Introduction

Non-muscle invasive bladder cancer (NMIBC) is confined to the mucosa and submucosa, and comprises approximately 75% of initially diagnosed bladder cancers (1). Although most of the patients with NMIBC are easily treated by the transurethral resection of bladder tumors, up to 80% and 15% of patients experience recurrence and progression, respectively, within five years (2,3). There are several therapeutic options for reducing the recurrence and progression of NMIBC. Among these, the intravesical instillation of Bacillus Calmette-Guérin (BCG) immunotherapy is more effective in reducing the rate of recurrence than the intravesical instillation of most of the prescribed chemotherapeutic agents (4).

The intravesical instillation of BCG is recommended as the standard treatment for intermediate to high risk NMIBC by current clinical guidelines (5,6). However, despite the intravesical instillation of BCG, a significant proportion of patients with intermediate to high risk NMIBC develop intravesical recurrence. Moreover, the treatment of BCG-unresponsive NMIBC is currently challenging. There are no reliable treatment options for these patients with BCG-unresponsive NMIBC, except radical cystectomy, which reported to show acceptable oncological outcomes. In this regards, reliable and safe non-invasive or less-invasive treatment options with acceptable oncological outcomes are awaited for the treatment of BCG-unresponsive NMIBC. The treatment of advanced or metastatic urothelial carcinoma has greatly advanced following the recent introduction of immunotherapeutic agents. These advancements have triggered an increasing interest in the use of immunotherapeutic agents for NMIBC, and especially for BCG-unresponsive NMIBC. The current review article aims to introduce and discuss the cutting-edge knowledge on the role of immunotherapy in BCG-unresponsive NMIBC and the currently available therapeutic strategies for its treatment. In addition, this article also summarizes the ongoing studies in this field.

Keywords: Administration; intravesical; Bacillus Calmette-Guérin vaccine (BCG vaccine); immunotherapy; urinary bladder neoplasms
can be considered in certain situations (6). Owing to the high mortality and morbidity of radical cystectomy, it is necessary to identify alternatives for the clinical treatment of patients with NMIBC who have failed on BCG therapy. Recent advancements in the field of immunological drugs have demonstrated their promising effects in advanced and metastatic settings (7), and there is accumulating evidence regarding the use of immunotherapy in treating the more indolent patient groups. These advancements have triggered an increasing interest in the use of immunotherapeutic agents for NMIBC, and especially BCG unresponsive NMIBC. Preliminary results of studies investigating the use of immunotherapeutic agents for the treatment of BCG unresponsive NMIBC have been recently released, which demonstrate the promise of immunotherapy in treating BCG unresponsive NMIBC (8). Numerous studies are being presently conducted in this field, and the results of these studies are awaited. The results of these studies can alter the current treatment strategies for BCG unresponsive NMIBC, and NMIBC in general, and clinicians need to consider such immunotherapeutic strategies for the treatment of BCG unresponsive NMIBC.

This review aimed to discuss the cutting-edge knowledge on the role of immunotherapy in BCG unresponsive NMIBC. The definition of BCG unresponsive NMIBC and the current treatment strategies for the management of BCG unresponsive NMIBC are summarized herein. The background for the use of immunotherapy for BCG unresponsive NMIBC is briefly discussed. We have additionally summarized the ongoing studies that are investigating the efficacy of immunotherapeutic agents for the treatment of BCG unresponsive NMIBC and BCG naive NMIBC.

