How I Do It: Maintenance avelumab for advanced urothelial carcinoma

Aly-Khan A. Lalani, MD
Department of Oncology, Juravinski Cancer Centre, McMaster University, Hamilton, Ontario, Canada

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For more than four decades, platinum-based chemotherapy regimens have served as the established standard-of-care for advanced urothelial carcinoma (aUC). However, advancements in our understanding of cancer biology and tumor microenvironment have reshaped the therapeutic landscape and prognosis of this incurable disease. Immune checkpoint inhibitors (ICIs) that target programmed cell death 1 (PD-1) and programmed cell death ligand 1 (PD-L1) are firmly established tools in aUC management, leading to enhanced life span and improved quality of life for patients.

In patients who achieved stable disease or better following platinum-based chemotherapy, maintenance therapy with the PD-L1 antibody avelumab significantly enhanced overall survival (OS) by approximately 7 months compared to best supportive care in the phase 3 JAVELIN Bladder 100 trial. As a result, avelumab received FDA approval in June 2020 as a maintenance therapy for aUC patients treated with first-line platinum-based chemotherapy. Therefore, aUC care plans should incorporate maintenance avelumab into standard first-line treatment regimens for these patients.

The objective of this brief article is to provide insight into the utilization of avelumab, identify patients who may benefit from this treatment, and review the methodology, advantages, potential side effects and their management.

Key Words: avelumab, advanced urothelial carcinoma, bladder cancer, metastatic, immune checkpoint inhibitor

Introduction

Avelumab is a human monoclonal antibody designed to target the programmed death-ligand 1 (PD-L1) protein. This therapeutic agent falls into a class of medications known as immune checkpoint inhibitors (ICIs). Its mechanism of action involves blocking the interaction between PD-L1, which is expressed on the surface of cancer cells, and programmed cell death protein 1 (PD-1), a receptor found on immune cells. The PD-1 and PD-L1 interaction plays a crucial role in shielding malignant cells from the immune system's surveillance. By binding to PD-L1, avelumab effectively inhibits this interaction, thereby helping to restore the immune system's ability to recognize and attack cancer cells.

Urothelial carcinoma, characterized by genomic instability, a high level of PD-L1 expression, and a relatively high tumor mutational burden, presents an appealing target for the utilization of ICIs like avelumab. These distinctive characteristics have shown a propensity for enhanced response to ICI therapy in tumor cells.[1] Various anti-PD-1 and anti-PD-L1 ICIs have received approval for the treatment of patients with advanced urothelial carcinoma (aUC). These approvals encompass a range of scenarios, including in

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Address correspondence to Dr. Aly-Khan Lalani, Division of Medical Oncology, Juravinski Cancer Centre, 699 Concession Street, Hamilton, ON L8V 5C2 Canada

