Beyond Platinum: Current Approaches to Advanced Bladder Cancer

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Presenters' disclosures of conflicts of interest are found at the end of this article.

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Abstract

There is an increasing focus on personalized treatment approaches in advanced and metastatic urothelial carcinoma (mUC). Recent advancements include biomarker-driven therapy selection, novel antibody-drug conjugates (ADCs), immune checkpoint inhibitors, and targeted therapies. Managing treatment-related toxicities remains crucial, requiring interprofessional collaboration to monitor and mitigate adverse events. At JADPRO Live 2024, presenters discussed these considerations for advanced practitioners.

Bladder cancer is the sixth most common cancer in the United States. The median age of diagnosis is 73, and in 2024, an estimated 83,000 new cases are expected, with approximately 16,800 deaths. While early stage disease can often be managed with localized treatments, nearly 10% of cases are diagnosed at an advanced or metastatic stage. Historically, platinum-based chemotherapy has been the cornerstone of treatment, but recent advances in immunotherapy, targeted therapy, and antibody-drug conjugates (ADCs) are transforming the management of advanced bladder cancer.

At JADPRO Live 2024, Arlene Siefker-Radtke, MD, Professor in Genitourinary Medical Oncology at MD Anderson Cancer Center, and Saneese K. Stephen, MPAS, PA-C, HAL APP Supervisor in Genitourinary Medical Oncology also at MD Anderson, discussed the latest updates in the management of metastatic urothelial carcinoma (mUC).

BLADDER CANCER

Most bladder cancer cases present with hematuria, which may be gross (visible) or microscopic. Some patients may experience irritative bladder symptoms, including discomfort or dysuria. Advanced disease may manifest as weight loss, abdominal pain, and bone pain, signaling disease progression. Nearly 10% of bladder cancer cases are already advanced or metastatic at diagnosis, and no well-established screening guidelines currently exist.

Staging

Staging criteria follow the National Comprehensive Cancer Network (NCCN) guidelines, with T2 disease

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(tumor invasion into the bladder muscle) being particularly significant due to its high risk for metastasis and recurrence. When bladder cancer progresses to T3 to T4 disease, it can involve lymph nodes or distant metastases, shifting the treatment focus toward palliative care rather than curative intent.

In metastatic bladder cancer, the first site of disease spread is usually the regional lymph nodes, followed by the lungs, liver, and bones, which are associated with a poor prognosis. Skin and central nervous system (CNS) metastases occur in later stages and indicate a particularly severe outlook. If left untreated, metastatic bladder cancer has a median survival of approximately 4 months.

Diagnostic Workup

The diagnostic workup for bladder cancer begins with cystoscopy, which is the gold standard for evaluating hematuria. Patients may also undergo transurethral resection of the bladder tumor (TURBT) to assess and remove visible disease. Imaging studies, including CT urography and MRI urography, are essential for detecting upper tract involvement. When muscle-invasive disease is suspected, a full-body CT scan is performed, and a bone scan may be necessary in cases with bone pain or elevated alkaline phosphatase levels. Routine laboratory tests include tumor markers such as CEA and beta-HCG, although these are not specific to bladder cancer.

"Immunohistochemistry and molecular testing are done very early for bladder cancer because bladder cancer is so aggressive, and people may not respond to the initial regimen," Mr. Stephen noted. Testing includes *HER2* and *FGFR3* alterations, which help in therapy selection.

FRONTLINE THERAPY

One breakthrough in urothelial cancer was the approval of enfortumab vedotin (Padcev; EV) with pembrolizumab (Keytruda), now considered the new frontline standard, eliminating the previous need for platinum eligibility criteria. Despite this, treatment guidelines still include options, such as gemcitabine with cisplatin and nivolumab, which offers an improved activity profile over platinum-based chemotherapy alone. Other options like dose-dense MVAC (methotrexate, vinblastine, doxorubicin, cisplatin) remain relevant to accommodate patients with different treatment needs.

Enfortumab Vedotin

Enfortumab vedotin is a humanized monoclonal antibody that targets Nectin-4, a protein expressed in over 80% of urothelial cancer tumors. Interestingly, even patients with low or undetectable Nectin-4 expression have shown responses. This treatment delivers a potent taxane-based cytotoxic agent (monomethyl auristatin E) directly into the tumor microenvironment. Once the antibody reaches the tumor, it is cleaved, releasing the toxic metabolite directly into cancerous tissue, resulting in localized and effective tumor destruction.

