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Treatment Patterns of Second-Line (2L) Metastatic Urothelial Cancer (mUC) in Spain

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BACKGROUND

- Urothelial carcinoma or cancer (UC) is the most common type of bladder cancer, representing 90% of bladder cancer cases.[1]
- Rates of recurrence and disease progression are high among UC patients (e.g., 78% will experience recurrence within five years);[1] metastatic urothelial carcinoma (mUC) is an area of significant unmet medical need.
- Guidelines from the European Society for Medical Oncology (ESMO) and the American Society of Clinical Oncology (ASCO) for second-line (2L) treatment of mUC require updating.[2,3] Recent developments and approvals of immunotherapy drugs are changing the standard of care for cancers and specifically mUC.
- In Europe over the past few months, three immunotherapy agents – nivolumab, permbrolizumab, and atezolizumab – were approved as 2L treatment of mUC. Vinflunine was approved for use in mUC in 2009.[4]

OBJECTIVE

- To understand the treatment patterns of patients receiving 2L treatment for mUC in Spain.

METHODS

Data

- Data were collected between February 2015 and March 2017 in a retrospective, non-interventional study that was conducted using a panel of Spanish physicians.
- Stringent sampling procedures linked with a panel management system were used to ensure representative demographics when recruiting across populations.
- Physicians provided information on 5 patients who started and stopped 2L treatment for mUC during the study period.
- Data were collected using a web-based electronic case report form (eCRF) from patients' medical records.

Study Sample

Physician Sample (n=50)

- Inclusion criteria: ≥2 years in clinical practice; ≥70% of time spent in clinical practice; treated ≥5 mUC patients over the past 2 years; able to provide data from 5 patient charts according to the study's patient inclusion/exclusion criteria; and provided informed consent to participate in the study

Patient Sample (n=241)

- Inclusion criteria: ≥18 years at study enrollment and started and stopped 2L (chemotherapy) treatment during the study period (stopping 2L treatment could have been due to completion of treatment regimen, discontinuation, or death)

Measures

Physician Characteristics and Prescribing Attitudes

- Demographics: age and sex
- Practice descriptors: years in practice, type, and setting
- Prescribing attitudes: Likert scale: 1=disagree completely to 5=agree completely

Patient Demographics and Disease Characteristics

- Demographics: age and sex
- Disease characteristics included: stage at diagnosis, primary tumor site, and histological subtype

Treatment Characteristics and Outcomes

- Lines of therapy were defined as the following three groups:
  - First-line therapy (1L):
    - Treatment with a platinum-containing chemotherapy regimen for metastatic or surgically-unresectable locally advanced urothelial cancer, or
    - Greater than 12 months after the completion of peri-operative (neo-adjuvant or adjuvant) treatment with a platinum agent in the setting of cystectomy for localized muscle-invasive urothelial cancer
  - Second-line therapy (2L):
    - Treatment after progression or recurrence after 1L treatment, or after recurrence within 12 months of neoadjuvant/ adjuvant treatment
  - Third-line therapy (3L):
    - Treatment after progression or recurrence after a previous 2L treatment
- Treatment type was classified according to non-platinum (mono) versus platinum-based (combination) therapy.
- Treatment characteristics: number of cycles, duration, time between treatment lines
- Eastern Cooperative Oncology Group (ECOG) grading system
- Response to treatment: complete, partial, stable disease, or disease progression
- Healthcare and resource utilization outcomes
- Number of hospital days for administration of chemotherapy
- Number of hospital days for monitoring/recovery

Statistical Analyses

- Descriptive statistics were reported as means with standard deviation or median and range for continuous variables and absolute frequencies and percentages for categorical variables.
- Differences between treatment types were examined in bivariate analyses using one-way ANOVAs for continuous variables.

