Treatment Patterns Among Patients With Advanced Urothelial Carcinoma (aUC) in the US

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Background

- Advanced urothelial carcinoma (aUC) is an aggressive, incurable disease with a poor long-term prognosis despite therapeutic advances.[1,2]
- Real-world studies conducted before the availability of programmed cell death-receptor 1/death-ligand 1 (PD-1/L1) inhibitors in the first-line (1L) treatment of aUC have shown that less than half (~40%) of patients in the United States (US) received 1L systemic therapy[3,4] and only 15–20% received second-line (2L) treatment, highlighting the need for alternative treatment options.[5]
- Platinum-based regimens have been standard-of-care 1L treatment for patients with aUC; however, up to half of patients may be ineligible for cisplatin-containing regimens.[6,7]
- Since their initial approval in April 2017 for 1L treatment, PD-1/L1 inhibitors have emerged as an effective therapeutic option for aUC patients who are ineligible to receive cisplatin.[8,9]
  - In June 2018, the US Food and Drug Administration (FDA) restricted the indication of PD-1/L1 inhibitors in this setting to patients with aUC who are cisplatin ineligible and whose tumours express PD-L1 or who are ineligible for any platinum-containing chemotherapy regardless of PD-L1 status.[10-12]
- A single study published following the FDA label change showed a decrease in PD-1/L1 inhibitor use and an increase in chemotherapy use in the 1L treatment of aUC.[13] However, current real-world data on PD-1/L1 inhibitor use in 1L, particularly use according to eligibility for cisplatin chemotherapy, are limited.

Objective

- To characterise 1L treatment patterns and subsequent 2L therapy in both cisplatin-eligible and ineligible patients with aUC in the US.

Methods

- This retrospective observational study comprised patients aged ≥18 years diagnosed with aUC from May 2016 to July 2020 with recorded activity (visit/administration) in the Flatiron Health electronic health record-derived database on or within 90 days after aUC diagnosis date (index).
  - The Flatiron Health database is a nationwide longitudinal database comprising de-identified patient-level structured and unstructured data, curated via technology-enabled abstraction. During the study period, the de-identified data originated from ~280 cancer clinics (~800 sites of care) in the US.
  - aUC was identified by International Classification of Diseases (ICD) diagnosis codes (ICD-9 188x, 189.1, 189.2, 189.3, or ICD-10 C65x, C66x, C67x, C68.0) and pathology consistent with stage IV urothelial carcinoma or node-positive urothelial carcinoma.
- The treated cohort received 1L therapy on or after the index date, with follow-up through to October 2020.
- Patient demographic and clinical characteristics and 1L/2L treatment patterns were described in the population overall and by cisplatin eligibility.
  - Cisplatin ineligibility was assessed based on the Galsky criteria[14] and defined as having any of the following clinical characteristics before treatment: Eastern Cooperative Oncology Group Performance Status ≥2, creatinine clearance <60 mL/min, history of hearing loss, congestive heart failure, chronic renal failure or neuropathy.

Results

Patient population

- A total of 4,063 patients met study criteria and were included in the overall cohort: 3,119 (76.8%) patients received 1L treatment (1L-treated cohort) and 944 (23.2%) did not receive any systemic therapy.
- Among the 1L-treated patients, 50.9% (n=1,588) were cisplatin ineligible and 49.1% (n=1,531) were cisplatin eligible (**Table 1**).
- 72.5% of patients were male, with a mean age of 72.5 years at advanced diagnosis. Almost half of patients (46.4%) were from the South region and 90.4% were from community practice settings, reflecting the Flatiron Health database population.
- Demographic characteristics were similar in the overall and the 1L-treated cohorts. Compared with cisplatin-eligible patients, cisplatin-ineligible patients were older at aUC diagnosis and a lower proportion were male.
- The bladder was the primary tumour site in 77.8% of patients, with the remainder split between renal pelvis (12.8%), ureter (8.7%) and urethra (0.7%).
- Kidney function at baseline was captured in 80% of the treated patients; 42.7% had creatinine clearance <60 mL/min and 38.5% had ≥60 mL/min.