The phase III trial that led to the FDA approval of EV with pembrolizumab randomized patients to receive either EV + pembrolizumab or chemotherapy (gemcitabine with cisplatin or carboplatin). The trial results demonstrated unprecedented efficacy, with a median overall survival (OS) of 31 months.

"We've never seen that before, but we've also never seen a phase III trial exceed the phase II trial data," Dr. Siefker-Radtke commented.

With a median follow-up of only 17 months, further data are needed to determine the actual median survival.

Gemcitabine, Cisplatin, and Nivolumab

Another promising regimen—gemcitabine with cisplatin and nivolumab (GEM-CIS + NIVO)—also demonstrated clinical benefit. This was the first frontline trial to show an advantage with the addition of a checkpoint inhibitor (nivolumab) to chemotherapy. Notably, this benefit was observed only with cisplatin-based chemotherapy, not carboplatin. Preclinical data suggest that cisplatin may enhance immune modulation more effectively than carboplatin, leading to a greater synergistic effect when combined with immunotherapy. Additionally, GEM-CIS + NIVO demonstrated an improved objective response rate (ORR), which could be particularly valuable in patients needing rapid tumor reduction.

GEM-CIS vs. MVAC

Since the late 1990s, the standard of care has included gemcitabine plus cisplatin (GEM-CIS) and methotrexate, vinblastine, doxorubicin, cisplatin (MVAC). However, the pivotal trial comparing these regimens did not show superiority

of GEM-CIS over MVAC. Instead, GEM-CIS became widely adopted due to its improved toxicity profile. Dose-dense MVAC (ddMVAC) continues to be used, particularly in the neoadjuvant setting, where it offers a better toxicity profile and potentially improved long-term survival outcomes.

Maintenance Therapy with Avelumab

For patients who begin treatment with a platinum-based regimen but did not receive GEM-CIS + NIVO, maintenance therapy with avelumab remains a standard option. Avelumab is indicated for patients with stable disease or better after frontline platinum therapy, and clinical trial data have shown that avelumab maintenance significantly improves survival while enhancing the durability of treatment responses.

OPTIONS AFTER IMMUNOTHERAPY

Erdafitinib: FGFR Inhibitor

Erdafitinib is a targeted FGFR inhibitor for use in patients who have progressed after both chemotherapy and immune checkpoint inhibitors. This treatment is specifically indicated for patients with *FGFR3* or *FGFR2* genetic alterations, including mutations or fusions. Clinical trial data demonstrated that patients treated with erdafitinib had a median overall survival (OS) of 12 months, compared to 7.8 months with single-agent taxane chemotherapy. Additionally, the ORR was significantly higher with erdafitinib, making it an effective cytoreductive option, even for patients with liver metastases, a group that traditionally responds poorly to single-agent immunotherapy or taxane-based chemotherapy.

Enfortumab Vedotin in the Second Line

For patients who did not receive EV with pembrolizumab in the frontline setting, EV remains a strong second-line treatment option. Its efficacy in urothelial cancer has been well established, making it a preferred alternative following the failure of initial therapies.

Sacituzumab Govitecan

Sacituzumab govitecan, an antibody-drug conjugate, was previously approved for use in advanced urothelial cancer. However, the company voluntarily withdrew its FDA approval after its phase III trial did not meet expectations. Despite this, the treatment remains listed in current clinical guidelines, while discussions are ongoing

Trastuzumab Deruxtecan for HER2+

An alternative for select patients is trastuzumab deruxtecan (T-DXd), now FDA-approved across multiple tumor types for patients with HER2 IHC 3+ expression. In the bladder cancer cohort, T-DXd showed a 56% ORR in IHC 3+ patients and 35% ORR in IHC 2+ patients.

Challenges with Platinum-Based Therapy

Platinum-based chemotherapy remains a cornerstone of bladder cancer treatment, but its long-term role is uncertain. A key question is whether platinum therapy should continue to be used after multiple lines of treatment and whether it becomes more difficult to administer in later lines. Cisplatin eligibility is a significant challenge, as only less than 50% of frontline bladder cancer patients—even when in their best condition—meet the criteria for cisplatin-based chemotherapy.

Another major issue is peripheral neuropathy, particularly from EV, which can complicate treatment sequencing. Patients are considered cisplatin-ineligible if they meet any of the following criteria: glomerular filtration rate (GFR) ≤ 60 mL/min, grade ≥ 2 neuropathy, significant hearing impairment, congestive heart failure, or poor performance status (ECOG PS = 2).