**Definition of BCG unresponsive NMIBC**

Patients who fail during or after BCG immunotherapy require alternative treatment strategies. The definition of BCG failure is vital for assessing disease prognosis. BCG failure can be categorized into four subgroups according to the timing and nature of recurrence, and includes the “BCG intolerance”, “BCG refractory”, “BCG relapse”, and “BCG unresponsive” subgroups (9). The term “BCG intolerant” is used when a patient is unable to receive the optimal BCG therapy due to adverse effects, and the BCG therapy has to be ceased (6). Although there can be differences in the dosage and duration, optimal BCG therapy must comprise induction therapy followed by maintenance therapy in patients with high risk (6). The “BCG refractory” subgroup comprises patients with persistent high-grade cancer following 6 months of induction therapy, or patients with cancers that have progressed 3 months after the commencement of induction therapy (10). “BCG relapse” indicates the recurrence of cancer after achieving a disease-free state after 6 months of BCG therapy. The “BCG refractory” subgroup generally comprises patients with poorer prognosis than the “BCG relapse” subgroup; however, “BCG relapse” within 6 months of last BCG exposure shows similar poor prognosis as the “BCG refractory” subgroup (9). In a previous prospective study, the survival of patients belonging to the BCG refractory subgroup was worse in comparison to that of the patients in the BCG relapse subgroup (11). In other words, as there are diverse definitions of BCG failure, the prognosis differs according to the definition of BCG failure (12).

For this reason, the International Bladder Cancer Group (IBCG) and the Genitourinary American Society of Clinical Oncology Group announced a novel, combined definition for the most aggressive subgroup of BCG failure, namely, the “BCG unresponsive” subgroup. According to their definition, BCG unresponsiveness is defined by the presence of persistent high-grade disease, or disease recurrence within 6 months of receiving at least two courses of intravesical instillation of BCG, after at least 5 of 6 induction doses along with at least 2 of 3 maintenance doses, or T1 high-grade disease at first evaluation following the induction of BCG alone after at least 5 of 6 induction doses. The BCG unresponsive subgroup of NMIBC specifically comprises patients with high risk of progression, for whom additional BCG therapy is unfeasible (1). This novel category is important for identifying what truly defines the failure of BCG therapy, which requires optimal treatment strategies following the discontinuation of BCG immunotherapy.

**Current treatment options for BCG unresponsive NMIBC**

Non-surgical treatment options for the treatment of patients who have failed on BCG therapy are limited, and radical cystectomy is therefore the most preferred option (5). Early radical cystectomy following BCG failure has been demonstrated to have better survival gains than delayed cystectomy (13,14). The risk of progression of NMIBC to muscle-invasive bladder cancer (MIBC) is another evidence that supports the benefits of radical cystectomy in patients
who have failed on BCG therapy (15). However, although early radical cystectomy has been shown to have survival benefits for patients who have failed on BCG therapy, the risks and benefits of cystectomy need to be carefully considered and balanced, owing to the high treatment-related morbidity and mortality (16,17).

Although repeated BCG instillation is not recommended, it is an affordable option for a highly selected population. In persistent tumors, secondary BCG inductions have an approximately 50% response rate following a single induction of BCG (18). However, more than three induction therapies are not recommended owing to a low response rate of 20%, and higher BCG-related toxicity (18,19). Chemo-radiation therapy is a potential alternative for early radical cystectomy with a complete response rate of 88% and a 5-year cancer specific survival rate of 84% (20). However, the toxicity of chemotherapeutic agents needs to be carefully considered because radiotherapy alone has no oncologic benefits for the treatment of NMIBC (21). Additionally, the role of chemoradiation therapy for patients with extensive carcinoma in situ remain to be determined (22).

Intravesical chemotherapy is another option for the treatment of patients who have failed on BCG and are unable to tolerate radical cystectomy. Valrubicin is the only approved chemotherapeutic agent for the treatment of patients who have failed on BCG therapy and have extensive carcinoma in situ. However, disease free rates of 6 months and 12 months are less than 20% (9,23). Recently, intravesical gemcitabine and docetaxel chemotherapy has been demonstrated to be effective in patients who have failed on BCG therapy (24). An early phase III trial demonstrated that intravesical gemcitabine has better efficacy than intravesical mitomycin C in a BCG refractory setting (25). A previous study reported that the recurrence free rate following intravesical gemcitabine therapy is superior to that following secondary BCG induction (26). The oncological outcome of intravesical docetaxel therapy is promising with a complete response rate of 56% within 6 weeks of induction therapy in phase I trial (27). Additionally, the follow-up results demonstrated that the long-term outcomes of intravesical docetaxel therapy are good, with 69% of patients being able to avoid cystectomy at 2-years (28). The combination of intravesical chemotherapy with other therapeutic strategies is gaining attention in the recent years. The most frequent combination is the sequential administration of gemcitabine/mitomycin C (29,30) or gemcitabine/docetaxel (31,32). Both the combination therapies show promising results in settings of BCG failure, however, as the oncological outcomes of intravesical chemotherapy are inferior to those of radical cystectomy, more reliable treatment strategies are necessary.

