Alternatives to BCG Immunotherapy for Bladder Cancer Treatment During Drug Shortages

EXPERT EDITORIAL

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Immunotherapy for cancer treatment has exploded in popularity in recent years, and its use has expanded from melanoma to other cancers, including urothelial bladder cancer. As data presented during the 2015 Genitourinary Cancers Symposium will reveal, agents such as pembrolizumab (Abstract 296) and MPDL3280A (Abstract 297) are being studied and are showing activity in patients with advanced urothelial carcinoma. Some would say this is not surprising and is an extension of the fact that immunotherapy for bladder cancer—using intravesical bacillus Calmette-Guérin (BCG) in the early stages of the disease—has been highly successful in reducing recurrence progression rates and decreasing rates of metastatic disease and death.[1]

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These findings have also raised awareness of the need for precision in the administration (dose, scheduling, and duration of therapy) of immunologic agents. Unfortunately, just when the urologic oncology world renewed enthusiasm for the in-depth study of BCG therapy, a worldwide shortage of this valuable biologic agent occurred from two major fronts. First, Sanofi Pasteur ceased production of BCG in 2012 (slated to go back in production sometime this year), and second, Merck reported substantial shortages in production of their product during 2014, leaving many patients with no access to intravesical immunotherapy.

In response to this shortage, several organizations and experts have put forward recommendations on "What Is the Urologist to Do in Times of BCG Shortage?" (This was the title of an article I coauthored with Donald L. Lamm, MD; Michael O'Donnell, MD; Badrinath Konety, MD MBA; Stephen B. Williams, MD, MBBS, FACS; John Taylor, III, MD, that was featured in *AUA News*, November 2014). However, as shown by the multidisciplinary interest in bladder cancer immunotherapy, this topic is relevant not only to urologists but also to medical oncologists (e.g., GU Cancers Symposium Abstract S293 will discuss trials being developed to study combining checkpoint inhibitors and BCG) and radiation oncologists (e.g., RTOG-0926 for patients for whom BCG failed).

BCG Best Practices for Bladder Cancer

Level 1 evidence supports that best practice for BCG therapy in non–muscle invasive bladder cancer (NMIBC) includes an induction course of BCG with six weekly instillations followed by maintenance BCG using three weekly instillations at 3, 6, 12, 18, 24, 30, and 36 months from initiation of induction therapy.[2] Importantly, based on the findings from the EORTC-30911 trial, even in patients at intermediate risk, 3-week maintenance BCG significantly reduced metastasis and overall and cancer-specific mortality to an extent that was even better than for patients at high risk.

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The importance of appropriate patient selection (e.g., excluding variant histologies such as micropapillary or small-cell histology) and patient preparation (e.g., repeat transurethral resection to ensure all papillary disease has been surgically removed) prior to initiation of intravesical therapy is especially relevant when considering which patients would not benefit from BCG, and therefore should not be offered the therapy. When BCG is in short supply, physicians should prioritize BCG use based on progression risk. For example, patients with intermediate-risk disease are at lower risk of progression than patients with high-risk disease. Therefore, oncologists should counsel patients with intermediate-risk disease and explain that BCG is reserved for the patients who are at higher risk of progression.

With this background, what options does the treating physician have in times when BCG is in short supply?

Transurethral Resection of Tumor Alone

All patients with NMIBC must be counselled appropriately and provided detailed information regarding their risk of—and the difference between—recurrence and progression. For patients with high-risk NMIBC (e.g., high-grade papillary or carcinoma in situ [CIS]), management with transurethral resection of tumor (TURBT) and observation alone is not appropriate. These patients should always be offered an alternative treatment. However, for patients with intermediate-risk disease (e.g., recurrent, multifocal, or low-grade Ta lesions), TURBT may represent a reasonable option, especially with enhanced optical technology followed by close surveillance.

