CASE REPORT

Durable Disease Control with PD-L1 Blockade in a Patient with Metastatic Urothelial Carcinoma and Multiple Cardiovascular Comorbidities: A Case Report

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Abstract. Introduction. Metastatic urothelial carcinoma (mUC) is an aggressive malignancy with poor prognosis. While platinum-based chemotherapy remains an important option in the first line setting, many older patients present with significant comorbidities precluding cisplatin use, necessitating alternative regimens or immune checkpoint inhibitors (ICIs). **Case presentation**. We present a 71-year-old female with severe cardiovascular and renal comorbidities—including NYHA class II heart failure, atrial fibrillation, grade III hypertension, and chronic kidney disease—who presented with severe weight loss and gross hematuria. Diagnostics revealed cT4aN2M1a (Stage IV) high-grade infiltrative urothelial carcinoma. To manage persistent bleeding, palliative hemostatic radiotherapy (21 Gy) was first administered. Deemed cisplatin-ineligible due to impaired renal function (GFR 35 mL/min), an ECOG performance status of 2, and advanced heart failure, she was successfully treated with a tailored six cycles of first-line carboplatin and gemcitabine (CG), demonstrating good clinical tolerance. Subsequently, 6 months after the end of CG therapy, progression in the regional and distant adenopathy was noted, and second-line atezolizumab was initiated. Remarkably, despite her extensive baseline cardiovascular disease, she tolerated the ICI well, achieving a progression-free survival (PFS) exceeding 5 years. **Conclusions**. Although this patient achieved an outstanding clinical outcome with no immune-related adverse events, a strong working knowledge of atezolizumab's cardiovascular safety profile is highly warranted. A short literaturereview documents the potential for rare but severe cardiovascular complications associated with ICIs. Consequently, vigilant cardio-oncology monitoring remains critical, especially during long-term ICI maintenance in patients with pre-existing severe cardiac conditions.

Keywords*: metastatic urothelial carcinoma, immune checkpoint inhibitors, cardio-oncology, long-term survival.*

Abbreviations: mUC – metastatic urothelial carcinoma
ICI – immune checkpoint inhibitors
PFS – progression-free survival
OS – overall survival
CT – computed tomography
OAC – oral anticoagulants

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INTRODUCTION

Urothelial carcinoma is the predominant histological subtype of bladder cancer and constitutes a major global public health burden. According to GLOBOCAN estimates, bladder cancer accounts for over 570,000 new cases and more than 210,000 deaths annually worldwide [1]. While the most patients are initially diagnosed with localized, non-muscle-invasive disease, a notable subset presents *de novo* with locally advanced or mUC, and many others eventually progress to this stage. mUC is characterized by a highly aggressive clinical course, predominantly affecting older adults, and carries a historically poor prognosis, underscoring the critical need for advanced therapeutic strategies [2].

The contemporary standard of care, as outlined by the National Comprehensive Cancer Network (NCCN) guidelines, emphasizes the use of platinum-based chemotherapy followed by the integration of immune checkpoint inhibitors as maintenance or subsequent-line therapies [3]. Despite high initial response rates to standard first-line platinum-based chemotherapy (such as gemcitabine plus cisplatin or carboplatin), long-term outcomes have been limited. The median overall survival for patients treated with these traditional regimens typically plateaus at around 14 to 15 months, with a 5-year survival rate remaining modest of approximately 13% to 17% [4].

However, the advent of ICIs has significantly altered the therapeutic landscape for patients who progress on platinum-based regimens. Clinical evidence from IMvigor211 and IMvigor210 trials has demonstrated the impact of second-line atezolizumab in this setting. While immunotherapy cannot be used in all the patients, long-term follow-up data from IMvigor211 revealed a distinct and remarkable subset of "long responders". After 24 months, the overall survival rate for patients treated with atezolizumab was 23%, compared to just 13% for those receiving standard chemotherapy, with median duration of response significantly prolonged. These findings emphasize that for a specific cohort of pretreated mUC patients, atezolizumab can induce highly durable, years-long remissions, fundamentally shifting survival expectations [4,5].