**Background for immunotherapy in BCG unresponsive NMIBC**

After the first intravesical BCG clinical trial by Morales and coworkers in 1976 (33), Lamm and coworkers performed a prospective randomized clinical trial to confirm the effects of BCG instillation in bladder cancer (34). Based on these results, BCG instillation has been regarded as the standard treatment for superficial bladder cancer (6), and the mechanism of action of BCG via stimulation of the immune system is well established (35). However, around 30% of patients with NMIBC do not respond to BCG and progress towards MIBC (36). These results triggered an increasing interest in novel agents for the treatment of unresponsive NMIBC, and the instillation of certain chemotherapeutic agents were subsequently studied. However, it was observed that the instillation of any single chemotherapeutic agent is unable to surpass the efficacy of BCG instillation (4). These historical and clinical studies supported the use of other immunotherapeutic agents for the treatment of systemic bladder cancer.

The identification of novel immunotherapeutic targets is important for the development of immunotherapeutic drugs. The genes that are involved in T-cell regulation were discovered in the 1980s using molecular biological techniques (37), and tumor inhibition using anti-cytotoxic T-lymphocyte antigen 4 (CTLA4) antibodies was reported in 1996 (38). Subsequently, several other immune checkpoints were sequentially identified. Currently, the primary immune checkpoints are anti-CTLA4, anti-programmed cell death 1 (PD-1), and anti-programmed cell death ligand 1 (PDL-1) (39). The discovery of these immune checkpoints, which regulate the immune response, resulted in the development of treatment strategies that can be positively exploited for influencing T-cell activity and generating clinically relevant antitumor activities. These discoveries triggered the approval of immune check point inhibitors as a novel class of immunotherapy, that were first approved by the U.S. Food and Drug Administration (FDA) in 2011.

These immune check point inhibitors were investigated for treating several types of cancer and were reported to be effective for treating tumors with high mutation rates. A study by The Cancer Genome Atlas (TCGA) revealed that
bladder cancer has a high mutation rate, with a mean of 7.7 per Mb within the coding regions (40). As aforementioned, bladder cancer has been reported to have a high mutational load, following adenocarcinoma of the lung, squamous cell carcinoma of the lung, and melanoma, among others. These genomic and epigenomic alterations in bladder cancer result in the profound formation of neoantigens, which are regarded as foreign proteins by the immune system. Thus, a high mutation rate and the increased formation of neoantigens in bladder cancer are associated with antitumor immune reactions, which enhance the effects of immune checkpoint inhibitors. Apart from these historical and clinical studies, recent advances in biology also support the use of other immunotherapeutic agents for the treatment of bladder cancer, and immune checkpoint inhibitors have been investigated for the treatment of patients with bladder cancer.

Initially, the efficacy of immunotherapy in treating previous systemically-treated MIBC was investigated, which yielded promising results. Based on these results, atezolizumab, a well-known anti-PDL-1 agent, was approved as a second-line therapy for MIBC in 2016 (41). Subsequently, other immune checkpoint inhibitors, including nivolumab, durvalumab, avelumab, and pembrolizumab, have been sequentially approved as second-line therapy for bladder cancer (42-45). Additionally, atezolizumab and pembrolizumab were approved as first-line therapy for cisplatin-ineligible bladder cancer (46,47). Following approval, the targets for immunotherapeutic agents were rapidly targeted for the treatment of NMIBC. The first targets for immunotherapy against NMIBC included targets for BCG unresponsive NMIBC as there were no satisfactory treatment options for BCG unresponsive NMIBC, and can advance the development of therapeutic targets for immunotherapy.