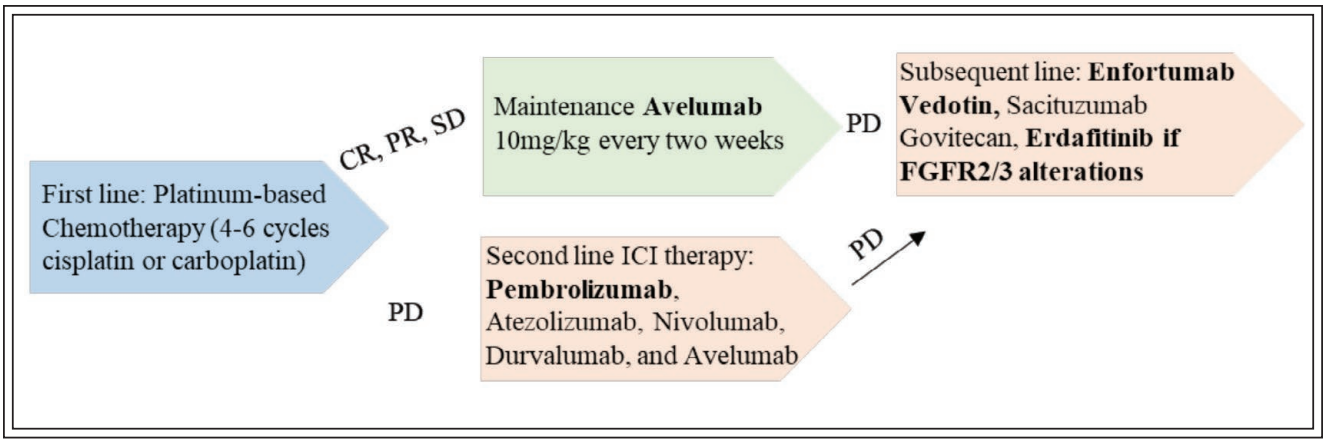

Figure 1. Advanced urothelial carcinoma treatment algorithm.
CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; ICI = immune checkpoint inhibitors. **Bolded** therapies are those with positive phase 3 trial results with overall survival benefits.

patients who achieved stable disease or better following platinum-based chemotherapy (avelumab), those who experienced disease progression after platinum-based chemotherapy (pembrolizumab, atezolizumab, nivolumab, durvalumab, and avelumab), individuals with PD-L1–positive tumors who are ineligible for cisplatin-based chemotherapy (pembrolizumab, atezolizumab), and patients who are not suitable for platinum-based chemotherapy in the first line (pembrolizumab, atezolizumab), Figure 1.[2-4]

Avelumab (brand name Bavencio) is the first and only ICI approved in the first-line maintenance setting for patients with aUC. Due to its immune-priming effects first-line chemotherapy predisposes the tumor to avelumab maintenance therapy resulting in enhanced antitumor activity while minimizing cumulative toxicity.

Brief historical perspective

Platinum-based chemotherapy has long served as the established standard-of-care for the first-line treatment of aUC in eligible patients.[5] Cisplatin-based regimens, such as cisplatin–gemcitabine or methotrexate, vinblastine, doxorubicin and cisplatin (MVAC), have demonstrated historical median overall survival (OS) benchmarks of 14-15 months and a 5-year OS ranging from 13%-15%.[6] For patients who are ineligible for cisplatin but are fit enough to receive chemotherapy, a combination of gemcitabine and carboplatin is utilized, providing antitumor benefits with reduced toxicity, albeit with diminished efficacy (median OS of 9-13 months).[7] Following chemotherapy, patients underwent observation and subsequently received ICI treatment (specifically pembrolizumab, a PD-1 inhibitor) as second-line therapy upon disease progression. The administration of pembrolizumab following platinum-based chemotherapy led to an improvement in median OS of approximately 3 months, from 7.4 months (95% CI, 6.1 to 8.3) in the chemotherapy group to 10.3 months (95%CI, 8.0 to 11.8) in the pembrolizumab group (hazard ratio for death, 0.73; 95% CI, 0.59 to 0.91; p = 0.002).[2]

In June 2020, a significant milestone was reached with the FDA approval of avelumab as a first-line maintenance therapy for patients who achieved stable disease with platinum-based chemotherapy. In the JAVELIN Bladder 100 trial, avelumab improved median OS by over 7 months from 14.3 months in the control group to 21.4 months (hazard ratio for death, 0.69; 95% CI, 0.56 to 0.86; p = 0.001). Survival rate at the 1-year mark was also enhanced (71.3% with avelumab compared to 58.4% in the control group).[8] Long-term follow up data from the trial demonstrated a median OS of 23.8 months with avelumab compared to 15 months with best supportive care alone (HR, 0.76; 95% CI, 0.63-0.91; p = 0.0036). Moreover, avelumab significantly enhanced progression-free survival, with 5.5 months compared to 2.1 months, respectively (HR, 0.54 [95% CI, 0.46-0.64]; p < 0.0001).[9] In patients that received maintenance avelumab for over a year (33.7% of patients) median OS was not reached (95% CI, 50.9 months-not estimable), and median PFS was 26.7 months (95% CI, 19.4-32.2).[10] Notably, subgroup analysis revealed that maintenance avelumab provides similar OS and PFS benefits, as well as comparable safety profiles, irrespective of whether cisplatin- or carboplatin-

based chemotherapy was administered as the first-line treatment.[11] These data further support maintenance treatment with avelumab as a global standard of care.

