NCCN Guidelines Updates: Management of Muscle-Invasive Bladder Cancer

Presented by Thomas W. Flaig, MD

ABSTRACT

The treatment landscape of bladder cancer has changed rapidly over the past several years. The 2019 version of the NCCN Guidelines has integrated changes to tumor staging that reflect an updated understanding of the natural history of the disease and will affect how patients are treated. Further, 5 PD-1/PD-L1 immune checkpoint inhibitors (ICIs) are approved for the treatment of bladder cancer. The FDA has limited use of ICIs as monotherapy in the first-line treatment of metastatic and advanced disease for patients who are platinum-ineligible or are cisplatin-ineligible with high PD-L1 expression and are candidates for ICIs. Ongoing predictive biomarker development and validation are needed in bladder cancer; the development of better biomarkers will be key in patient selections for therapy going forward.

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"There has been no major change in the incidence of bladder cancer in the United States for 40 years, and for 30 years there has been almost no therapeutic development for localized or advanced disease. However, in the past few years, 5 immune checkpoint inhibitors [ICIs] have been approved for the treatment of bladder cancer," said Thomas W. Flaig, MD, Professor of Medicine and Associate Dean, University of Colorado School of Medicine. "We now have a lot more latitude for treating patients, and we have support to pursue more aggressive therapy," he continued.

Background

In the United States, bladder cancer is the fourth most common cancer in men, accounting for approximately 7% of all newly diagnosed cases in 2019, and is the eighth most common cause of cancer death in men.[1] Bladder cancer typically occurs in older individuals, with the average age of onset of 73 years. More than 75% of patients are male, and this sex difference is not fully explained. Smoking is an identified risk factor. Traditionally, treatment involves cisplatin-based combinations, but this treatment is difficult for many older patients or those with significant comorbidities to tolerate.

"In general and historically, treatment of bladder cancer mirrors treatment of lung cancer," Dr. Flaig continued.

Dr. Flaig focused his discussion at the NCCN 2019 Annual Conference on muscle-invasive bladder cancer (MIBC; stages T2–4), which is present in approximately 25% of all patients with bladder cancer. "After the tumor invades the muscularis propria, the diagnosis is MIBC," he told the audience. "Without treatment, MIBC will progress to metastatic or incurable disease. Definitive therapy should be offered to all patients with MIBC who are candidates for surgery or radiation." Treatment options include surgery with neoadjuvant cisplatin-based therapy, concurrent chemoradiotherapy (CRT), or other options for patients ineligible for cystectomy.

Recent Updates to NCCN Guidelines

The updated NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Bladder Cancer distinguish between patients with stage II disease who are and are not candidates for cystectomy. For eligible patients, use of neoadjuvant cisplatin-based therapy followed by radical or partial cystectomy is a category 1 recommendation. "A small number of select patients fall into the partial cystectomy category; these are patients with a solitary lesion in a suitable location," Dr. Flaig explained.

Furthermore, concurrent CRT is also a category 1 recommendation for primary treatment of stage II disease in cystectomy candidates. For patients ineligible for cystectomy, the recommended primary treatment is concurrent CRT or radiotherapy.

Staging Changes

In 2017, AJCC incorporated changes in staging criteria for stage III bladder cancer. For example, stage IIIA now includes N1 (single regional lymph node in the true pelvis), and stage IIIB incorporates N2 and N3. "The treatment of stage IIIA [disease] is largely the same in the NCCN Guidelines. The struggle is to take clinical trial data from 20 years ago and apply it to the new staging schema," Dr. Flaig explained.

Another staging change is that stage IIIB now captures patients with more extensive, but not distant metastatic, disease. Therefore, because stage IIIB includes more extensive regional disease, disease management is approached

differently. In practice, chemotherapy is used to downstage patients or concurrent CRT is used.

"If I have a patient with lymph node involvement staged as IIIB, I would give upfront chemotherapy and assess [their] response. In patients experiencing a complete response, a small portion may be able to receive consolidation cystectomy or consolidation CRT. Patients who experience a partial response are treated with cystectomy or CRT, or as we treat metastatic disease," he said (Figure 1).

Another approach for stage IIIB disease would be upfront concurrent CRT, with no additional therapy for patients who achieve complete response. Those with a partial response and positive lymph nodes have a range of options, including surgical consolidation or treatment as metastatic disease. Patients who are downgraded can be considered for intravesical therapy in limited circumstances.

