Current Topics in the Management of Non-Muscle-Invasive Bladder Cancer

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ABSTRACT

The current NCCN Guidelines for Bladder Cancer reflect the most up-to-date, evidence-based data relating to the evaluation and management of non-muscle-invasive bladder cancer (NMIBC). The most notable revision to the guidelines this year is the addition of pembrolizumab for a high-risk subset of patients not responding to bacillus Calmette-Guérin (BCG). It is anticipated that current BCG shortages will offer unique opportunities to promote and enhance clinical trials for patients with bladder cancer. Recent efforts to more precisely define BCG-unresponsive disease (adopted by the FDA) have been critical to standardizing definitions and evaluating the efficacy of clinical trials in bladder cancer.

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The treatment of non-muscle-invasive bladder cancer (NMIBC) is rapidly evolving, according to Philippe E. Spiess, MD, MS, FRCS(C), Assistant Chief of Surgical Services, and Senior Member in the Department of Genitourinary Oncology, Moffitt Cancer Center. “It’s critical for all healthcare providers who see patients with bladder cancer to become familiar with and refer to the NCCN Guidelines on a regular basis because they are continuously updated,” he said at the NCCN 2020 Virtual Annual Conference. “They are evidence-based, taking only the most rigorous, robust data for integration and adoption in the treatment of our patients.”

Perhaps the most important update to the NCCN Guidelines in NMIBC is the addition of pembrolizumab for recurrent or persistent disease, particularly in patients with bacillus Calmette-Guérin (BCG)-unresponsive high-risk NMIBC specifically with carcinoma in situ with or without papillary bladder tumors. Other topical issues in the field include recently standardized definitions for patients unresponsive to BCG (the most commonly used intravesical immunotherapy for treating early-stage bladder cancer), as well as potential ramifications of an ongoing BCG shortage.

Bladder Cancer Numbers

Bladder cancer is the sixth most common cancer in the United States, affecting approximately 20 in 100,000 men and women each year. White men are at the highest risk for bladder cancer, accounting for approximately 40% of all new cases. Although the average age at diagnosis is 73 years, approximately 90% of those diagnosed will be aged >55 years.¹ “So, although this is a cancer that most commonly affects elderly patients, we clearly see it in a

younger population as well,” Dr. Spiess noted. “However, risk factors such as smoking are very critical in the potential development of this malignancy.”

According to Dr. Spiess, bladder cancer is also the most expensive cancer to manage, with the bulk of that cost associated with the required surveillance of these patients, which costs approximately \$4 billion every year in the United States.¹ “Often patients require repeated and regular surveillance cystoscopy and urine cytology,” he said. “These repeated procedures are very expensive as a whole in terms of dollars spent within our healthcare system.”

Bladder Cancer Staging

The staging of bladder cancer, from non-muscle-invasive to muscle-invasive, is highly categorical. For NMIBC, carcinoma in situ (CIS or Tis) is defined as high-grade disease confined to the bladder lumen. “People get somewhat concerned with in situ disease, because it often doesn’t follow a stepwise gradient from in situ to superficial invasion. Often, in situ disease can progress to muscle-invasive disease, and can potentially metastasize thereafter,” Dr. Spiess explained. CIS, particularly when associated with other high-grade components, is therefore often associated with a high risk of disease progression and is a potential indication to provide more-aggressive treatment.

Bladder cancer is further classified by risk group (low, medium, and high), according to the American Urological Association (AUA) Bladder Cancer Consensus Guidelines (Table 1). “These [guidelines] are very relevant, because each classification is associated with risks for recurrence and disease progression,” he said. “As we increase in risk

Table 1. AUA Bladder Cancer Risk Groups

Low Risk	Intermediate Risk	High Risk
LG solitary Ta $\leq$ 3 cm	Recurrence within 1 year, LG Ta	HG T1
PUNLMP	Solitary LG Ta $<$ 3 cm	Any recurrent, HG Ta
	LG Ta, multifocal	HG Ta, $<$ 3 cm (or multifocal)
	HG Ta, $\leq$ 3 cm	Any CIS
	LG T1	Any BCG failure in HG patient
		Any variant histology
		Any LVI
		Any HG prostatic urethral involvement

Abbreviations: AUA, American Urological Association; BCG, bacillus Calmette-Guérin; CIS, carcinoma in situ; HG, high grade; LG, low grade; LVI, lymphovascular invasion; PUNLMP, papillary urothelial neoplasm of low malignant potential.

category, we ultimately get more aggressive in terms of the treatment strategies we offer to patients.”

“I emphasize the importance of this table [Figure 1] because many studies and a lot of our treatment strategies are highly dependent on the risk category of the patient,” he added.

NCCN and Other Bladder Cancer Guidelines for NMIBC

According to the NCCN Guidelines,² patients should be stratified into non-muscle-invasive and muscle-invasive disease after primary evaluation and surgical treatment (a transurethral resection of bladder tumor [TURBT] is usually the first treatment). Dr. Spiess’ discussion focused only on NMIBC of clinical stage Ta, T1, and Tis.

Per the NCCN Guidelines, patients classified with low-grade Ta disease have the option of observation or intravesical therapy. If a patient has high-grade Ta disease and has had an incomplete resection, or there is suspicion that resection was incomplete, TURBT should be repeated.² “Providers and patients always ask why re-resection is important,” he said. “It’s critical, because you want to make sure that you do not have more locally advanced disease, such as muscle-invasive bladder cancer. We also know that the efficacy of agents is significantly better after you’ve completed a complete resection in terms of recurrence-free and progression-free survival.”

In patients with high-grade Ta tumors, BCG is the preferred treatment option after re-resection, followed by intravesical chemotherapy or observation.