In addition to OS and PFS benefits, avelumab also enhances the overall quality of life (QoL) for patients with aUC. A post-hoc analysis of the JAVELIN Bladder 100 trial used a quality-adjusted time without cancer symptoms or toxicity (Q-TWiST) analysis to assess between-treatment differences in patient QoL.[12] The Q-TWiST analysis is an integrated, single-value measure that incorporates efficacy, safety, and patient-reported outcomes to help contextualize the true clinical benefit of an intervention. Mean OS was separated into three health states: time with all-cause grade ≥ 3 toxicity (TOX) prior to progression, time without all-cause grade ≥ 3 toxicity or symptoms of disease progression (TWiST), and time after progression or relapse (REL). Although time in TOX was slightly higher with avelumab compared to best supportive care alone, patients on maintenance avelumab achieved greater quality-adjusted time by progressing more slowly (shorter REL) and living longer (greater OS).

Who are the ideal candidates for prescribing avelumab?

Patients with unresectable, locally advanced or metastatic UC whose disease has not progressed following treatment with first-line platinum-based chemotherapy and are eligible to receive ICI therapy.

Further identification-practical considerations

The approval of avelumab as a maintenance treatment for patients with aUC necessitated a reassessment of our approach to patient counseling at the time of starting upfront chemotherapy. It is important to note that the treatment of aUC is considered palliative, focusing on care plans that concentrate on symptom management and thereby also improve quality and quantity of life.

Previously, the standard approach involved initiating first-line platinum-based chemotherapy and then closely monitoring the patient until disease relapse, at which point they would transition to second-line treatment with an ICI such as pembrolizumab. However, the approval of avelumab as a first-line maintenance treatment introduced a paradigm shift in patient care. Now, patients would benefit from discussion around and introduction of ICI therapy (with avelumab) once disease control is demonstrated with first line platinum chemotherapy. Eligible patients would thus move on from chemotherapy to ICI treatment, allowing them to benefit from the survival advantages of first-line therapy while also experiencing a longer period without disease progression.

This shift in treatment strategy requires a change in mindset when discussing the treatment plan with patients. By the end of the chemotherapy phase, patients often experience treatment fatigue. Therefore, it becomes crucial to prepare them in advance for the continuation of "switch-maintenance" treatment and the differential side effect profile of ICI therapy compared to chemotherapy. Ensuring that patients fully comprehend the treatment plan, ideally upfront, and are actively involved in the decision-making process will potentially improve compliance with this approach throughout treatment.

Practice prescribing information

1. Avelumab is administered as an intravenous infusion (IV) at 10 mg/kg body weight over 60 minutes every 2 weeks until disease progression or unacceptable toxicity following 4 to 6 cycles of first-line platinum-based chemotherapy (gemcitabine + cisplatin and/or gemcitabine + carboplatin) and within 4-10 weeks after the last dose.
2. Dose escalations or reductions are not recommended for avelumab. Doses may be delayed or discontinued based on toxicity. It is recommended that treatment is maintained until disease progression or unacceptable toxicity. Clinically stable patients with initial evidence of disease progression may remain on treatment until disease progression is confirmed.
3. Avelumab should not be administered as an IV push or bolus.
4. Important considerations: the use of corticosteroids or immunosuppressants prior to starting treatment should be avoided as they may interfere with ICI (i.e. avelumab) efficacy.
5. Premedication with an antihistamine and acetaminophen prior to the first 4 infusions is recommended and should be considered for subsequent infusions based on clinical judgment and prior infusion reactions.
6. Monitoring recommendations: CBC, chemistry, liver and thyroid function tests are recommended at baseline, before each dose and as clinically indicated. Renal function tests and blood glucose should be measured at baseline and periodically during the treatment. Clinical toxicity assessment for infusion-related reactions, fatigue, immune-mediated reactions, including GI, skin, respiratory, neurologic, cardiac, ophthalmic and endocrine toxicities should be examined at each visit.