Table 1. Baseline demographic and clinical characteristics among patients in the total cohort and 1L-treated patients, overall and by cisplatin eligibility

Characteristics	Total aUC patients	1L-treated patients	1L-treated cisplatin-ineligible patients	1L-treated cisplatin-eligible patients
	(N=4,063)	(n=3,119)	(n=1,588)	(n=1,531)
Gender				
Male	2,944 (72.5%)	2,264 (72.6%)	1,070 (67.4%)	1,194 (78.0%)
Age at advanced diagnosis, years				
Mean (SD)	72.5 (8.93)	72.2 (9.01)	75.0 (7.88)	69.4 (9.22)
US region				
Northeast	583 (14.3%)	433 (13.9%)	238 (15.0%)	195 (12.7%)
Midwest	534 (13.1%)	423 (13.6%)	218 (13.7%)	205 (13.4%)
South	1,884 (46.4%)	1,504 (48.2%)	763 (48.0%)	741 (48.4%)
West	582 (14.3%)	457 (14.7%)	212 (13.4%)	245 (16.0%)
Unknown	480 (11.8%)	302 (9.7%)	157 (9.9%)	145 (9.5%)
Practice type				
Academic	389 (9.6%)	234 (7.5%)	120 (7.6%)	114 (7.4%)
Community	3,674 (90.4%)	2,885 (92.5%)	1,468 (92.4%)	1,417 (92.6%)
Smoking history				
History of smoking	3,012 (74.1%)	2,296 (73.6%)	1,147 (72.2%)	1,149 (75.0%)
No history of smoking	1,037 (25.5%)	812 (26.0%)	436 (27.5%)	376 (24.6%)
Unknown/not documented	14 (0.3%)	11 (0.4%)	5 (0.3%)	6 (0.4%)
Site of primary tumour				
Bladder	3,162 (77.8%)	2,382 (76.4%)	1,152 (72.5%)	1,230 (80.3%)
Renal pelvis	519 (12.8%)	419 (13.4%)	243 (15.3%)	176 (11.5%)
Ureter	354 (8.7%)	296 (9.5%)	181 (11.4%)	115 (7.5%)
Urethra	28 (0.7%)	22 (0.7%)	12 (0.8%)	10 (0.7%)
ECOG Performance Status				
0	812 (20.0%)	757 (24.3%)	278 (17.5%)	479 (31.3%)
1	1,012 (24.9%)	937 (30.0%)	434 (27.3%)	503 (32.9%)
2+	521 (12.8%)	470 (15.1%)	470 (29.6%)	0 (0%)
Missing/unknown	1,718 (42.3%)	955 (30.6%)	406 (25.6%)	549 (35.9%)
Creatinine clearance				
<60 mL/min	1,507 (37.1%)	1,333 (42.7%)	1,333 (83.9%)	0 (0%)
≥60 mL/min	1,308 (32.2%)	1,200 (38.5%)	149 (9.4%)	1,051 (68.6%)
Missing	1,248 (30.7%)	586 (18.8%)	106 (6.7%)	480 (31.4%)

1L, first-line; aUC, advanced urothelial carcinoma; ECOG, Eastern Cooperative Oncology Group; SD, standard deviation; US, United States.

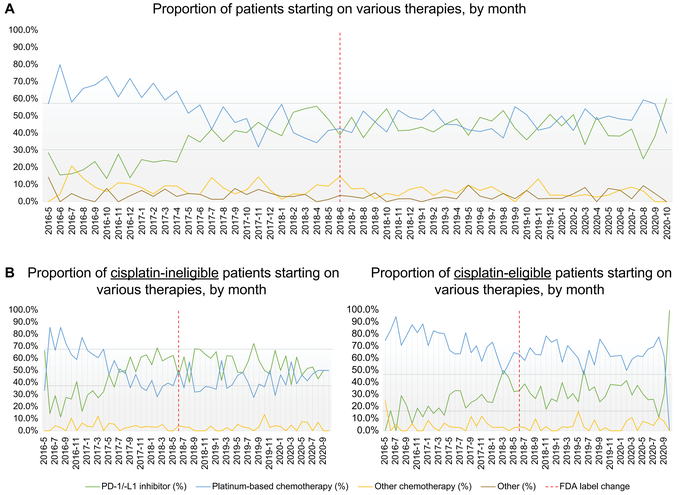
Trends in 1L therapy over the study period

