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# Advanced Urothelial Cancer: Updates in Frontline Systemic Therapy

The treatment of urothelial cancer can present challenges given the tendency for patients with early-stage tumors to experience rapid progression to advanced disease following standard management. Additionally, recent data on the use of immunotherapy in the frontline setting have left many wondering where to place that category of agents in the treatment paradigm.

Experts discussed these topics in a virtual CancerNetwork® *Around the Practice* presentation, “Advanced Urothelial Cancer,” held on July 14, 2021, and moderated by Petros Grivas, MD, PhD. Members of the audience also participated in an interactive online platform by submitting responses to polling questions that were subsequently discussed by the panelists.

## Typical Presentation of Urothelial Carcinoma

When polled about the patients treated in their clinics, most respondents indicated that between 30% and 40% of their practice consists of patients who have locally advanced or metastatic urothelial cancer. In the discussion following the poll, the panel discussed risk factors for the disease and typical patient presentation at the time of diagnosis.

Neeraj Agarwal, MD, noted common risk factors in the United States that he reviews with all his trainees, including White race, male sex, and having environmental and social risk factors such as exposure to

hydrocarbons and a smoking history. Thomas Powles, MBBS, MD, pointed out that in his practice in the United Kingdom, metastatic disease is often seen in the clinic following progression from an earlier setting, also speaking to the long patient journey in this disease.

The discussion then shifted to disease prognosis in these patients, with physical functioning and assessment standards such as the Bajorin criteria, defined as performance status plus the presence of visceral metastases, which have come into play for most of the panel.<sup>1</sup> Powles noted specifically that patients with node-only disease in the absence of visceral metastases do well irrespective of systemic therapy. Other factors influencing treatment success include renal function, cisplatin eligibility, and albumin levels.

## Diagnostic and Treatment Challenges

As the panel moved forward in their discussion, they noted that diagnosis of both early and metastatic disease can sometimes be quite challenging, because early indicators of disease tend to be nonspecific to bladder cancer.

“Urinary tract infections [UTIs] are of course a much more common cause of dysuria. You can have kidney stones suspected, so it’s important [in] somebody who has long-standing symptoms [that] they keep coming back [for monitoring],” said Guru Sonpavde, MD. “Start suspecting bladder

cancer when you see hematuria, even microscopic hematuria, because this cancer does colonize in the lining of the bladder and does tend to cause hematuria early on. That is something to be vigilant about; voiding symptoms are not always UTIs or infections, so always be mindful of that, especially in women. It tends to get misdiagnosed frequently as UTIs for a while.”

Considering systemic treatment, Agarwal discussed a study he coauthored. The results indicated that less than half of patients with metastatic disease treated in the frontline setting received this care and that about 15% to 20% received it as second-line therapy.<sup>2</sup>

“These data were based on the studies done until 2018, so we did not have enfortumab vedotin [Padcev] or sacituzumab govitecan [Trodelvy], which were just approved [by the FDA in 2019 and 2020, respectively]. But PD-1/PD-L1 inhibitors were already approved in the United States, so these data were alarming to me,” Agarwal said.

### Guidelines Recommendations

Per professional guidelines such as those from the National Comprehensive Cancer Network (NCCN)<sup>3</sup> and the European Society for Medical Oncology, treatment choice in the frontline setting typically hinges on whether the patient is fit for cisplatin-based chemotherapy, which has the highest level of evidence in this patient population. In patients who cannot receive the frontline standard of gemcitabine plus cisplatin, gemcitabine plus carboplatin is an acceptable treatment alternative.

“The reality is that both of these [doublets], in recent...randomized studies, [demonstrated similar] response rates: between 45% and 55% for gemcitabine plus cisplatin and between 45% and 50% for gemcitabine plus carboplatin,” Powles said. “Median progression-free survival for both regimens [is about] 6 to 8 months, and overall survival for both regimens is in the area of 12 to 14 months.”

Another patient subgroup that has emerged includes those who are not

eligible for cisplatin and highly express PD-L1. For them, atezolizumab (Tecentriq) and pembrolizumab (Keytruda) are approved and supported by level 3b evidence per the NCCN.<sup>3-5</sup>

“[Approval was based] off single-arm trials at relatively modest numbers. The original trials had an all-comer population, but the labels were [later] restricted when the randomized trials were performed,” said Powles.<sup>6</sup> Those randomized trials didn’t show or haven’t yet shown an advantage for immune checkpoint inhibitors [ICIs] over standard chemotherapy. What we’ve learned is that if you give up-front ICIs, the response rates [are] lower than [with] chemotherapy. Many patients progress, and then you don’t get the opportunity to sequence in other drugs.”

Continuing with the topic of placement of immunotherapy in the frontline setting, Powles pivoted the discussion to maintenance therapy with the PD-L1 antibody avelumab (Bavencio).

“The global community currently [considers] the standard of care [to be] gemcitabine [plus cisplatin or carboplatin], followed by maintenance avelumab in those patients who are not progressing,” he said.