TABLE 1. **First-line maintenance Avelumab for aUC: side effects, frequency and management**[13]

Side effect	Frequency/incidence	Management
Infusion-related reactions	Total 25% Grade 3 0.5% Grade 4 0.2%	Premedicate patients with an antihistamine and acetaminophen prior to the first 4 infusions and for subsequent infusions based upon clinical judgment and presence/severity of prior infusion reactions. Monitor patients for signs and symptoms of infusion-related reactions, including pyrexia, chills, flushing, hypotension, dyspnea, wheezing, back pain, abdominal pain, and urticaria. Interrupt or slow the rate of infusion for Grade 1 or Grade 2 infusion-related reactions. Permanently discontinue avelumab for Grade 3 or Grade 4 infusion-related reactions.
Immune-mediated pneumonitis	1.2%	Delay avelumab for Grade 2, and permanently discontinue for discontinue for Grade 3 or Grade 4. Administer systemic corticosteroids.
Immune-mediated colitis	1.5%	Delay avelumab for Grade 2 or Grade 3, and permanently discontinue for Grade 4 colitis. Administer systemic corticosteroids.
Hepatotoxicity and immune-mediated hepatitis	0.9%	Delay or permanently discontinue avelumab based on tumor involvement of the liver and severity of aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin elevation. Administer systemic corticosteroids.
Immune-mediated adrenal insufficiency	0.5%	For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement, as clinically indicated. Delay avelumab treatment for Grade 3 or Grade 4 endocrinopathies until clinically stable or permanently discontinue depending on severity. Administer systemic corticosteroids.
Immune-mediated hypophysitis	0.1%	Hypophysitis can present with acute symptoms associated with mass effects such as headache, photophobia, or visual field defects. Hypophysitis can cause hypopituitarism. Initiate hormone replacement, as clinically indicated. Delay avelumab treatment for Grade 3 or Grade 4 endocrinopathies until clinically stable or permanently discontinue depending on severity.
Immune-mediated thyroid disorders	Thyroiditis 0.2% Hyperthyroidism 0.4% Hypothyroidism 5%	Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism. Initiate hormone replacement for hypothyroidism or institute medical management of hyperthyroidism, as clinically indicated. Delay avelumab treatment for Grade 3 or Grade 4 endocrinopathies until clinically stable or permanently discontinue depending on severity.
Immune-mediated type I diabetes mellitus	0.1%	This can present with diabetic ketoacidosis. Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated. Delay avelumab treatment for Grade 3 or Grade 4 endocrinopathies until clinically stable or permanently discontinue depending on severity.
Immune-mediated nephritis with renal dysfunction	0.1%	Delay avelumab treatment for Grade 2 or Grade 3, and permanently discontinue for Grade 4 increased blood creatinine.

TABLE 1 (Cont'd). **First-line maintenance Avelumab for aUC: side effects, frequency and management**[13]

Side effect	Frequency/incidence	Management
Immune-mediated dermatologic adverse reactions	5%	These include rash or dermatitis. Exfoliative dermatitis including Stevens Johnson Syndrome (SJS), drug rash with eosinophilia and systemic symptoms (DRESS), and toxic epidermal necrolysis (TEN), has occurred with PD-1/PD-L1 blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-exfoliative rashes. Delay avelumab treatment for suspected and permanently discontinue for confirmed SJS, TEN, or DRESS.
Other immune-mediated adverse reactions	< 1%	Other clinically significant immune-mediated adverse reactions occurred at an incidence of < 1% in patients who received avelumab or were reported with the use of other PD-1/PD-L1 blocking antibodies. For myocarditis, permanently discontinue avelumab for Grade 2, Grade 3, or Grade 4. For neurological toxicities, delay avelumab treatment for Grade 2 and permanently discontinue for Grade 3 or Grade 4.

Side effects of avelumab

ICIs enhance the reaction of the immune system against tumor cells and are associated with unique immune-related adverse effects (irAEs) that can range from mild to life-threatening. These side effects tend to be distinct from those of conventional chemotherapy and can occur in any organ system or tissue at any time after the initiation of treatment, including long after the completion of treatment. Early identification of irAEs and appropriate management can improve quality of life and safety for patients. Monitoring liver enzymes, creatinine and thyroid function periodically throughout treatment is imperative. The most common side effects for avelumab include fatigue (35%), musculoskeletal pain (24%), urinary tract infection (20%), and rash (20%).

