of a urinary bladder tamponade	195 (6.0)	121 (6.4)	70 (5.4)
Transurethral resection of the bladder	1,666 (51.6)	923 (48.8)	719 (55.9)
Continuous irrigation of the bladder	1,054 (32.7)	598 (31.6)	444 (34.5)
Ureter splint	721 (22.3)	414 (21.9)	296 (23.0)
Transfusions	574 (17.8)	372 (19.7)	192 (14.9)

UC, urothelial carcinoma.

Clustering techniques

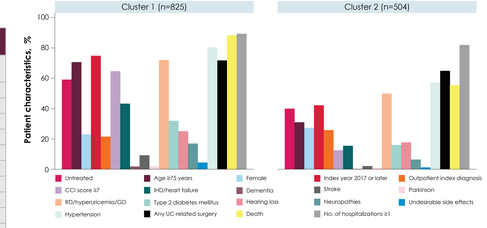
- After identifying outliers (AOK PLUS, n=22; GWQ, n=24), and patient clusters; the standard, which sets the threshold at 50% of dissimilarity, indicated a 2-cluster solution for both databases
- Clusters with the highest proportion of untreated patients (AOK PLUS, cluster 2 with 87.2% untreated patients; GWQ, cluster 1 with 59.0% untreated patients) also had the highest proportion of patients who were older (AOK PLUS, 81.9% aged ≥75 years; GWQ, 70.6% aged ≥73 years) and had higher CCI scores (AOK PLUS, 63.5% with CCI score of ≥7; GWQ, 64.6% with CCI score of ≥6) (**Figures 1 and 2**)
- All patients in AOK PLUS cluster 2 required home care (**Figure 1**) and were more likely to receive their index diagnosis in smaller hospitals (bed count <500) vs cluster 1 patients (39.1% vs 28.6%, respectively; observed in k-means clustering; data not shown)

Figure 1. Cluster analysis with dichotomized variables for patients in AOK PLUS



CCI, Charlson Comorbidity Index; **GD**, glomerular disease; **IHD**, ischemic heart disease; **RD**, renal disease; **UC**, urothelial carcinoma.

Figure 2. Cluster analysis with dichotomized variables for patients in GWQ



CCI, Charlson Comorbidity Index; **GD**, glomerular disease; **IHD**, ischemic heart disease; **RD**, renal disease; **UC**, urothelial carcinoma.

LIMITATIONS

- The administrative claims data used were designed for billing purposes, which may lead to measurement errors due to coding inaccuracies
- Both the AOK PLUS and GWQ datasets contain information from routine medical practice but lack valuable clinical data, such as vital signs or laboratory test results, that could have strengthened the analyses
- Due to database regulations in Germany and data accessibility, the AOK PLUS and GWQ patient cohorts were analyzed independently. Results, except for Kaplan Meier estimations, were first combined using meta-analysis methods and then presented in aggregate form
- Claims data may not capture all relevant aspects of a patient's medical history; thus, the accuracy of cluster assignments may have been impacted, and important associations may have been overlooked
- The optimal number of clusters can be subjective; different clustering methods or criteria may yield varying cluster solutions, making it challenging to determine the correct number of clusters

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DISCLOSURES G. Niegisch reports talks and symposia for Astellas, AstraZeneca, BMS, medac, Pfizer, and Roche; has served on advisory boards for BMS, Ipsen, Janssen, Merck, Pfizer, Roche, and Sanofi; and has received travel and accommodation expenses from Merck, Pfizer, AstraZeneca, and Roche. **M. Kearney** is an employee of Merck and holds stock and other ownership interests in Merck, Novartis, and UCB. **J. Krieger** is an employee of Cytel and has served in a consulting or advisory role for Merck. **U. Osowski** is an employee of Merck Healthcare Germany GmbH, Weiterstadt, Germany, an affiliate of Merck KGaA and holds stock and other ownership interests in Merck. **C. Weinhold** is an employee of Merck Healthcare Germany GmbH, Weiterstadt, Germany, an affiliate of Merck KGaA. **B. Deiters** is an employee of GWQ ServicePlus AG. **U. Maywald** was an employee of AOK PLUS at the time of the study. **S. Guenther** is an employee of and holds stock and other ownership interests in Merck. **T. Wilke** is an employee of IPAM, which received financial support to conduct the claims data analyses. **M.-O. Grimm** has served in a consulting or advisory role for Astellas Pharma, AstraZeneca, Bayer/Vital, BMS, Eisai, EUSA Pharma, Ipsen, Merck, MSD, Pfizer, Roche Pharma AG, and Takeda; has received travel, accommodations, and expenses from BMS and Merck; has received honoraria from Astellas Pharma, AstraZeneca, BMS, EUSA Pharma, Ipsen, MSD, and Pfizer; and has received research funding from BMS and Intuitive Surgical. **ACKNOWLEDGMENTS** The study was sponsored by Merck (CrossRef Funder ID: 10.13039/100009945) and was previously conducted under an alliance between Merck and Pfizer. Editorial support was provided by Hiba Al-Ashtal of Clinical Thinking and was funded by Merck.

Poster No. 2386P. Presented at the ESMO Congress 2023, 20-24 October 2023; Madrid, Spain.