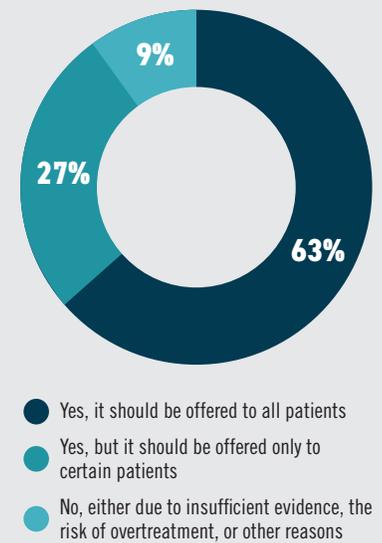
Grivas then posed a question to the audience about their preferred management of patients who are not eligible for cisplatin in the frontline setting but have high PD-L1 expression. Between carboplatin plus gemcitabine or an ICI, about 75% of respondents said they would opt to stick with chemotherapy. The panel agreed that if a patient such as this presented to their practice, the preferred course of treatment would involve frontline chemotherapy with avelumab maintenance.

### Maintenance Therapy

When polled about the role of frontline maintenance in advanced urothelial carcinoma, 63% of respondents said they offer it to all their patients and another 27% reported using it in certain patients (Figure).

“Patients do well with chemotherapy, but resistance occurs very quickly and

**FIGURE. AUDIENCE POLL: Do you think first-line maintenance therapy has a role in the management of advanced urothelial carcinoma?**



there’s a real frustration,” said Powles. “Second-line therapy is too late for most patients—even those patients who get second-line chemotherapy or second-line ICIs. When the cancer [is] growing fast, the principle is, can we just maintain that control?”

In discussing the evolution of maintenance therapy in this patient population, Powles then pointed to a study he coauthored on the use of lapatinib (Tukysa) maintenance in those with *HER1/HER2* overexpression.<sup>7</sup> That was among the first trials to examine this principle, although the end points remained unreached. However, these results did not shut the door on the principle of maintenance therapy altogether.

“When the ICIs came out, it became apparent that second-line immune therapy with pembrolizumab was too late for most...and first-line ICIs didn’t get it under control in enough patients,” Powles said. “It’s sort of that Goldilocks effect of not too late and not too early, which is why I think that the [JAVELIN Bladder 100 trial (NCT02603432)] turned out to be a success.”

**“I don’t have any reason to wait for disease progression to happen before I can talk about immunotherapy... this is a fantastic opportunity for our patients to receive an immunotherapy in the first line.”**

—Neeraj Agarwal, MD

The phase 3 trial served as the rationale for the approval of avelumab in the front-line maintenance setting after the agent resulted in an improvement in overall survival vs best supportive care in both the overall cohort (HR, 0.69; 95% CI, 0.56-0.86;  $P = .001$ ) and patients with PD-L1–positive tumors (HR, 0.56; 95% CI, 0.40-.079;  $P < .001$ ).<sup>8,9</sup>

“In general, I offer maintenance avelumab to all the patients who satisfy the criteria in the trial. That includes patients with complete response, partial response, or stable disease with 4 to 6 cycles of platinum-based chemotherapy,” said Sonpavde. He went on to say that he considers holding maintenance only for certain patients—those with lymph node–positive disease, in whom he is confident of complete remission, out of concern of overtreatment.

“The vast majority of patients are progressing. Only [about] one-fifth of these patients are ever going to receive second-line therapy because they [progress] so fast,” Agarwal said. “Based on those 2 reasons, I don’t have any reason to wait for disease progression to happen before I can talk about immunotherapy. For me, this is a fantastic opportunity for our patients to receive an immunotherapy in the first line without having to wait for disease progression.<sup>1</sup>”

### Patient Case Discussion

Grivas then brought the conversation to its practical application in a patient case.

### CASE

A man, aged 78 years, presents with frontline PD-L1–positive metastatic urothelial carcinoma. He has an ECOG performance status of 1, creatinine clearance of 50 mL/min, and grade 2 peripheral neuropathy.

“This patient has a creatinine clearance of 50 mL/min. Sonpavde and colleagues had published data on splitting the cisplatin between the creatinine clearance of 50 and 60 mL/min. But based on peripheral neuropathy, I would not be inclined to do that. In this case, not only is kidney function impaired but the patient also has neuropathy, and that brings him into the realm of cisplatin ineligibility. It makes it more clear to me, so I would definitely offer carboplatin rather than an ICI alone,” said Agarwal.

“I agree that the JAVELIN paradigm of carboplatin and gemcitabine for 4 to 6 cycles followed by switch maintenance avelumab is reasonable, but I think we should remember pembrolizumab. The higher level of evidence would favor the JAVELIN paradigm because it’s a phase 3 trial, but I think that first-line pembrolizumab or atezolizumab is reasonable in this patient,” Sonpavde said.

When choosing chemotherapy followed by maintenance immunotherapy in a patient such as this, Powles did consider the toxicity profile of this regimen. “Not everyone has that easy journey, and many patients are beginning to struggle a

little bit by the time they get to cycle 4, 5, or 6. Then there comes a question about how hard you want to push the toxicity, whether you want a dose reduction, or if you want to give all 6 cycles...[For] many patients, if they’ve had a rough journey with chemotherapy and want a few weeks off, I understand that.”

Despite a patient’s potentially difficult journey through cycles of chemotherapy, Powles concluded by highlighting the overall tolerable safety profile of maintenance immunotherapy.

“[What] we do know is [that] the adverse [effect] profile of avelumab and the other ICIs, and quality-of-life data, do suggest that things would be relatively stable. On the whole, it’s reasonable to say to patients, ‘The second part of the journey’s probably a bit easier than the first part,’” he concluded. ■

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EDITOR’S NOTE: Interview quotes slightly modified for readability.