Editorial

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Treatment strategies for the Bacillus Calmette-Guérin–unresponsive non-muscle invasive bladder cancer

Bladder cancer is stratified into non-muscle invasive bladder cancer (NMIBC) and muscle-invasive bladder cancer (MIBC) by the penetration of the tumor into the muscular layer; this is the pivotal marker for determining the treatment strategy [1]. Approximately 75%–80% of bladder cancers are diagnosed as NMIBC. Transurethral resection of bladder tumors (TUR-Bs) is the initial treatment of choice for tumor resection and staging. NMIBC can be classified into low, intermediate, and high-risk groups according to the pathologic stage, grade, tumor size, multiplicity, concomitant carcinoma *in situ* (CIS), lymphovascular invasion, and the presence of variant histology [2]. In intermediate and high-risk NMIBC, intravesical Bacillus Calmette-Guérin (BCG) administration is strongly recommended. The American Urological Association guideline recommends one year of maintenance BCG therapy for patients with intermediate-risk and three years for patients with high risk.

Dr. Morales was the first to use intravesical BCG therapy to treat bladder cancer. Since then, intravesical BCG therapy following TUR-B has been the mainstream treatment in NMIBC for intermediate to high-risk patients. The mechanism of BCG treatment is explained by the activation of the immune system and its direct cytotoxicity. Direct cytotoxicity triggers tumor cell death promoting antigen presentation and cytokine release that activates anti-tumor immunity, mediated by NK cells, macrophages, and CD8+ cytotoxic T-cells [3].

BCG failure is defined according to each definition. BCG intolerance refers to persistent bladder cancer due to the inability to receive adequate BCG administration because of its toxicity. BCG unresponsiveness includes BCG refractory and relapsing. BCG refractory refers to the persistence of high-grade tumors after six months of BCG administration despite receiving adequate therapy or any stage of disease progression within three months of the first BCG cycle. BCG relapsing is the recurrence of high-grade tumors after achieving a disease-free state after six months of adequate BCG therapy [2].

The BCG unresponsive rates ranged from 30%–50%. The standard therapy for unresponsive BCG in high-risk bladder cancer is radical cystectomy. Nevertheless, intravesical therapy using various chemotherapeutics can be attempted in patients deemed unfit for that procedure [4].

Valrubicin is a chemotherapeutic semisynthetic analog of the anthracycline doxorubicin, administered directly into the urinary bladder. In a pivotal phase III open-label study, valrubicin was administered weekly for six weeks, and in a phase II/III open-label study, valrubicin (800 mg) was intravesically administered for six or nine weeks. In both studies, valrubicin showed a complete response rate of 18% in CIS patients after BCG failure [5]. Valrubicin was approved by the United States Food and Drug Administration for BCG refractory bladder cancers with the CIS stage treatment.

Gemcitabine is another chemotherapeutic agent used in the neoadjuvant or adjuvant settings for MIBC treatment and metastatic bladder cancers. In a retrospective study, intravesical gemcitabine instillation led to a cumulative 5-year disease progression in 19% of the patients with BCG refractory disease and 22% of the patients with other types of BCG failure. Among 69 patients, 25 achieved a complete response, 19 achieved a partial response, and 20 showed no response. Generally, most patients were tolerant to intravesical gemcitabine treatment [6]. In a phase II trial of intravesical gemcitabine in patients refractory to BCG, gemcitabine showed potential as an alternative treatment for patients who are ineligible for a radical cystectomy. Patients with refractory or intravesical BCG-intolerant bladder cancer were administered 2,000 mg of intravesical gemcitabine twice weekly for three consecutive weeks. Of a total of 30 eligible patients, 15 achieved a complete response. However, 12 pa-

tients experienced recurrences, with a median recurrence-free survival of 3.6 months. The one-year recurrence-free rate for patients with complete response was 21%. Subsequently, 11 patients underwent radical cystectomy following intravesical gemcitabine treatment [7]. In another phase II trial for BCG failure, after at least two prior courses of intravesical BCG treatment, 2,000 mg of gemcitabine was intravesically injected weekly for six consecutive weeks, then monthly for up to 12 months. Of the 47 patients evaluated, 47% showed a complete response at 3-month follow-up cystoscopy. The one- and two-year recurrence-free survival rates were 28% and 21%, respectively [8]. The gemcitabine and mitomycin C combination treatment was also evaluated. In a retrospective multicenter study, 1,000 mg of gemcitabine was intravesically administered, retained for 90 minutes, and then treated with 40 mg of mitomycin C and retained for another 90 minutes. In a total of 47 patients, complete response rate was seen in 68%. Furthermore, one- and two-year recurrence-free survival rates were 48% and 38%, respectively. During the median follow-up period of 26 months, 30% of the patients were free from recurrence without progression [9].

