Improving Outcomes for Patients With Advanced Urothelial Carcinoma

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

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Abstract

At JADPRO Live 2019, Petros Grivas, MD, PhD, and Jeannette Hammond, PA-C, reviewed data regarding mechanistic activity, efficacy, and safety of approved and emerging therapies for advanced or metastatic urothelial carcinoma, the selection of appropriate lines of therapy, and strategies for managing adverse events.

The sixth-most common cancer, urothelial carcinoma led to an estimated 17,670 deaths in the US in 2019, and as of 2016, nearly 700,000 people in the US were living with the disease. In addition, because the average age at diagnosis is 73, patients often present with medical comorbidities that pose challenges to providers who are determining treatment regimens. At JADPRO Live 2019, Petros Grivas, MD, PhD, and Jeannette Hammond, PA-C, of University of Washington/Seattle Cancer Care Alliance/Fred Hutchinson Cancer Research Center, discussed approved and emerging therapeutic options for advanced or metastatic urothelial carcinoma. The presenters also evaluated strategies for managing adverse events associated with approved therapies.

Ms. Hammond, a physician assistant at Seattle Cancer Care Alliance and a teaching associate at the University of Washington School of Medicine, noted that while urothelial and bladder cancer are often used interchangeably, the distinction is one of histological vs. anatomic origin, respectively. Urothelial cancer most commonly arises from the bladder, said Ms. Hammond, but it can involve other parts of the urinary tract, including the pelvis of the kidney, ureters, and urethra.

NONMUSCLE–INVASIVE BLADDER CANCER

As Ms. Hammond reported, 75% of new cases of bladder cancer fall into the category of nonmuscle–invasive disease, and between 30% and 80% of patients will recur within 5 years. Bacillus Calmette-Guérin (BCG), given intravesically (via bladder instillation), is the main therapy used for intermediate and high risk, said Ms. Hammond, but immediate postoperative intravesical gemcitabine or mitomycin may decrease the risk of recurrence in certain cases. Ms. Hammond also reported a manu-

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facturing national shortage of BCG. Although the American Urological Association has guidelines about how to prioritize patients, this shortage is an ongoing problem that requires the continuous attention of multiple stakeholders.

For patients with BCG-unresponsive disease, the standard treatment is radical cystectomy and pelvic lymph node dissection. As Ms. Hammond explained, however, a number of patients are not fit enough for radical cystectomy because of medical comorbidities or poor performance status, while some patients may refuse cystectomy. Unfortunately, said Ms. Hammond, there have been limited treatment options available for these patients, although there are ongoing clinical trials of checkpoint inhibitors and other agents in this population.

In January 2020, the immune checkpoint inhibitor pembrolizumab received FDA approval for the management of patients with BCG-unresponsive carcinoma in situ who either can't get or refuse radical cystectomy. In April 2020, the FDA approved mitomycin gel for the treatment of low-grade urothelial carcinoma of the upper urinary tract (kidney pelvis/ureter).

MUSCLE-INVASIVE BLADDER CANCER

The remaining 25% of cases at initial presentation fall into the category of muscle-invasive bladder cancer, which is treated with a combination of definitive localregional therapy with systemic therapy. There is a strong rationale for introducing chemotherapy before surgery, said Ms. Hammond, who noted that neoadjuvant cisplatin-based chemotherapy offers an overall survival benefit and earlier attempt for eradication of micro-metastasis, which can be the most common cause of cancer-related morbidity and mortality.

"Neoadjuvant cisplatin-based chemotherapy also offers an opportunity to assess tumor biology and behavior in vivo real time, which can have both prognostic and management implications down the road," said Ms. Hammond. "We can also look at biomarkers in tumor tissue, blood, urine, or stool for research."

There are a couple of different regimens used in the (neo)adjuvant setting, said Ms. Hammond: gemcitabine/cisplatin is more commonly used and could be associated with potential side effects, including fatigue, kidney impairment, nausea, vomiting, peripheral neuropathy, tinnitus, hearing loss, risk of infection, bleeding, blood clots, mouth sores, among others; another regimen is dose-dense or accelerated MVAC (methotrexate, vinblastine, doxorubicin, cisplatin) with growth factor support and is associated with a relatively shorter time to surgery. Retrospective datasets and a phase II clinical trial have shown comparable pathological complete response rates between gemcitabine/cisplatin and accelerated MVAC regimens (either can be used in this setting).