CASE PRESENTATION

A 71-year-old female gender patient, with no significant family history, presented with an extensive cardiovascular medical history, including essential hypertension, chronic heart failure (NYHA class II), paroxysmal atrial fibrillation, grade I mitral regurgitation, grade I tricuspid regurgitation, chronic kidney disease, and chronic venous insufficiency (CEAP class C2). Chronic medication included betablockers, angiotensin converting enzyme (ACE) inhibitors, mineralocorticoid antagonists, calcium channel blockers and oral anticoagulants (OAC). The onset of symptoms was marked by dysuria, significant unintentional weight loss (approximately 15 kg over two months), and gross hematuria. Further diagnostic workup was initiated.

Cystoscopic examination revealed a left-sided infiltrative bladder mass measuring approximately 4 cm, involving the left ureteral orifice partially and the right ureteral orifice completely. Histopathological analysis confirmed high-grade infiltrative urothelial carcinoma. For staging purposes, thoraco-abdominal computed tomography (CT) was performed, revealing locally advanced and metastatic bladder cancer staged as cT4aN2M1 (Stage IV):

- **cT4a**: infiltrative-vegetative tumor measuring 20 × 72 mm, with loss of the fat plane between the tumor and the uterine cervix over a 22 mm segment, as well as ureteral encasement resulting in grade II–III left-sided ureterohydronephrosis.

- **N2**: bilateral external iliac lymph node involvement (9 × 8 mm on the left and 10 × 14 mm on the right).
- **M1a**: latero-aortic lymph node metastases (Figure 1)

Following biopsy, the patient developed complete urinary retention, requiring placement of a Foley ureterovesical catheter. Empirical antibiotic therapy with Ciprofloxacin 250 mg twice daily was initiated, dose was adjusted based on the renal clearance.

Based on clinical, imaging, and histopathological findings, a multidisciplinary oncologic evaluation was conducted to outline a therapeutic strategy. However, prior to the initiation of systemic treatment, the patient experienced a severe episode of gross hematuria resulting in a significant acute drop in hemoglobin levels. Considering the active hemorrhage and the high baseline bleeding risk (HAS-BLED score of 5), the OAC therapy was discontinued, despite the high thromboembolic risk (CHA_2DS_2-VA score of 7). To achieve local control of the bleeding, an urgent radiation oncology consultation was requested, and palliative hemostatic radiotherapy was successfully administered for the bladder (total dose of 21 Gy delivered in 3 fractions of 7 Gy each) and the OAC were stopped due to the increased risk of bleeding.

In accordance with the ESMO and NCCN guidelines, first-line palliative chemotherapy was initiated. The patient was deemed ineligible for cisplatin-based therapy due to her impaired performance status (ECOG 2), reduced renal function (GFR 35 mL/min), advanced age, and severe chronic heart failure (NYHA class III). Consequently, a carboplatin and gemcitabine regimen was selected. To optimize safety and tolerability given her frailty and extensive comorbidities, the standard protocol was modified. She received carboplatin (AUC 4.5–5) and gemcitabine (1000–1250 mg/m²) administered exclusively on day 1 of a 21-day cycle (q3w), deliberately omitting the standard day 8 and day 15 gemcitabine doses. Under this regimen, the patient successfully completed six treatment cycles with good clinical tolerance and minimal adverse effects. Following the completion of chemotherapy, a cardio-oncology re-evaluation was performed. Given the high thromboembolic risk and the absence of recurrent bleeding episodes, the decision was made to resume the OAC therapy.

Six months following the completion of the modified first-line carboplatin and gemcitabine regimen, routine restaging imaging revealed disease progression, demonstrating the enlargement of both regional and distant lymphadenopathy. Given the disease progression and the ongoing ineligibility for more aggressive therapy, second-line systemic therapy with an ICI was warranted; thus, atezolizumab was initiated. Remarkably, despite the age and significant comorbidities, the patient proved excellent clinical tolerance and imagistic response to immunotherapy (Figure 2). She did not experience any significant irAEs, cardiovascular or otherwise. Most notably, the atezolizumab therapy yielded an extraordinary and durable clinical benefit, resulting in a PFS that now exceeds 5 years with a complete remission of both the adenopathy and the primary tumor.

DISCUSSION

The management of mUC in elderly patients with extensive cardiovascular and renal comorbidities represents a formidable clinical challenge. We reported a remarkable case of a 71-year-old female with stage IV mUC and significant frailty and an ECOG performance status of 2—who achieved an ongoing, complete clinical remission and a PFS exceeding five years on second-line atezolizumab. This case underscores not only the potential for ICI to induce profound and durable responses, but also their

viability and safety in highly comorbid patients deemed unfit for aggressive conventional therapies.