RESULTS

Physician Characteristics and Attitudes

- The mean age of physicians (n=50) was 43.3 (± 7.7) years, 60% were male, and were practicing for 14.2 (± 5.8) years on average. The majority practiced at a university setting (88%) (**Table 1**).

Table 1. Physician Characteristics

Physician Characteristics	n=50
Age, Years	
Mean (SD)	43.3 (7.7)
Range	30-59
Male[a]	60.0%

Physician Characteristics	n=50
Years in Practice	
Mean (SD)	14.2 (5.8)
Range	5-29
Practice Setting	
University Hospital	88.0%
Non-University Hospital or Cancer Centre	12.0%

Note: [a]Data were missing for one physician; SD=standard deviation.

- Physicians note that there is a great unmet need for more efficacious mUC treatments (mean 4.52 [± 0.65] of 5.00) and safer/ better tolerated mUC treatments (4.26 [± 0.72] of 5.00) for their patients (**Table 2**).

Table 2. Prescribing Attitudes of Physicians Treating Patients with mUC

Prescribing Attitudes	Mean	SD
There is a great unmet need for more efficacious mUC treatments for my patients.	4.52	0.65
There is a great unmet need for safer/better tolerated mUC treatments for my patients.	4.26	0.72
The side effect/tolerability profile is one of the main considerations in my prescribing decisions for my patients.	4.10	0.65
I believe side effects are worth the risk if the agent will achieve the best response for the patient for my patients.	4.08	0.72
When treating mUC, the ability of a drug to delay progression has the greatest impact on a patient's quality of life.	4.08	0.75
The side effect/tolerability profile of a treatment has a large influence on the dosing schedule I employ (i.e., length of time on therapy, number of doses) for my patients.	4.04	0.75
When treating mUC, side effects and tolerability of a drug have the greatest impact on a patient's quality of life.	3.88	0.69
Treating this disease is satisfying for me as a physician.	3.88	1.06
I am comfortable managing the side effects for my metastatic urothelial patients.	3.76	0.96
My mUC patients play a large role in treatment decisions.	3.74	0.99
I only prescribe agents specifically indicated for use in mUC.	3.52	1.05
I prefer to prescribe agents that are approved for multiple indications, not just mUC.	3.22	1.02
I tend to make more of my prescribing decisions based on personal experience versus clinical data.	3.18	1.12

Agree Completely=5

Disagree Completely=1

Note: mUC=metastatic urothelial cancer; SD=standard deviation

Patient Characteristics

- Among the 241 patients with mUC, patients were on average 62.6 (± 8.9) years at metastatic diagnosis and 63.5 (± 9.0) at 2L treatment initiation (**Table 3**).
- The majority of patients were male (81%), had metastatic cancer at diagnosis (88%), and had a primary tumor site of urinary bladder (76%) and histology of being transitional cell (80%) (**Table 3**).
- 73% of patients underwent cystectomy and 73% of these patients received neo-adjuvant or adjuvant chemotherapy (**Table 3**).

Table 3. Patient and Disease Characteristics of Patients with mUC

Patient Characteristics	n=241
Age at Metastatic Diagnosis, Years	
Mean (SD)	62.6 (8.9)
Range	39-94
Age at 1L Treatment, Years	
Mean (SD)	63.1 (8.9)
Range	39-94
Age at 2L Treatment, Years	
Mean (SD)	63.5 (9.0)
Range	39-95
Male	81.3%
Initial Diagnosis as Metastatic	87.6%

Disease Characteristics	n=241
Primary Tumor Site for mUC	
Urinary Bladder	75.5%
Renal Pelvis	11.6%
Ureter	10.0%
Urethra	0.8%
Don't Know	2.1%
Histology of Primary Tumor for mUC	
Transitional Cell	80.1%
Squamous Cell	10.8%
Adenocarcinoma	7.5%
Other	0.0%
Don't Know	1.7%
Cystectomy	73.3%
Among Cystectomy Patients, Also Received Neo-Adjuvant or Adjuvant Chemotherapy	72.7%