Docetaxel exerts an anti-tumor effect by inhibiting microtubule depolymerization in cancers. Intravesical docetaxel was evaluated in patients with BCG failure. In a retrospective study, 75 mg of docetaxel was administered into the empty bladder and retained for 2 hours. In patients with a complete response, docetaxel was administered every six weeks during the induction period and monthly after three months. In a total of 33 patients, 61% achieved a complete response. One- and two-year recurrence-free survival rates were 45% and 32%, respectively [10]. Another study on intravesical docetaxel treatment for BCG refractory patients showed comparable results. In patients with a complete response, 75 mg of docetaxel was administered intravesically every six weeks and every nine months for maintenance therapy. Of 13 patients, 10 achieved a complete response; six were recurrence-free at the 13-month median follow-up [11].

Nanoparticle albumin-bound (nab)-paclitaxel is improved for greater solubility and lesser toxicity than traditional taxanes. A phase II study on nab-paclitaxel showed durable responses in patients with NMIBC unresponsive to BCG. Every six weeks, the enrolled patients were administered 500 mg of nab-paclitaxel intravesically; maintenance treatments were applied every six months in the complete response cases. Of 28 enrolled patients, 35.7% showed complete response and maintained substantial responses for 12 months. At a mean follow-up of 21 months, 67.8% of patients ended the study without progression or metastasis [12].

Immunotherapy has revolutionized cancer treatment and is expanding the application of urologic oncology, especially bladder cancers. The KEYNOTE-057 trial revealed the efficacy of Pembrolizumab monotherapy in patients with NMIBC unresponsive to BCG. In an open-label, single-arm, phase II study, 200 mg of Pembrolizumab was intravenously injected every three weeks for up to 24 months. Of 101 eligible patients, 96 were evaluated for efficacy, and 39 patients (41%) achieved a complete response at the end of 3 months. The median duration of a complete response was 16.2 months. Furthermore, 18 of the 39 patients with a complete response remained recurrence-free at 12 months [13]. The SWOG S1605 study is ongoing and presented interim analysis results. In this study, 1,200 mg of atezolizumab was intravenously injected every three weeks for one year. Of 172 enrolled patients, 128 were eligible for efficacy analysis; 20 of the 74 patients (27%) with CIS achieved a complete response at six months. The 12-month recurrence-free survival rate in the patients with a complete response was 54%.

Targeted therapies like Vicinium and Adstiladrin were also evaluated. Vicinium is a combinatorial protein of epithelial cell adhesion molecule antibodies and Pseudomonas Exotoxin A, which inhibits protein synthesis. In a phase II study, 30 mg of Vicinium was administered intravesically every six or 12 weeks. It showed a complete response in 20 out of 46 patients (44%). At the end of the study, the overall disease-free rate was 16% [14]. The results of the phase III trial on Vicinium are in progress. In this phase III, single-arm study, Vicinium was administered twice weekly for six weeks, then once a week for six weeks. For up to two years, biweekly maintenance treatment was continued in patients with a complete response. The three-month complete response rate was 40%, while 52% remained consistent for 12 months of follow-up. The rate of radical cystectomy was 10% for the complete responders at three months versus 32% for non-responders.

Adstiladrin (nadofaragene firadenovec-vncg) has a therapeutic strategy; whereby a copy of the human interferon alfa-by gene is delivered to the urothelium. This is done by the non-replicating, recombinant, adenovirus vector, rAd-IFNα, and mediated by Syn3, a polyamide surfactant that enhances viral transduction. In a phase III multicenter, open-label trial, 75 mL of Adstiladrin was administered intravesically with repeated doses at three, six, and nine months without a high-grade recurrence. In a total of 198 eligible patients, 157 patients were evaluated for the analysis and 151 patients were evaluable for the efficacy analysis. Among them, 103 patients had CIS, 55 (53.4%) of them showed a complete response at three months, and 25 (45.5%) remained disease-free

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for 12 months [15]. On December 16, 2022, the FDA approved Adstiladrin for the treatment of high-risk BCG unresponsive NMIBC, with CIS or without papillary tumors.

Intravesical Valrubicin, Adstiladrin, and systemic Pembrolizumab are approved by the FDA for BCG unresponsive NMIBC. Other than radical cystectomy, procedures for BCG-failure treatment to preserve the bladder are ongoing. In the future, it is expected that an enhanced drug delivery system would facilitate the therapeutic effects of alternative treatments in BCG-failure bladder cancers.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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