Historically, patients experiencing disease progression following first-line platinum-based chemotherapy faced a dismal prognosis, with median survival typically measured in months. However, the introduction of PD-L1 inhibitors such as atezolizumab has fundamentally altered this therapeutic landscape. Data from the IMvigor210 and IMvigor211 trials revealed a distinct paradigm shift in metastatic urothelial carcinoma. While median overall survival (OS) improved across unselected patient populations, the most pronounced OS benefit was observed in cohorts with PD-L1 expression > 5%. An important characteristic emerging from both studies is that a clinically significant subset of patients achieves a highly durable response, visually represented by the flattening of the OS curves after approximately two years of treatment. These patients represent a unique cohort of "long-responders" who attain sustained, long-term remission under immune checkpoint inhibition [5,6]. Our patient's history perfectly exemplifies this long-tail survival benefit, demonstrating complete responses is attainable even in the presence of poor baseline prognostic factors.

Beyond the general phenomenon of long-term ICI responders, the specific pattern of this patients metastatic spread may explain her outcome. At the time of progression, the patient presented with regional and distant lymphadenopathy (N2M1a) without evidence of solid visceral metastases. Recent evidence suggests that lymph node-only mUC represents a distinct, highly immuno-responsive clinical entity. This concept was recently validated by a post-hoc exploratory analysis of the phase III CheckMate 901 trial. The trial evaluated first-line nivolumab combined with gemcitabine/cisplatin versus chemotherapy alone. In the subgroup of patients with lymph node-only metastatic disease, the addition of PD-1 blockade yielded a staggering objective response rate (ORR) of 81% and a complete response (CR) rate of 63%—nearly double that of chemotherapy alone. Furthermore, the analysis revealed that over half of all complete responders in the entire trial belonged to this lymph node-only subgroup. While CheckMate 901 investigated a different ICI in the frontline setting, it definitively establishes that urothelial tumours metastasizing exclusively to the lymphatic system are exquisitely sensitive to immune checkpoint blockade. Therefore, our patient's lymph node-predominant metastatic profile likely played role in achieving a complete, durable, 5-year remission on second-line atezolizumab [7,8].

A unique aspect of this clinical case is the patient's exceptional tolerance to immunotherapy despite her frailty and baseline status. The administration of systemic antineoplastic agents in the setting of arterial hypertension, advanced heart failure, and paroxysmal atrial fibrillation (with a high CHA_2DS_2-VA score) necessitates cardio-oncologic oversight. Remarkably, our patient experienced no irAEs throughout her prolonged treatment course. However, while she represents a best-case scenario, the expanding integration of ICIs into standard oncological practice demands a high index of suspicion for their unique toxicity profiles.

Although generally better tolerated than cytotoxic chemotherapy, ICIs are associated with a distinct spectrum of autoimmune toxicities. Among these, cardiovascular irAEs, while relatively rare, are of concern due to their rapid onset, fulminant progression, and high mortality rates [9–11]. The main cardiovascular irAEs include immune-related myocarditis (irMyocarditis), pericarditis, vasculitis, acute coronary syndrome (ACS), conduction disorders (including complete heart block), atrial and ventricular arrhythmias, Takotsubo syndrome, non-inflammatory left ventricular dysfunction, and heart failure. Although the risk appears to be increased in

patients with pre-existing cardiovascular comorbidities [9–11], this should not limit access to optimal oncologic therapy but instead emphasize the importance of vigilant monitoring and sustained multidisciplinary collaboration.