Dr. Grivas, an associate professor at the University of Washington School of Medicine and Clinical Director, Genitourinary Cancers Program at UW Medicine, reported that there is level I evidence supporting the use of cisplatin-based combination neoadjuvant chemotherapy. A meta-analysis of 10 randomized trials (2,688 patients) comparing cisplatin-based combination neoadjuvant chemotherapy plus local therapy vs. definitive local therapy alone has shown improved overall survival for patients with neoadjuvant chemotherapy as well as a lower risk of recurrence (Advanced Bladder Cancer Meta-analysis Collaboration, 2003). As Dr. Grivas reported, however, non–cisplatin-based chemotherapy in the neoadjuvant or adjuvant setting in bladder cancer has no proven overall survival benefit and should not be used. Immunotherapy and combination chemotherapy/immunotherapy regimens are being actively investigated in this space, Dr. Grivas added, but clinical trials with more patients and longer follow-up are needed. Moreover, the less definitive, but often important in selected cases, role of adjuvant cisplatin-based chemotherapy was discussed, along with the very interesting ongoing clinical trials evaluating immune checkpoint inhibitors or anti-FGFR targeted therapy.

For patients with metastatic urothelial carcinoma who are cisplatin-ineligible (approximately 50% of patients), two immune checkpoint inhibitors are options in the first-line setting for those whose tumors exhibit high PD-L1 expression based on the appropriate companion assay (or cannot tolerate even carboplatin in the US), and as Dr. Grivas reported, both atezolizumab and pembrolizumab have demonstrated similar level of evidence based on single-arm phase II trials (Balar

et al., 2017a, 2017b; Table 1). However, carboplatin/gemcitabine is another option for those cisplatin-ineligible, chemotherapy-naive patients in the first-line setting. Patients without prior chemotherapy who can receive cisplatin usually receive gemcitabine/cisplatin in this setting. Clinical trials are usually preferred, as in any treatment setting.

"There are six large, randomized, phase III clinical trials in the first-line setting that will help shape the future landscape of how these patients are treated when they are diagnosed with metastatic disease, but we don't have all the answers yet," said Dr. Grivas. "We have to wait for the data to mature, but one take-home point as of today is if you have low PD-L1 expression in tumor tissue and you are not fit for cisplatin but you are fit for carboplatin, you should get chemotherapy and not checkpoint inhibitor alone for the moment."

For patients with PD-L1–high tumors, Dr. Grivas added, longer follow-up is needed to determine whether checkpoint inhibitor alone may beat, or not, chemotherapy, but the data is not yet mature. Moreover, we are awaiting the actual data from the DANUBE and JAVELIN Bladder 100 phase III trials very soon; the first trial did not meet the co-primary endpoints, but the second did and is anticipated that it may likely change clinical practice (after regulatory review of the data).

IMMUNOTHERAPY IN THE PLATINUM-REFRACTORY SETTING

In the salvage setting, FDA approval of PD-L1 (atezolizumab, durvalumab, avelumab) and PD-1 inhibitors (pembrolizumab, nivolumab) have left clinicians with several immune checkpoint inhibitors available to use. Both pembrolizumab and atezolizumab have been tested in a phase III randomized trial vs. salvage chemotherapy, said Ms. Hammond, who noted that pembrolizumab demonstrated overall survival benefit as the primary endpoint and has level I evidence in this setting (Bellmunt et al., 2017).

According to Ms. Hammond, although atezolizumab doesn't have the same level of evidence of use as pembrolizumab in this setting, the phase III trial suggested less toxicity and longer duration of response vs. salvage chemotherapy (Powles et al., 2018; Table 2).

Because of their mechanism of action, immune checkpoint inhibitors are also associated with immune-related adverse reactions. As Ms. Hammond explained, the profiles are largely similar, but there may be slight differences. There are also occasional severe side effects, said Ms. Hammond, so patients and providers need to be very mindful to recognize and report early any concerning symptom. According to Dr. Grivas, managing these side effects often requires a multidisciplinary approach, like the tumor board set up at the Seattle Cancer Care Alliance.

"At our institution, we have an immunotherapy-related adverse event tumor board to manage these patients," said Dr. Grivas. "Sometimes we are able to get patients through treatment without side effects, and sometimes we have to stop treatment and administer steroids (and other immunosup-

Table 1. Metastatic Urothelial Carcinoma First-Line, Cisplatin-Ineligible: Immune Checkpoint Inhibitors

	Atezolizumab	Pembrolizumab
Phase	Phase II (IMvigor cohort 1)	Phase II (KEYNOTE-052)
N	119	370
Dosing	1,200 mg every 3 weeks	200 mg every 3 weeks
ORR	23% (9% CR)	29% (7% CR)
Duration of response	70% of responses ongoing at 17.2 months	82% of responses ongoing at ≥ 6 months
Median OS	15.9 months	Not reached
Median PFS	2.7 months	2 months
Rate of grade 3/4 treatment-related AEs	16%	19%

Note. ORR = overall response rate; CR = complete response; OS = overall survival; PFS = progression-free survival. Information from Balar et al. (2017a, 2017b).