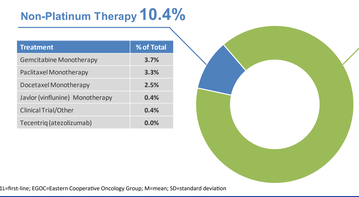
Note: 1L=first-line; 2L=second-line; M=mean; mUC=metastatic urothelial cancer; SD=standard deviation

RESULTS, Continued

1L Treatment

- 90% of patients received platinum-based combination 1L treatment. The most common treatments were gemcitabine + cisplatin (50%) and gemcitabine + carboplatin (24%) (**Figure 1**).
- 73% of patients had an ECOG status at 1L initiation of Grade 0 or 1.
- The average 1L duration was 5.7 (± 2.3) months.
- Duration of treatment for 1L non-platinum therapy was 7.0 (± 4.4) months and for platinum-based therapy was 5.6 (± 1.9) months (p=0.005).
- 60% of patients had complete or partial response, 15% had stable disease, and 25% had disease progression following 1L treatment.

Figure 1. First-Line (1L) Treatment for mUC (n=241)



Treatment	% of Total
Gemcitabine Monotherapy	3.7%
Paclitaxel Monotherapy	3.3%
Docetaxel Monotherapy	2.5%
Javlor (vinflunine) Monotherapy	0.4%
Clinical Trial/Other	0.4%
Tecentriq (atezolizumab)	0.0%

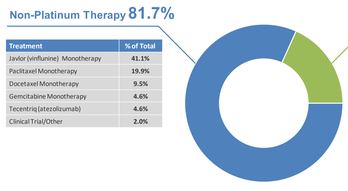
Treatment	% of Total
Gemcitabine + cisplatin	49.8%
Gemcitabine + carboplatin	23.7%
Carboplatin + docetaxel	7.9%
Gemcitabine + cisplatin + docetaxel	5.0%
Methotrexate, vinblastine, doxorubicin and cisplatin (MVAC)	3.3%
Clinical Trial/Other	0.0%

Note: 1L=first-line; EGOC=Eastern Cooperative Oncology Group; M=mean; SD=standard deviation

2L Treatment

- The majority of patients received non-platinum-based 2L monotherapy (82%), with most treated with vinflunine (41%) and paclitaxel (20%) (**Figure 2**).
- Physician and patient characteristics did not differ significantly by 2L treatment type, with the exception of age at 2L initiation that was higher for those receiving platinum-based 2L therapy (overall=63.5 [± 9.0] years; non-platinum=62.9 [± 8.5] years, platinum=66.2 [± 10.7] years, p=0.030).
- The distribution of ECOG status at 2L initiation did not differ by treatment types (p=0.171). Specifically, over half the patients had an ECOG status of Grade 0 or 1 regardless of 2L treatment type (overall=54%; non-platinum=54%, platinum=52%).
- The primary rationale for choice of 2L treatment was efficacy (non-platinum=70%, platinum=86%, p<0.05). Patient comorbidities or performance status was the second most important reason for treatment choice (non-platinum=16%, platinum=7%, p>0.05). Guidelines (national or hospital) were important drivers of treatment choice among 6-7% of physicians regardless of treatment.
- The average time from 1L to 2L treatment was 6.0 (± 6.2) months and average 2L duration was 4.2 (± 2.2) months.
- Non-platinum-based treatments compared with platinum-based-treatments were associated with significantly shorter duration of time from end of 1L to start of 2L (5.1 [± 4.2] versus 10.1 [± 0.5] months, p<0.001) and time on 2L treatment (4.0 [± 1.9] versus 5.0 [± 3.0] months, p=0.005).