Lastly, among the staging changes, T4b disease was moved to a new group of stage IVA.

Integrating Systemic ICIs

"Bladder cancer has a long history of immunotherapy. Bacillus Calmette-Guérin was first used to treat bladder cancer in 1976, based on a study of 9 patients," Dr. Flaig said.[2]

Bladder cancer is significantly driven by environmental (eg, smoking) and occupational exposures. As a rule, drugs used in the treatment of lung cancer and cancers that have a shared tobacco exposure correlation are also effective in bladder cancer, such as platinum-based combinations, gemcitabine, taxanes, and, more recently, immunotherapy with ICIs.

Furthermore, the mutation frequency of bladder cancer is similar to that of lung cancer and melanoma. Dr. Flaig noted that in cancers with high mutation frequency, "We think ICIs have had the biggest impact." The mechanism of action of ICIs differs from that of chemotherapy. ICIs release the "brakes" on the immune system, which may have been triggered by the cancer itself, thereby allowing the immune system to identify and attack tumors that express PD-L1. For chemotherapy, although patients achieve a high response rate in the first-line treatment for metastatic disease, responses are relatively transient, whereas for ICIs, although only a subset of patients will respond, responses are durable.

Several ICIs were FDA-approved in 2016 and 2017 based on results of several trials. Thus, the following options are currently available for immunotherapy in metastatic bladder cancer: nivolumab, pembrolizumab, atezolizumab, durvalumab, and avelumab.

In 2017, Bellmunt et al[3] confirmed the efficacy of pembrolizumab as second-line therapy for advanced urothelial carcinoma. In this phase III trial, which randomly assigned 542 patients whose disease had progressed on platinum-based therapy to either pembrolizumab or investigator's choice of chemotherapy (vinflunine, paclitaxel, or docetaxel), pembrolizumab demonstrated significantly improved overall survival compared with chemotherapy by 27% (P=.002).

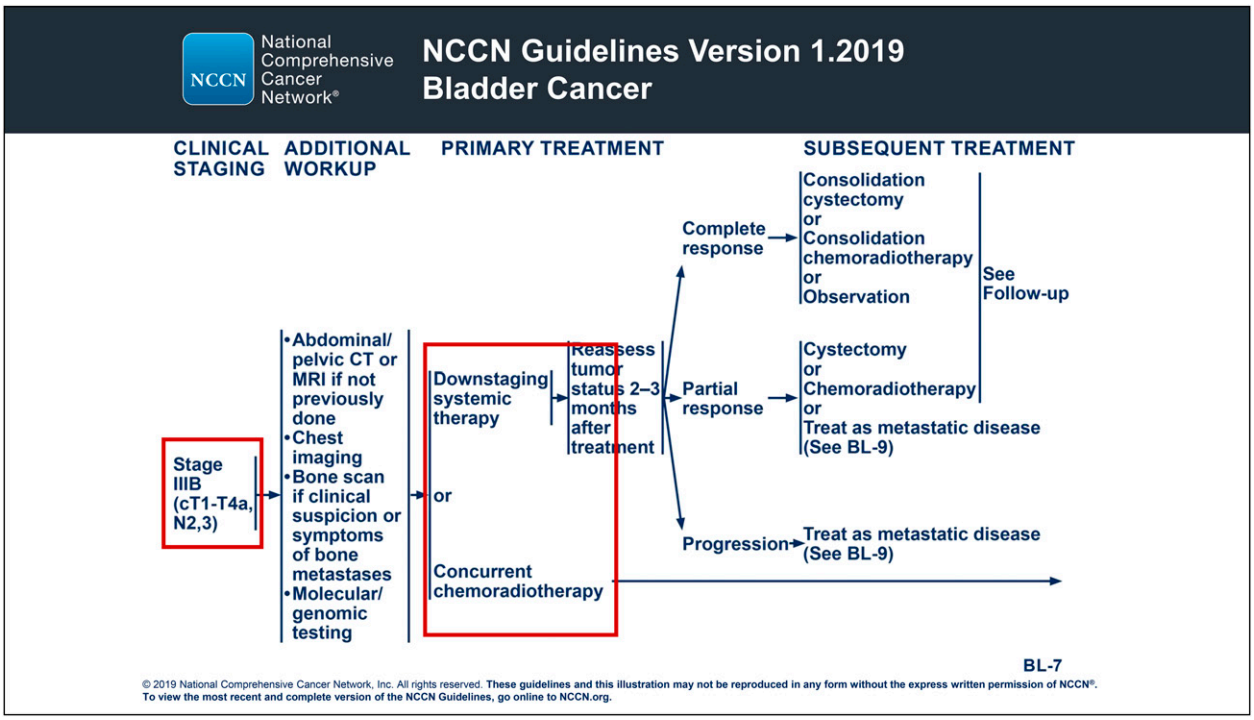

Figure 1. Management of stage IIIB disease from the NCCN Guidelines for Bladder Cancer.