Patients with T1 tumors are also strongly advised to repeat TURBT or consider cystectomy for high-grade tumors. If there is no residual disease in a patient with a T1 tumor, follow with BCG (preferred), intravesical chemotherapy, or observation in highly selected cases, he advised.

The AUA and Society of Urologic Oncology (SUO) have developed recommendations for diagnosing and

treating NMIBC.³ Dr. Spiess noted that the European Association of Urology (EAU) has laid out guidelines similar to the AUA/SUO, although they differ in listing variant histology of urothelial carcinoma or presence of lymphovascular invasion (in high-risk tumors) as an indication for considering early radical cystectomy.⁴ “It’s important to realize, and there are data to support this, that early cystectomy in this setting has been associated with significantly better survival,” he said.

There have also been global efforts (including from the EAU) to standardize definitions associated with treatment, including the importance of differentiating between BCG-unresponsive disease, BCG-relapsing disease, and low-grade recurrence after BCG in patients with intermediate-risk tumors. This is important for allowing comparisons of clinical trial populations and for defining endpoints that would point to the need for more aggressive treatment in any given patient.

Problems With Use of Intravesical Therapies for NMIBC

According to Dr. Spiess, there have been concerns in recent years regarding BCG shortages. He anticipates that these shortages will be ongoing, thus underlining the importance of novel clinical trials that will elevate the benchmarks of treatment efficacy for patients with NMIBC.

In addition to the impact on patient care due to national shortages of BCG, the efficacy of BCG also varies depending on the strain used. Furthermore, BCG efficacy concerns are related to certain subtypes and variants of bladder cancer, notably papillary, micropapillary, and plasmacytoid histologies. “There have also been somewhat limited, disappointing long-term results examining the outcomes of BCG beyond 2 or 3 years,” he said. “And salvage intravesical therapies, for the most part, have had disappointing response rates between 20% and 40%.”

A 2019 study published in *Urology* highlighted the fact that, although BCG has been available now for many years, the number of patients being treated with it has increased continually, particularly those with high-grade T1 tumors and CIS.⁵ At the same time, production has not kept up with demand, mainly due to factors such as plant shutdowns resulting from possible batch contamination, which has contributed to a shortage of BCG supply.

Adding to the likelihood that BCG will remain in short supply is its cost, but not in the manner one might think.⁶ “The price of BCG has somewhat plateaued, so from a pharmaceutical standpoint, it’s not really a drug for which there is significant enthusiasm around expanding production,” Dr. Spiess said.

Recent Changes in NMIBC Treatment Response and Study Definitions

According to Dr. Spiess, recent changes to study definitions have been critical to the field. “It’s important to understand that the FDA approved a very rigorous definition of BCG-unresponsive NMIBC, and this was a pivotal point in the management of bladder cancer,” he said.

A 2016 article published in the *Journal of Clinical Oncology* was instrumental in defining this classification.⁷ The article classifies BCG failures and defines “unresponsive” as “BCG-refractory and BCG-relapsing disease. The term BCG-unresponsive, which essentially includes BCG-refractory and BCG-relapsing (within 6 months of last BCG exposure), is meant to denote a subgroup of patients at highest risk of recurrence and progression for whom additional BCG therapy is not a feasible option. These patients can be considered for single-arm studies.”

Pembrolizumab Added to Guidelines for Recurrent or Persistent Disease

Treatments for patients who have Ta, T1, or Tis recurrent or persistent cancer are outlined in Figure 1. Importantly, pembrolizumab was recently added to the guidelines earlier this year, based on results from the KEYNOTE-057 trial (ClinicalTrials.gov Identifier: NCT02625961). In the single-arm, open-label, phase II trial of 102 patients, the 3-month response rate was 40.2%. Among the 41 patients who achieved a complete response, 58.5% maintained this favorable response at last follow-up (median, 16.7 months).

Figure 1. NCCN Guidelines for non—muscle-invasive bladder cancer recurrent or persistent disease. Version 3.2020. Available at NCCN.org. All rights reserved. NCCN Guidelines and this Illustration may not be reproduced in any form without the express written permission of NCCN.

The trial also showed an acceptable side-effect profile with the drug, with adverse events reported in approximately 18% of patients.

Based on reported results of the KEYNOTE-057 trial, the FDA's Oncologic Drug Advisory Committee (ODAC) voted 9 to 4 in supporting the approval of pembrolizumab for patients with BCG-unresponsive, high-risk NMIBC specifically with CIS with or without papillary bladder tumors ineligible for or electing not to undergo cystectomy. The FDA approved the use of pembrolizumab in this clinical context on January 8, 2020, and shortly thereafter it was integrated into the NCCN Guidelines.

Suitable alternatives for patients nonresponsive to BCG or unsuitable candidates for cystectomy include hyperthermic mitomycin C, intravesical gemcitabine/docetaxel, intravesical rAd-IFN α /Syn3, ALT-803 (IL-15 analogue), and oncolytic viruses.

Dr. Spiess noted 2 specific areas of research that should stay on oncologists' radar: the use of oncolytic viruses and the use of mycobacterium phlei cell wall–nucleic acid complex (MCNA), although the latter was denied

approval by the FDA for the treatment of patients with NMIBC at high risk for recurrence and progression after failed treatment with BCG. “Nevertheless, these 2 areas of research in particular have received a lot of interest in recent months and years,” he said. “I think there's more to follow in terms of potential novel agents that can have some utility.”

He added that the role of immunotherapy in NMIBC is another exciting area to follow, and immunotherapy combinations are currently being studied in both BCG-resistant and BCG-naïve patient populations.

“Now that our definitions of BCG-unresponsive disease are much more rigorous, I definitely think there likely will be some novel strategies adopted in years to come,” Dr. Spiess concluded.

Disclosures: Dr. Spiess has disclosed that he has no relevant financial relationships.

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