Figure 2. Second-Line (2L) Treatment for mUC (n=241)

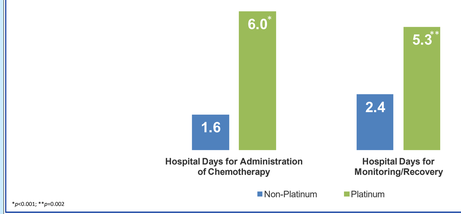


Treatment	% of Total
Javlor (vinflunine) Monotherapy	41.1%
Paclitaxel Monotherapy	19.9%
Docetaxel Monotherapy	9.5%
Gemcitabine Monotherapy	4.6%
Tecentriq (atezolizumab)	4.6%
Clinical Trial/Other	2.0%

Treatment	% of Total
Gemcitabine + cisplatin	5.4%
Gemcitabine + carboplatin	5.4%
Gemcitabine + cisplatin + docetaxel	3.3%
Carboplatin + docetaxel	2.1%
Methotrexate, vinblastine, doxorubicin and cisplatin (MVAC)	1.7%
Clinical Trial/Other	0.4%

- Non-platinum-based treatments compared with platinum-based treatments were associated with significantly fewer hospital days for chemotherapy administration (p<0.001) and fewer hospital days for monitoring or recovery (p=0.002) (**Figure 3**).

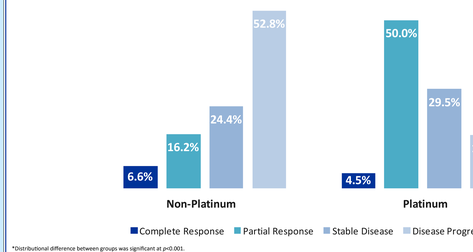
Figure 3. Healthcare Resource Use for Patients with mUC Treated with Second-Line (2L) Non-Platinum (n=125) versus Platinum-Based (n=27) Treatment



*p<0.001; **p=0.002

- Of those who received 2L treatment, 6% of patients achieved a complete response, 22% partial response, 25% stable disease, and 46% had disease progression. According to 2L treatment type, patients who received platinum-based therapy had substantially improved responses (p<0.001) (**Figure 4**).

Figure 4. Response to Second-Line (2L) Treatment among Patients with mUC (n=241)*



*Distributional difference between groups was significant at p<0.001.

3L Treatment

- Of the 241 patients who received 2L mUC treatment, only 23 (10%) were reported having 3L treatment.
- The average time from 2L to 3L treatment of 2.4 (± 1.2) months. Time from 2L to 3L treatment was significantly shorter among those who received 2L non-platinum versus platinum-based treatment (1.9 [± 1.0] versus 3.5 [± 1.1] months, p=0.005).

LIMITATIONS

- The present study represents a convenience sample, thus certain subgroups of physicians may have been over-represented and results may not generalize to the entire physician population. However, the panels have a stringent sampling procedure in place to help reduce this bias and ensure a representative sample across multiple demographics.
- Physician inclusion criteria was designed to minimize the use of patient records with missing data.
- Although physicians were asked to refer to patient charts when providing patient responses, a formal chart collection was not performed verifying physicians' responses.
- The present study relied on retrospective chart review to describe current treatment patterns and outcomes, preventing certain confounders from being measured and accounted for in analyses. For example, data for healthcare resource use were not available for the entire sample.
- Due to the descriptive nature of the data in this study, causality cannot be inferred.

CONCLUSIONS

- The most common 2L mUC treatment is non-platinum-based monotherapy.
- Compared to non-platinum treatments, platinum-based treatments had higher number of hospital days for chemotherapy administration, however much improved responses.
- Consistent with guidelines, patients with longer time between therapy lines were more likely to receive platinum-based therapy.
- A high unmet need for mUC patients is suggested both in physician attitudes as well as poor health outcomes for 2L mUC patients that may now be addressed with the recent approval of immunotherapies.
- Information in this study provided on 1L and 2L treatment is critical for understanding real-world practice, especially since clear and updated 2L treatment guidelines for mUC are lacking.

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