According to the 2022 ESC Guidelines on cardio-oncology, the clinical presentation of cardiovascular irAEs is highly heterogeneous. irMyocarditis can manifest along a broad clinical spectrum, ranging from an entirely asymptomatic elevation in cardiac biomarkers to fulminant cardiogenic shock accompanied by severe ventricular arrhythmias or advanced atrioventricular block. When myocarditis is suspected, the initial diagnostic should include a 12-lead ECG, cardiac troponin measurement, and transthoracic echocardiography (TTE). While endomyocardial biopsy (EMB) remains the gold standard for a definitive diagnosis—evidenced by multifocal inflammatory cell infiltrates and overt cardiomyocyte loss—aclinical diagnosis is frequently established non-invasively. This requires a new or significant elevation in cardiac troponin combined with either cardiac magnetic resonance (CMR) imaging meeting the modified Lake Louise criteria (major criterion) or a combination of minor clinical, electrical, and functional criteria, strictly after excluding acute coronary syndrome and infectious etiologies[12]. ICI-related pericarditis may present in isolation or as myopericarditis, typically manifesting with classic pleuritic chest pain, a pericardial friction rub, or progressing to a hemodynamically significant pericardial effusion and cardiac tamponade. This diagnosis relies predominantly on TTE to detect and quantify effusions and assess hemodynamic compromise, supported by characteristic ECG changes (diffuse ST-segment elevation and PR depression) and, when needed, CMR to confirm active pericardial inflammation[12]. ICI can also precipitate ACS. This arises from T-cell mediated localized inflammation within existing atherosclerotic plaques leading to accelerated atherosclerosis or plaque rupture. Patients typically present with classic ischemic symptoms, and the diagnosis strictly follows standard ACS protocols, requiring dynamic cardiac troponin elevations, ischemic ECG changes, and urgent coronary angiography to identify a culprit lesion. Conduction disorders, ranging from isolated first-degree atrioventricular (AV) block to life-threatening complete heart block or ventricular tachyarrhythmias, may emerge either as isolated phenomena or, more ominously, as early manifestations of underlying fulminant myocarditis. Any new conduction abnormality in an ICI-treated patient mandates immediate 12-lead ECG, and a comprehensive evaluation to rule out concurrent myocardial inflammation. Finally, Takotsubo syndrome presents as an acute ACS mimic characterized by acute chest pain, dyspnea, and ischemic ECG alterations—triggered by profound systemic inflammatory stress or an ICI-induced cytokine storm. Its diagnosis relies heavily on TTE demonstrating transient regional wall motion abnormalities (such as classic apical ballooning) that extend beyond a single epicardial coronary territory, coupled with coronary angiography demonstrating the absence of obstructive coronary artery disease. Furthermore, CMR is crucial in this setting to differentiate Takotsubo syndrome from acute ICI-myocarditis, as the former typically lacks the classic focal late gadolinium enhancement associated with true myocardial necrosis [12].

Despite the severe clinical implications of cardiovascular irAEs, their overall incidence remains relatively low. Contemporary real-world pharmacovigilance registries estimate the overall incidence of cardiovascular toxicities in between 1% and 5% across all ICI therapies. Immune-related myocarditis, the most widely recognized and fatal complication, occurs in approximately 1% of patients receiving ICI monotherapy, though the risk is more than double with dual checkpoint blockade. Despite its rarity, it demands extreme vigilance due to an alarming mortality rate that can approach

30% to 50%. Other complications, including isolated pericardial disease, conduction disorders, and acute coronary syndromes, are generally reported in less than 1% to 2% of patients treated with ICIs. However, the real incidence of subclinical cardiovascular toxicity, such as asymptomatic left ventricular dysfunction or minor biomarker elevations, is likely higher, further highlighting the necessity of routine baseline and serial cardiac evaluations [13,14].

CONCLUSIONS

In conclusion, this case highlights a durable clinical response—exceeding five years of progression-free survival with complete disease remission—achieved with second-line atezolizumab in a frail, elderly patient with metastatic urothelial carcinoma. Despite possessing a highly complex cardiovascular and renal risk profile, including NYHA class III heart failure and a high CHA_2DS_2-VA score, the patient tolerated the immune checkpoint inhibitor well without experiencing any immune-related adverse events. This case reinforces the transformative potential of immunotherapy, demonstrating that the "long-responder" benefit can be attained even in highly comorbid populations, a phenomenon potentially augmented by favorable disease biology such as lymph node-only metastases. Most importantly, it underscores the indispensable role of a multidisciplinary approach. While the catastrophic risk of cardiovascular irAEs is well-documented, severe pre-existing heart disease should not completely exclude patients from potentially life-saving treatments.

Author contributions:

A.C. and I.R.C. conceived the original draft preparation. F.M. was responsible for the data acquisition, collection and assembly of the articles, R.S.G was responsible for the conception and design. F.M. and V.S. were responsible with the supervision of the manuscript.

Compliance with Ethics Requirements:

"The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from the patient included in the study"

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