Transcript Details

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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Chairperson's Perspective: Reframing First-Line and Subsequent Care in Advanced Urothelial Carcinoma – Clinical Implications of the Updated NCCN Guidelines

Opening:
Welcome to ReachMD. This activity, titled "Reframing First-Line and Subsequent Care in Advanced Urothelial Carcinoma: Clinical Implications of the Updated NCCN Guidelines" is provided by Axis Medical Education.

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Dr. Hoffman-Censits:
Hello and welcome to this educational activity. I'm Dr. Jeannie Hoffman-Censits. Today we'll be discussing guideline-driven treatment options for advanced urothelial cancer. So let's begin.

For decades, we used cisplatin eligibility to define and determine treatment plan for patients with unresectable and advanced urothelial cancer. Now, this was a challenge, as the average age of patients who presented with urothelial cancer is 73 and it's a smoking-related disease. Factors such as impaired renal function, hearing loss, peripheral neuropathy, heart failure, and impaired functional status meant that about 1/2 of our patients coming to treatment in the frontline setting are ineligible for cisplatin. And this of course affected patient outcomes.

In 2023, the Nectin-4 targeted antibody-drug conjugate enfortumab vedotin paired with pembrolizumab became the preferred frontline regimen for platinum eligible and ineligible patients. And because of the clinical activity of this regimen paired with relative tolerability, even in frail patients, the latest NCCN guidelines have eliminated the cisplatin eligibility decision-point in frontline decision-making.

So how did we get here? In the last few years, a multitude of phase 3 trials have shifted the standard frontline practice for advanced urothelial cancer. In the JAVELIN 100 trial, patients responding to frontline platinum therapy were randomized to maintenance avelumab versus best supportive care, leading to modest response and durable survival benefit in the avelumab treated group.

Taking this one step further, platinum combined with checkpoint nivolumab in this study, followed by nivolumab maintenance, led to superior survival outcomes compared to chemotherapy alone in the frontline setting.

In the same era as the CheckMate 901 trial, when platinum alone was standard, in EV-302, enfortumab and pembrolizumab was tested against platinum, leading to a near doubling in overall survival compared to cis or carboplatin in a population of mixed platinum eligible patients. Notably, all patient subgroups fared better with enfortumab and pembrolizumab, even in poor risk patients with liver and visceral metastasis and in frailness defined by cisplatin eligibility, this profound survival benefit was durable at a recent 2.5-year follow-up.

Now, what about the second-line setting? Most patients will derive some clinical benefit from enfortumab and pembrolizumab, and some will even have a durable complete response. But for primary progressors or those who are intolerant or progress after initial response, what's next? For now, there's little data to guide and trials are forthcoming and retrospective experiences are being shared. But in the meantime, the NCCN has provided a roadmap for options for consideration based on biomarkers and patient comorbidities such as peripheral neuropathy.

When making follow-up treatment decisions, following enfortumab and pembrolizumab, follow-up biopsy, if feasible, could be considered for repeat testing or banking for clinical trials. Many patients have the option for next-line platinum, which has shown some activity in retrospective series. When feasible, biomarker-directed therapy may also be an option, and of course these choices can be made in sequence in later lines of therapies.

In some instances, like in my clinic for predominantly variant subtypes, like, say, predominantly small squamous cell bladder cancer, I might start with platinum and immune therapy. And in this setting, if there's progression after that first line of therapy with platinum and a checkpoint, what can we use in the second-line and beyond setting? We know that enfortumab alone and potentially in combination has activity, and biomarker-directed therapy is also available.

So approved biomarker-directed therapies, and this means where there's tangible proof that the patient provides to us based on their tumor samples, are trastuzumab deruxtecan, a HER2-directed antibody-drug conjugate, as well as erdafitinib, which is an oral targeted therapy against the FGFR3 pathway. Both can be reasonably well tolerated in a late-line setting and effective for patients with treatment-refractory urothelial cancer.

In the post-platinum and post-checkpoint setting, enfortumab alone led to durable survival benefit over single-agent taxane or vinflunine. These are also other choices listed in the NCCN guidelines as useful under certain circumstances.

So let's talk about toxicity management for enfortumab and pembrolizumab. Though it's generally well tolerated, here are some things to look out for.

So the combination can cause hyperglycemia, and we see this in particular in patients that have baseline poorly controlled diabetes. So if possible, they should see their primary care doctor or endocrinologist to optimize management before starting. Hold treatment if the glucose is over 250 and especially if you have to use steroids, this could be of concern.

Skin toxicity is quite common in the combination and early low-grade skin toxicity is actually even more common. So in our clinic, we are following patients usually for each treatment in early cycles. Because the treatment is usually so effective in the patients that we're giving it to, I tend to hold treatment rather than pushing especially through early skin toxicity. Holding as well as dose reduction can be effective, but we also think about supportive care such as topical steroids through low-grade toxicity. For higher-grade toxicity, if you have to use systemic steroids, you're certainly holding enfortumab and then often referring patients to dermatology for extra help, including consideration of biopsy or the use of biologic therapy.