- In the 1L-treated cohort (n=3,119), an increase in PD-1/L1 inhibitor use was observed from the start of the study (May 2016) to May 2018, from <30% to >50% of use, which reflects the time period between the first approvals of PD-1/L1 inhibitors in aUC and the FDA label change (**Figure 1A**).
- Use of chemotherapy decreased from 85% in June 2017 to 40% in March 2018.
- Starting from the second quarter of 2018, the trends stabilised, with about 40% of patients receiving PD-1/L1 inhibitors and 50% of patients receiving chemotherapy.
- When stratified by cisplatin eligibility, a higher proportion of cisplatin-eligible patients were treated with chemotherapy over the study period, whereas a higher proportion of cisplatin-ineligible patients were treated with PD-1/L1 inhibitors, beginning about 1 year after their approval (**Figure 1B**).

1L and 2L treatment patterns

- Among the overall cohort of aUC patients (N=4,063), 76.8% (n=3,119) received 1L treatment and 32.6% (n=1,326) received 2L treatment; therefore, 67.4% of the study population did not receive 2L therapy (**Figure 2**).
- Among treated patients, the median follow-up time was 8.52 (interquartile range [IQR]: 3.9–17.1) months; median follow-up time was shorter for cisplatin-ineligible patients than for cisplatin-eligible patients (6.97 [IQR: 3.2–15.2] and 9.97 [IQR: 4.8–19.8] months, respectively) (**Table 2**).
- Nearly 40% of patients treated in 1L received PD-1/L1 inhibitor monotherapy (**Table 2**).
  - A larger proportion of cisplatin-ineligible (48.2%) than cisplatin-eligible (26.3%) treated patients received PD-1/L1 inhibitor monotherapy in 1L (**Table 2**).
- Among 1L-treated patients, only 42.5% received 2L therapy, with differences based on cisplatin eligibility (**Table 2**).
  - 36.8% of cisplatin-ineligible patients received 2L therapy vs 48.4% of cisplatin-eligible patients.
- More cisplatin-ineligible patients (44.6%) than cisplatin-eligible patients (26.1%) who were treated in 1L died following 1L therapy (**Table 2**).

Figure 1. Trends in 1L therapy over the study period: (A) 1L-treated cohort; (B) cisplatin eligibility



1L, first-line; FDA, US Food and Drug Administration; PD-1/L1, programmed cell death-receptor 1/death-ligand 1.

Table 2. Treatment patterns of aUC patients by cisplatin eligibility

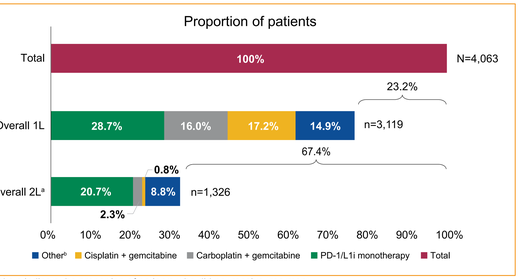
	1L-treated patients (n=3,119)	1L-treated cisplatin-ineligible patients (n=1,588)	1L-treated cisplatin-eligible patients (n=1,531)
1L therapy type			
PD-1/L1i monotherapy	1,168 (37.4%)	765 (48.2%)	403 (26.3%)
Carboplatin + gemcitabine	649 (20.8%)	355 (22.4%)	294 (19.2%)
Cisplatin + gemcitabine	697 (22.3%)	193 (12.2%)	504 (32.9%)
Other[a]	605 (19.4%)	275 (17.3%)	330 (21.6%)
Post-1L status[b]			
Received 2L therapy	1,326 (42.5%)	585 (36.8%)	741 (48.4%)
Still on 1L	212 (6.8%)	98 (6.2%)	114 (7.4%)
No therapy post-1L	473 (15.2%)	197 (12.4%)	276 (18.0%)
Died after 1L	1,108 (35.5%)	708 (44.6%)	400 (26.1%)
Follow-up time, months			
Mean (SD)	12.3 (11.2)	10.8 (10.4)	13.9 (11.8)
Median [Q1, Q3]	8.52 [3.9, 17.1]	6.97 [3.2, 15.2]	9.97 [4.8, 19.8]