Lower-Dose, Longer-Duration BCG

Many experts believe that the most prudent course of action during a drug shortage is to reduce the dose, but not the duration, of BCG therapy to less than 1 year. Meaning, patients would be treated with one-third the dose of BCG for induction and at least 1 year of maintenance, rather than being treated with full-dose induction and no maintenance. This treatment plan is based on the study from Oddens et al. that showed that one-third dose of BCG for 3 years was not statistically inferior to the full dose for 1 year (recurrence-free survival was 62.6% with one-third dose and 58.8% with the full dose).[3]

This would permit treatment of three times the number of patients without risk of harm for 1 year, as long as one-third dose is continued thereafter. It should be noted that this study did show that one-third BCG for 1 year was less optimal than full-dose BCG for 3 years, so this recommendation must only be considered in the context of BCG shortage. For those who may be concerned about a reduced immune response for patients treated with lower-strength BCG, interferon alpha can be added to boost cytokine response.

Intravesical Chemotherapy

Intravesical chemotherapy alternatives to BCG include gemcitabine, mitomycin-C, and valrubicin, which has been approved by the U.S. Food and Drug Administration (FDA) for patients for whom BCG has failed.

Gemcitabine

Clinical experience with intravesical gemcitabine suggests that this agent has the least side effects. It can be used as a weekly instillation of 1-2 gm in 50 cc of sterile water for 90 minutes, for 6 weeks. Some studies have also used monthly maintenance therapy, but this is most often reserved for when BCG fails.

Mitomycin-C instillations

The largest experience with intravesical chemotherapy is with mitomycin-C. This is best administered as a concentrated solution of 40 mg in 20 cc normal saline, again for 6 weeks with or without monthly maintenance therapy. However, data are emerging that suggests that this agent might not be as well tolerated as other agents. Additionally, mitomycin-C itself has been in short supply twice in last 5 years.

Valrubicin

Valrubicin has been approved for CIS; however, the drug has substantial associated costs, and data are not conclusive regarding efficacy. If used, the most common dosage is 800 mg weekly for 6-8 weeks.

Other agents

Other agents that have been used in this situation include docetaxel, nab-paclitaxel, thiotepa, and epirubicin, but experience in the United States with these drugs has been limited.

Combination Chemotherapy

Borrowing from lessons learned in systemic chemotherapy for bladder cancer, combination chemotherapy for intravesical use has gained traction. Although this has mainly been studied in patients for whom BCG failed, it remains an option when BCG is not available, especially for patients with highest-risk disease (e.g., large T1, high-grade disease with CIS). Radical cystectomy or selected multimodal therapy options should be the primary recommendation to patients with highest risk disease who are BCG naive and to patients for whom BCG has failed.

Gemcitabine and mitomycin or gemcitabine and docetaxel

Data from Lightfoot et al. have shown efficacy with high response rates (after BCG has failed) using combination of gemcitabine plus mitomycin instilled sequentially with dwell times of 60-90 minutes followed by a year of monthly maintenance for those who demonstrate a complete response.[4] Drs. Lamm and O'Donnell have also reported the use of combination gemcitabine followed by docetaxel (37.5 mg in 50 ml of sterile normal saline) for six weekly instillations followed by monthly maintenance for 12-24 months (personal communications 2014).

Radical Cystectomy

Of course, whether in times of BCG shortage or excess, the primary goal of treating patients with bladder cancer is to their ensure survival. Thus, for patients with NMIBC who are at the highest risk of disease progression (e.g., deep T1, variant histology, multifocal tumors, or recurrent disease after BCG) and are surgical candidates, radical cystectomy with appropriate urinary diversion must be offered. This achieves the best oncological control of disease and, when provided in a timely fashion, can result in prolonged survival in more than 80% of patients. Notably, both the American Urological Association and European Association of Urology recommend radical cystectomy as the preferred option for patients for whom BCG has failed, with limited evidence supporting the next best bladder-preserving therapies.

BCG from Other Countries

Although there is some variation between strains of BCG with minor variation in immunologic activity, most existing data suggest that BCG from different sources all have activity when used for bladder cancer. However, until the FDA engages BCG suppliers from outside of the United States (something that the Bladder Cancer Advocacy Network has been championing), this option remains available only to patients willing to travel to other countries, such as the Netherlands, India, and Japan. ●

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(The complete reference list can be found in the online version of this article at gucasym.org/dn.)