Peripheral neuropathy is also pretty common. In my experience, it tends to happen a little bit later for patients who are doing well on enfortumab and pembrolizumab for a longer period of time, where we tend to hold after they've had some degree of response.

In this situation, if possible, dose reduction again or holding enfortumab altogether for those with great response to therapy can be a strategy where you can keep patients on the therapy for longer just with pembrolizumab maintenance.

Adjunctive therapies for neuropathic pain such as gabapentin, pregabalin, and duloxetine can be helpful. Also we encourage physical therapy and visits with rehabilitation medicine.

For trastuzumab deruxtecan, the lower dose 5.4 mg/kg was tested in treatment-refractory solid tumors expressing HER2. Nevertheless, the following should be closely managed, including baseline and follow-up echocardiogram. And because of the risk of pneumonitis with trastuzumab deruxtecan, close monitoring of any new pulmonary symptoms or new findings on imaging concerning for pneumonitis should be taken quite seriously.

Because of infusion reactions, nausea and vomiting and neutropenia, we use prophylaxis for patients as we would per the NCCN guidelines.

Patients starting erdafitinib should have baseline and close follow-up with ophthalmology evaluations to evaluate for the development of central serous retinopathy, as well as close follow-up and electrolyte management for on-target hyperphosphatemia. Modifications such as modification in diet and phosphate binders can be considered for the patients, and dose modifications are well outlined in the package insert.

Multidisciplinary care of patients with locally advanced and metastatic urothelial cancer in oncology is a team effort. So it's not just the physician that the patient sees, but a team of people that include physician extenders, nurse practitioners, and infusion room nurses that see the patient on a much more regular basis, and they can provide follow-up to us, ask questions, discuss management with patients on non-day 1 visits. Our telephone triage systems throughout oncology practices are robust, and it's important to keep them educated into some of the side effects that we're particularly looking out for, especially high-grade rashes when we're starting enfortumab and pembrolizumab.

Multidisciplinary care including consultants in dermatology, pulmonary, ophthalmology, endocrinology, physical medicine and rehab, pain and palliative care, cardiology, hepatology and GI as well as primary care providers are integral to the care of our patients.

Other team members such as social workers, nurse navigators, educators and pharmacists also play a really key role, especially with oral targeted therapy. Many centers now also have oncology urgent care to help with symptom management and hopefully prevent admissions to the hospital.

And finally, many centers over the last decade have developed a robust infrastructure for multidisciplinary management of immune-related adverse events for any kind of checkpoint toxicity, including in combination with enfortumab.

Now, what about navigating transitions from local to systemic therapy and then back again? As a medical oncologist with expertise in treating locally advanced and metastatic urothelial cancer, I partner very closely with urologists who are often referring patients with locally advanced or metastatic urothelial cancer to clinic. But it’s different now than my relationship with our urology colleagues maybe 5 or 10 years ago, patients are living a lot longer with this very highly effective systemic therapy that we give either in the frontline or in sequence.

The urology role is shifting and expanding, and our urologists are considering palliative surgery for patients with later-stage disease, for a patient that's been stable on therapy but maybe with a late growth in a primary tumor. Radiation has again taken on an additional role, either during treatment breaks or to a tumor where an oligometastatic lesion is growing and the rest of the tumor is remaining stable on frontline therapy.

We often will hold therapy and consider radiation and maybe restart. This can allow for a longer duration on each line of therapy versus switching to a completely different regimen. And palliative and supportive role of IR, interventional radiology, has really developed beyond just percutaneous nephrostomy tube management, which is a common procedure for patients with urothelial cancer, into considering things like vertebroplasty or even again local management to an oligo progressing lesion in the setting of otherwise stable disease.

Shared decision-making in cancer care is vital, particularly for patients with advanced urothelial cancer. It's a fundamental method of care that's central to individualizing treatment. It involves a multidisciplinary team approach to ensure optimal care for and communication with the patient and their family. The initial step involves promoting productive dialogs that encourage active patient-clinician collaboration, facilitating the process of a care plan development, and supporting the co-creation of a comprehensive care plan. It's crucial to ensure that the patient's goals of therapy are included when selecting treatment.

So for key takeaways, patients with advanced urothelial cancer are living longer than ever before. Platinum eligibility no longer directs first-line treatment decisions. More patients, even with those with markers of frailty, will be eligible for first line enfortumab and pembrolizumab. Outcomes can be durable with this regimen, even with enfortumab discontinuation and/or pembrolizumab hold. And most patients will have some degree of clinical benefit or response, but we’d like to see how they're tolerating their early cycles before making treatment decisions.

Early toxicity management with dose modification and supportive care in the management of enfortumab and pembrolizumab is absolutely paramount. If patients have progression after enfortumab and pembrolizumab, there are no clear dogmatic second-line go-to options, but there are treatments available.

Treatment choice is predicated on patient comorbidities such as neuropathy, functional status as well as goals of care. Platinum-based therapy as well as biomarker-directed care are options in the second-line and beyond.

Multidisciplinary care and shared decision-making are critical to ensure optimal patient outcomes.

With that, we'll conclude today's activity. Thank you for your participation.

Closing:
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