[a]Patients who received treatments other than PD-1/L1i monotherapy, carboplatin + gemcitabine, and cisplatin + gemcitabine were classified as "Other".
[b]Post-1L treatment status or status at end of study follow-up if 1L treatment was ongoing.
1L, first-line; 2L, second-line; aUC, advanced urothelial carcinoma; PD-1/L1i, programmed cell death-receptor 1/death-ligand 1 inhibitor; Q, quartile; SD, standard deviation.

Limitations

- Data in the Flatiron Health database are collected primarily in the community oncology setting through routine clinical care and not for research purposes; therefore, non-random missingness is present for several variables of interest, and data on healthcare received outside of the Flatiron Health network of practices are not available.
- To assess cisplatin eligibility, we used the Galsky criteria to the extent that data were available. Importantly, comorbidities were underreported, which may have impacted our designation of cisplatin eligibility.
- Patients who initiated therapy later in the study period may not have had enough follow-up time to observe 2L treatment, which may have led to underestimates of 2L treatment rates.
- Finally, the number of patients diagnosed in 2016 may be smaller as a result of the timing (October 2016) when the source database was launched.

Figure 2. Proportion of aUC patients receiving 1L and 2L treatment, by type of systemic therapy



Brackets indicate the proportion of patients who did not receive treatment.
[a]Owing to data limitations, it cannot be determined whether PD-1/L1i use in 2L is maintenance or 2L therapy.
[b]Patients who received treatments other than PD-1/L1i monotherapy, carboplatin + gemcitabine, and cisplatin + gemcitabine were classified as "Other".
1L, first-line; 2L, second-line; aUC, advanced urothelial carcinoma; PD-1/L1i, programmed cell death-receptor 1/death-ligand 1 inhibitor.

Discussion and Conclusions

- In this analysis of the Flatiron Health Database consisting of oncology practices in the US, approximately three-quarters of patients received systemic treatment following aUC diagnosis.
  - The proportion of patients who received 1L therapy in our study is higher than found in previous studies in the US[3-5]; however, prior studies preceded the approval of PD-1/L1 inhibitors in the 1L treatment of aUC, which may be driving higher current 1L treatment utilisation rates.
  - Although 1L treatment utilisation has increased, about one-quarter of aUC patients did not receive any 1L treatment and two-thirds did not receive 2L therapy, indicating the persistence of high unmet treatment needs.
- Use of 1L PD-1/L1 inhibitors has stayed between 30% and 50% since their approvals for the treatment of aUC, despite a more restrictive indication implemented by the FDA in June 2018.
  - Although a higher proportion of cisplatin-ineligible vs eligible patients were treated 1L with PD-1/L1 inhibitors, there was considerable use of PD-1/L1 inhibitors in cisplatin-eligible patients.
  - This finding may reflect patient preference/requests for PD-1/L1 inhibitors, misclassification of cisplatin eligibility, or a change in cisplatin eligibility between the time of classification and treatment.
- Among 1L-treated patients, a lower proportion of cisplatin-ineligible patients received 2L therapy and a higher proportion died after 1L treatment relative to cisplatin-eligible patients.
- There remains significant unmet need for safe and efficacious therapies for patients with aUC in 1L and 2L settings, particularly for patients who are cisplatin ineligible.

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