Table 2. Metastatic Urothelial Cancer: Immune Checkpoint Inhibitors in Salvage Setting

	Atezolizumab	Nivolumab	Pembrolizumab	Avelumab	Durvalumab
Phase	Phase III randomized vs. chemotherapy	Phase II single-arm	Phase III randomized vs. chemotherapy	Phase Ib	Phase I/II
N	931	265	542	249 (161 pts ≥ 6 mo f/u)	191
Dosing	1,200 mg every 3 wk	3 mg/kg every 2 wk	200 mg every 3 wk	10 mg/kg every 2 wk	10 mg/kg every 2 wk
ORR	13.4%	19.6%	21.1%	17%	17.8%
Duration of response	63% of responses ongoing at median f/u of 21.7 mo	77% of responses ongoing at median f/u of 7 mo	72% of responses ongoing at median f/u of 14.1 mo	96% of responses ongoing at 6-mo f/u	50% of responses lasting ≥ 6 mo
Median OS, mo	8.6	8.7	10.3	6.5	18.2
Median PFS, mo	2.1	2.0	2.1	1.5	1.5
Grade 3/4 treatment-related AEs	20%	18%	15%	8%	6.8%

Note. ORR = overall response rate; f/u = follow-up; OS = overall survival; PFS = progression-free survival; AE = adverse events. Information from Bellmunt et al. (2017); Patel et al. (2018); Powles et al. (2017, 2018); Sharma et al. (2017).

pressive agents). I think it is very important to have a quick multidisciplinary approach and to utilize expertise, not only from oncology, but also from other specialties, for the multifaceted and comprehensive management of often complex cases."

FGFR INHIBITORS AND ANTIBODY-DRUG CONJUGATES

As Ms. Hammond reported, the FDA approved in April 2019 the first targeted therapy for patients with advanced urothelial cancer. Urothelial cancer is a mutation-rich cancer, said Ms. Hammond, and erdafitinib targets the FGF receptor, particularly activating mutations or fusions. Erdafitinib received accelerated FDA approval for platinum-refractory advanced urothelial cancer with *FGFR2* or *FGFR3* mutation or fusion. A phase III clinical trial comparing erdafitinib to chemotherapy, or erdafitinib to pembrolizumab is currently ongoing.

"This is definitely one of the most exciting developments in urothelial cancer," said Ms. Hammond, who noted that overall response rate is around 40% with this oral drug (Loriot et al., 2018). Despite the high response rate, Ms. Hammond cautioned that clinicians need to be mindful of some "interesting types" of toxicities and logistics associated with this agent.

"Patients can get elevated phosphate levels, so they are put on a low-phosphate diet and sometimes require phosphate binders," she said. "There are also potential ocular toxicities associated with this drug, including keratitis, visual field deficits, retinal issues, etc." Patients are typically seen by an ophthalmologist/optometrist at least once a month for the first 4 months and then at least every 3 months while they are on the drug. There can also be other side effects, while a number of patients may be eligible for dose increase, depending on toxicities and phosphorus level; the package insert has many details.

"I think it is a very important point to test our patients with metastatic urothelial carcinoma early on to see if they have a relevant genomic alteration not only for this FDA-approved drug, but also for other agents on clinical trials," Dr. Grivas added. "We check on FGF receptor, while there are also other targets that we can identify and utilize in clinical trials. There is a real need for biomarkers to select the right treatment for the right patient at the right time."

Moreover, the FDA granted accelerated approval to the antibody-drug conjugate (ADC) enfortumab vedotin for patients with advanced urothelial cancer after platinum-based chemo-

therapy and immune checkpoint inhibitor in December 2019 based on impressive results in a single-arm phase II trial, while the phase III trial comparing that ADC to salvage chemotherapy is ongoing. Very promising data is also emerging with other ADCs, e.g., sacituzumab govitecan, which later received fast track review designation by the FDA, as well as anti-HER2 compounds. Clinical trials are vital for drug development in this challenging cancer.

Disclosure

Dr. Grivas disclosed financial relationships with AstraZeneca, Bavarian Nordic, Bayer, Bristol-Myers Squibb, Clovis Oncology, Debiopharm, Driver, EMD Serono, Exelixis, Foundation Medicine, Genzyme, GlaxoSmithKline, Heron Therapeutics, Immunomedics, Janssen, Merck, Mirati Therapeutics, Pfizer, QED Therapeutics, Roche, Seattle Genetics (all unrelated to this article, in the last 2 years). Ms. Hammond has no conflicts of interest to disclose. This symposium was supported by educational grants from Astellas, Seattle Genetics, and Merck Sharp & Dohme Corp.

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