For cisplatin-ineligible patients, gemcitabine with carboplatin is an alternative, but it is also associated with toxicities including neutropenia, neutropenic fever, and hospital readmissions.

MANAGING SIDE EFFECTS

Enfortumab Vedotin

Enfortumab vedotin is widely used in the first-line setting, but it presents notable toxicity risks, including rash, peripheral neuropathy, diarrhea, hyperglycemia, and pneumonitis.

"Peripheral neuropathy is a common cause of dose reductions. Some patients may have preexisting neuropathy, but if it's getting worse or it's getting to the point of a grade one or two even, treatment should be held to allow recovery," Mr. Stephen said. Management strategies involve dose reduction, pregabalin, gabapentin, and physical/occupational therapy.

Dermatologic toxicities are a major concern with EV, as they can cause severe skin reactions, including bullous dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis (TEN).

"Steroids are part of our toolkit, including antihistamines and dermatology referrals," Mr. Stephen said.

Early recognition is critical, as "Skin lesions can progress very quickly and can be fatal with the development of TEN and subsequent complications."

Hyperglycemia is another frequent side effect, occurring in approximately 13% of patients, often within the first few weeks of treatment. Patients with diabetes should undergo strict glucose monitoring before and during treatment, and they should avoid high-sugar meals.

Pneumonitis is a potential adverse event with EV and its attribution can be difficult when combined with immune checkpoint inhibitors, which also carry a risk of pneumonitis. Patients should be monitored closely for respiratory symptoms. Importantly, dose reduction is an option for EV but not for immunotherapy, making toxicity management complex when these drugs are used in combination.

Erdafitinib

Erdafitinib has ocular and metabolic side effects. Ocular side effects have been reported at a fairly high number, and include serous retinopathy, retinal detachment, but it can also be some lower-level side effects such as dry eyes and cataracts. Some patients may experience dry eyes and cataracts, which, while less severe, still require careful monitoring. Patients should report any vision changes immediately, and regular ophthalmology evaluations should be scheduled.

"You want to get your ophthalmologist on speed dial, get the patient quickly examined, and hold the treatment, as it can become irreversible if it's not treated or managed early," Mr. Stephen said.

Hyperphosphatemia is another common side effect of erdafitinib and must be managed proactively. Patients should be advised to limit foods high in phosphorus, such as processed foods, lentils, and black-eyed peas. If dietary adjustments are insufficient, phosphate binders or phosphaturic agents may be necessary.

Skin toxicity can also occur with erdafitinib, requiring steroid creams and dermatology referrals for proper management.

Trastuzumab Deruxtecan

Trastuzumab deruxtecan (T-DXd), used in HER2-positive urothelial cancer, has potential risks for cardiac, pulmonary, and renal toxicity, requiring careful monitoring.

"Trastuzumab is associated with cardiotoxicity. Check the echocardiogram first. Keep a timetable to monitor every 3 months on treatment, get a basic understanding of the patient's cardiovascular risk status, and control their blood pressure," advised Mr. Stephen. Managing hypertension and cardiovascular risk factors is essential to reducing the likelihood of cardiac complications.

Pulmonary toxicity is another significant risk, with patients potentially developing interstitial pneumonitis and acute respiratory distress syndrome (ARDS).

"Pulmonary toxicity, interstitial pneumonitis, and acute respiratory distress syndrome—these are problematic side effects that can happen," Mr. Stephen said. "So you want to be cautious while monitoring patients on treatment. Get their breathing status and assess their symptoms."

Frequent respiratory assessments should be performed, and any new symptoms such as shortness of breath should be promptly evaluated.

Renal toxicity, including nephrotic syndrome, is another concern with trastuzumab deruxtecan, making renal function monitoring an essential part of patient management.

"There are a lot of things to monitor on trastuzumab that can be detrimental to patients' overall health, so you want to pay close attention." Mr. Stephen concluded.

Disclosure

Dr. Siefker-Radtke has served on advisory boards for AbbVie, Astellas, AstraZeneca, Basilea, Bicycle Therapeutics, Bristol Myers Squibb, Genentech, G1 Therapeutics, Gilead, Ideeya Biosciences, Immunomedics, Janssen, Loxo, Merck, Mirati, Nektar Therapeutics, Seattle Genetics, and Taiho. Mr. Stephen has no relevant financial relationships to disclose.