"At 6 months, progression-free survival was approximately 30% in both arms. However, at 1.5 years, approximately 20% of patients in the pembrolizumab group were progression-free, whereas nearly all patients in the chemotherapy arm had experienced disease progression," he said. Based on these overall trial results, pembrolizumab was approved by the FDA.

"Most responses to ICIs occur in the first 6 months. The ongoing nature and durability of this response is what is noteworthy. Most patients who experienced response are still on treatment. One of the most promising features is the high likelihood of durability of response, in contrast with chemotherapy," he elaborated. Anti–PD-1 and anti–PD-L1 checkpoint inhibitors have similar side-effect profiles. At least 20% of patients in the trial experienced side effects, such as fatigue, pruritus, musculoskeletal pain, and decreased appetite.[3]

"Immunotherapy may activate many organ systems, so there are immune-related adverse events [irAEs], including skin, gastrointestinal, pulmonary, endocrine, and hepatic effects," Dr. Flaig said. For treatment of irAEs, glucocorticoids are used initially. Re-treatment with an ICI should not be pursued if a patient experiences severe toxicity.

"You need to be highly vigilant to detect irAEs. Rash, pneumonitis, hepatitis, and colitis are detected through clinical visits and laboratory monitoring. Other irAEs, such as hypophysitis, adrenal insufficiency, and cardiologic effects, may be more difficult to identify," he told the audience.

Sequencing Therapy

"Treatment options for metastatic bladder cancer are more complicated in 2019 than they were in 2015. Pembrolizumab and atezolizumab are now approved for use in the first line in select patients who are platinum-ineligible with low PD-L1 expression. PD-1 inhibitors can be used second- and third-line, post-platinum," he continued.

The updated 2019 NCCN Guidelines for Bladder Cancer include a new category of patients with locally advanced/metastatic bladder cancer: those who are platinum-ineligible with no PD-L1 expression. Preferred first-line regimens for these patients are atezolizumab and pembrolizumab; other options include gemcitabine and gemcitabine/paclitaxel. Patients who are cisplatin-ineligible but carboplatin-eligible should receive carboplatin over ICIs in first-line treatment.

"This guideline has become more complicated in the first line with these changes," Dr. Flaig said. "But there are very good data for post-platinum use of pembrolizumab as a category 1 recommendation. Alternative options in this post-platinum setting include atezolizumab, nivolumab, durvalumab, and avelumab." The preferred regimens for those who are cisplatin-eligible and chemotherapy-naïve are gemcitabine/cisplatin or dose-dense methotrexate/vinblastine/doxorubicin/cisplatin (ddMVAC) with growth factor support.

Due to the lack of standardization, each pharmaceutical company has its own platform for testing the PD-L1 biomarker, which is presumed to predict response, complicating measurements with individual assays for the same biologic marker. PD-L1 expression has turned out to be an imperfect biomarker for ICI response. "My sense is that many of us do not check predictive biomarkers regularly," Dr. Flaig noted.

Future Considerations

Several ongoing clinical trials are currently being conducted in MIBC that are examining combinations of ICIs, ICIs plus chemotherapy, and neoadjuvant use of ICIs. Concern about the validity of PD-L1 as a biomarker for response to ICIs has led to the study of other approaches for potential biomarkers, including molecular-based subtypes. "The best management for any patient with cancer—including bladder cancer—is a clinical trial. Participation in clinical trials is strongly encouraged," Dr. Flaig stated.

One important initiative underway is the Co-expression Extrapolation (COXEN) Program to predict chemotherapy response in patients with localized MIBC (ClinicalTrials.gov identifier: NCT02177695). This is an NCI-sponsored initiative sponsored by SWOG that is designed to use the COXEN program to assess patient response to 5 different chemotherapy agents. This phase II, open-label, parallel-group initiative will enroll approximately 184 patients with MIBC.

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