Side effects identified in trial participants by organ system and their prevalence (%):

1. General: fatigue (35%), fever, chills (15%), edema (13%).
2. Cardiovascular: hypertension (10%), hypotension (2%), myocarditis (rare).
3. Dermatological: rash, pruritus (20%) (1% severe), erythema multiforme (rare).
4. Gastrointestinal: diarrhea (17%) (may be severe, 2% colitis), constipation (16%), nausea, vomiting (16%), anorexia, weight loss (14%), abdominal pain (13%).
5. Hematological: anemia (16%).
6. Hepatobiliary: ↑ LFTs (5%) (2% severe; 1% autoimmune hepatitis), pancreatitis (rare, in combination with axitinib).
7. Immune: antibody response (4%).
8. Metabolic/Endocrine: hypothyroidism (12%), hyperthyroidism (6%), hyperglycemia (4%); diabetes mellitus (type 1; rare), adrenal insufficiency (2%).
9. Musculoskeletal: musculoskeletal pain (24%), other - rheumatoid arthritis (rare).
10. Nervous system: myositis (< 1%), Guillain-Barre syndrome (rare), Myasthenia gravis (rare).
11. Ophthalmic: uveitis (rare).
12. Renal: nephrotoxicity (2%) (nephritis - rare).
13. Respiratory: cough, dyspnea (14%), pneumonitis (3%).
14. Urinary: urinary tract infection (20%).

Management of irAES

Dose reductions are not recommended for avelumab. Treatment should be delayed or permanently discontinued depending on irAE severity. In general, treatment should be delayed for severe (Grade 3) irAEs and permanently discontinued for life-threatening (Grade 4), and recurrent severe (Grade 3) irAEs that require systemic immunosuppression. Side effects along with their frequency and management can be found in Table 1.

Practical counseling of uro-oncology patients

Patients with aUC are often older (8^{th}-9^{th} decade of life) and potentially frail at the time of their advanced/metastatic disease diagnosis. There can be substantial comorbidities accumulated along their lifespan.

Disease progression can often be physically devastating beyond the mental and psychological impact of their cancer. Therefore, there is often an urgent need to achieve – and maintain – disease response or stability through effective systemic anticancer therapy. To date, platinum-based chemotherapy continues to be a global standard for first-line treatment – though other combinations are being tested against this treatment. For patients who achieve disease stability on this chemotherapy, it is critical to maintain this benefit for as long as possible. Avelumab offers an option to do so with level I evidence for OS benefit.

Practically, I find that the care plan discussion at the start of first-line chemotherapy should clearly answer the pertinent question patients have: "What next then?" Explaining the 'switch maintenance' approach to patients at the earliest possible time will improve patient understanding, enhance compliance, and provide reassurance that active treatment will be continued even in the face of potential response to 4-6 cycles of chemotherapy. Outlining the time window to switch to avelumab (generally 4-10 weeks post chemotherapy completion) will also be a relief for patients that need some time to recover from the known physical and mental toxicities of chemotherapy.

In terms of management on treatment, I find that physician, nursing, and treatment unit awareness of the potential infusion reactions (largely low grade) will also help with patient compliance and confidence in this treatment approach. The administration of appropriate supportive pre-medications (outlined above) will help support the vast majority of patients through this important maintenance therapy. Treatment units globally are generally experienced with infusion reactions across cytotoxic or other systemic anticancer regimens; nuanced awareness is beneficial when considering avelumab and other ICIs in this context.

Finally, maintaining close clinical and radiographic follow up in this maintenance setting is important even though these are patients, by definition, who benefitted from platinum-based chemotherapy. This will allow capturing progression as early as possible to afford the next line (post-chemotherapy, post ICI) options that are increasingly available for aUC. Ultimately, this will help ensure that many effective agents are available to our aUC patients to collectively improve their quality and quantity of life along their cancer journey.

Conclusions

The introduction of maintenance avelumab in the treatment armamentarium for patients with aUC (who experienced stable disease or better on first line chemotherapy) has been shown to meaningfully improve their OS and QoL. Given the prevalence of ICI-based therapies across cancer programs globally, this treatment is largely straightforward in clinics that are experienced in treating aUC with systemic therapies. Discussing and incorporating this treatment in all eligible patients early in their treatment plans will help ensure our patients receive the most effective lines of therapy for this diverse disease. □

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