## Immunotherapy in the Treatment of Metastatic Urothelial Carcinoma at a Tertiary Referral Center in Portugal

## Experiência com Imunoterapia no Carcinoma Urotelial Metastizado num Centro de Referência Português

**Keywords:** Carcinoma, Transitional Cell; Immunotherapy; Urinary Bladder Neoplasms/drug therapy
**Palavras-chave:** Carcinoma de Células de Transição; Imunoterapia; Neoplasias da Bexiga Urinária/tratamento farmacológico

Urothelial cancer is the seventh most common cancer in Portugal. Despite local therapy, one-third of patients experience recurrence and develop metastatic disease[1] and an additional 5% of patients have distant metastases at diagnosis.[2] For those, platinum-based combination chemotherapy is the standard of care, even though a significant proportion of patients are ineligible for chemotherapy due to comorbid conditions.[3] Moreover, platinum regimens usually show short-term responses.[3] Immunotherapy has challenged the paradigm of metastatic disease after first line platinum-based combination chemotherapy, with longer overall survival and a higher objective response rate. The aim of this study was to evaluate the clinical outcomes of real-world patients with metastatic urothelial cancer treated with immunotherapy at a Portuguese tertiary center.

The authors retrospectively selected 20 patients from an approved anonymized database of a tertiary referral center, with informed consent for treatment and data analysis. Patients presented with advanced urothelial cancer that recurred or progressed after platinum-based chemotherapy and received treatment with immunotherapy (pembrolizumab or atezolizumab).

Descriptive analyses were performed using standard summary statistics and survival was assessed using Kaplan–Meier survival analysis with 95% confidence intervals (CI). Patients, disease, and treatment characteristics are summarized in Table 1. Median overall survival (OS) was 11.8 months (95% CI, 8.1 to 15.5) in patients treated with both drugs. Median progression-free survival was 7.8 months (95% CI, 6.0 to 9.6). The objective response rate (ORR) was 20% (three partial responses and one complete response on follow-up computed tomography (CT) scan). Treatment-related adverse events of any grade were reported in 45% of the patients with the most common being fatigue and pruritus. Grade 3 events were reported in 10% of patients, with no grade 4 or 5 events.

Despite limitations of sample size and retrospective design, efficacy in the real-world population is in line with the results of seminal trials. The median OS was comparable to the 10.3 months in the KEYNOTE-045[4] trial. The ORR was also comparable to the KEYNOTE-045[4] trial (21%) and higher than in the IMvigor210[5] trial (16%).

In our study, the included patients were older and had worse performance status, reinforcing the safety of immunotherapy and a low incidence of severe adverse events in

Table 1 – Demographic, disease, and treatment characteristics

| Demographics and disease characteristics | Patients (n = 20) |
|---|---|
| **Age** - years | |
| Median | 72.5 |
| Range | 48 - 84 |
| **Sex** | |
| Male | 15 (75%) |
| Female | 5 (25%) |
| **ECOG performance status** | |
| 0 | 9 (45%) |
| 1 | 11 (55%) |
| **Histological type** | |
| Pure urothelial | 16 (80%) |
| Mixed | 4 (20%) |
| **Primary tumor location** | |
| Bladder | 15 (75%) |
| Renal pelvis/Ureter | 5 (25%) |
| **Initial staging** | |
| Non-metastatic | 18 (90%) |
| Metastatic | 2 (10%) |
| **Metastasis location at progression** | |
| Non-visceral | 10 (50%) |
| Visceral | 10 (50%) |
| **Treatment** | **Patients (n = 20)** |
| **Initial surgical treatment** | |
| Cystectomy | 15 (65%) |
| TURBT | 2 (10%) |
| Nephroureterectomy | 5 (25%) |
| **Context of most recent systemic therapy** | |
| Neoadjuvant platinum | 2 (10%) |
| Platinum for metastatic disease | 18 (90%) |
| **Immunotherapy** | |
| Pembrolizumab | 16 (80%) |
| Atezolizumab | 4 (20%) |
| **Immunotherapy duration** - months | |
| Median | 8 |
| Range | 2 - 51 |
| **Treatment discontinuation** | |
| Progression/Death | 16 (80%) |
| Adverse events | - |
| **Time between drug indication and administration** - days | |
| Median | 49.5 |
| Range | 14 - 126 |

ECOG PS: Eastern Cooperative Oncology Groupe performance status; PD-L1 expression was tested using the Dako PD-L1 assay; TURBT: transurethral resection of bladder tumor

the elderly and less selected patients. In our experience, there was a substantial time gap between the decision to start immunotherapy and approval/administration. Three patients died waiting for treatment. Therefore, there is an imperative need for a faster drug approval by the national medicines agency and the creation of early drug access in high-volume referral centers.

## AUTHOR CONTRIBUTIONS

VQ: Study design, data acquisition, analysis and interpretation, writing of the manuscript.

LM: Study design, data analysis and interpretation, critical review of the manuscript.

RJ, JL: Data acquisition, analysis and interpretation, critical review of the manuscript.

AF: Study design, data interpretation, critical review of the manuscript.

## PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

## DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

## COMPETING INTERESTS

The authors have declared that no competing interests exist.

## FUNDING SOURCES

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

## REFERENCES

1. Stein JP, Lieskovsky G, Cote R, Groshen S, Feng AC, Boyd S, et al. Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1,054 patients. J Clin Oncol. 2001;19:666-75.
2. Kirkali Z, Chan T, Manoharan M, Algaba F, Busch C, Cheng L, et al. Bladder cancer: epidemiology, staging and grading, and diagnosis. Urology. 2005;66:4-34.
3. Galsky MD, Hahn N, Rosenberg J, Sonpavde G, Hutson T, Oh W, et al. A consensus definition of patients with metastatic urothelial carcinoma who are unfit for cisplatin-based chemotherapy. Lancet Oncol. 2011;12:211-4.
4. Bellmunt J, de Wit R, Vaughn DJ, Fradet Y, Lee JL, Fonf L, et al. Pembrolizumab as second-line therapy for advanced urothelial carcinoma. N Engl J Med. 2017;376:1015-26.
5. Hoffman-Censits JH, Grivas P, Van Der Heijden MS, Van-Der-Heijden M, Dreicer R, Loriot Y, et al. IMvigor 210, a phase II trial of atezolizumab (MPDL3280A) in platinum-treated locally advanced or metastatic urothelial carcinoma (mUC). J Clin Oncol. 2016;34:355.

Vasco QUARESMA✉[1], Lorenzo MARCONI[1,2], Roberto JARIMBA[1], João LIMA[1], Arnaldo FIGUEIREDO[1,2]
1. Urology Department. Centro Hospitalar e Universitário de Coimbra. Coimbra. Portugal.
2. Faculty of Medicine. University of Coimbra. Coimbra. Portugal.
✉ **Autor correspondente:** Vasco Quaresma. vpdquaresma@gmail.com
**Recebido/*Received*:** 12/07/2022 - **Aceite/*Accepted*:** 21/12/2022 - **Publicado/*Published*:** 01/02/2023

https://doi.org/10.20344/amp.18837