**Immunotherapy for BCG unresponsive NMIBC: ongoing trials**

The recent preliminary results of pembrolizumab, in addition to the recently published results of the study on high-risk BCG unresponsive patients, who declined to undergo or were ineligible for cystectomy, indicated that the treatment options investigated in the studies were superior to the currently available treatment strategies. The study reported that pembrolizumab induced a complete response in nearly 40% of patients with BCG unresponsive NMIBC. Grade 3–4 treatment-related adverse events were observed in 12.7% of the study population, although treatment-related adverse events of any grade were observed in 64.7% of the study population. In other words, it is thought that immunotherapy is effective for treating BCG unresponsive bladder cancer, and could offer oncologically superior and safe treatment options for the treatment of these patients in the near future, although the results from phase 3 randomized clinical trials are awaited.

Numerous studies are presently evaluating the effects of various immunotherapeutic agents for the treatment of BCG unresponsive NMIBC, which are summarized in Table 1. Two ongoing phase 3 randomized studies are evaluating pembrolizumab or nivolumab for the treatment of BCG unresponsive NMIBC, and the results of these studies are awaited. The results of these studies are expected to be published within the next few years, and these results are expected to massively alter the treatment pattern for BCG unresponsive NMIBC. Several simultaneous phase 2 studies on numerous immunotherapeutic agents combined with or without various types of drugs are being currently performed, and the results of these studies are expected to be published within 5 years. Other types of immunotherapeutic agents are also being currently investigated. For instance, BCG in combination with ALT-803, a pharmacological grade IL-15/IL15Rα complex fused to an IgG1 Fc, in which IL-15 is mutated to further increase the biological activity and agonism of the IL-2 and 15βy receptors, is also being evaluated in clinical trials, and the development of other types of immunotherapeutic agents are awaited.

Other immunotherapy using vaccine and gene therapy is currently evaluated for BCG unresponsive NMIBC. Vaccine is theoretically regarded as an attractive option for BCG unresponsive NMIBC because lifelong defense mechanism for cancer could be obtained using vaccine treatment. However, majority ongoing clinical trials using vaccine, such as Ty21a, a live attenuated bacterial vaccine that protects against typhoid, and RUTIVAC-1 is currently focused on BCG naive bladder cancer (48). For patients with NMIBC exposed to prior BCG, the results of PANVAC, a recombinant virus vector vaccine containing gene for human carcinoembryonic antigen, mucin-1 and costimulatory molecules, combined with BCG, are awaited (48). Gene therapy, another novel stream treatment method for BCG unresponsive NMIBC, is treatment methods using nucleic acid delivered into a host’s cell, which was usually recruited for treating genetic disorders. Among gene therapy, immunogene therapy is targeting the
Table 1 Ongoing studies using immunotherapeutic agents for BCG-unresponsive NMIBC

<table>
<thead>
<tr>
<th>Identifier</th>
<th>Agents</th>
<th>Phase</th>
<th>Estimated number</th>
<th>Intervention model</th>
<th>Masking</th>
<th>Estimated completion</th>
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<td>November 25, 2024</td>
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<td>NCT03022825</td>
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<td>December 31, 2021</td>
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<tr>
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<tr>
<td>NCT04164082</td>
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<td>Single group</td>
<td>Open label</td>
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<td>NCT03519256</td>
<td>Nivolumab ± BMS-986205, BCG</td>
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<td>NCT02625961</td>
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<td>NCT03950362</td>
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<td>NCT03317158</td>
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<td>NCT03892642</td>
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<td>1b</td>
<td>27</td>
<td>Single group</td>
<td>Open label</td>
<td>October 2025</td>
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</table>

BCG, Bacillus Calmette-Guérin.

Immunotherapy for BCG unresponsive NMIBC: future directions

Immunotherapy could be the mainstream treatment option or one of the standard treatment options not only for MIBC, but also for BCG unresponsive NMIBC, if the results of the current ongoing trials, which are expected in a few years, are promising. BCG naive NMIBC could serve as the other target for immunotherapy in the near future, although some biomarkers are necessary for selecting the appropriate treatment targets for optimizing the individualized treatment options for patients with bladder cancer. In addition, due to the world-wide BCG shortage, the novel treatment methods with reliable effects for BCG naive NMIBC is desperately awaited.

Some studies have aimed to evaluate the effects of immunotherapeutic agents on BCG naive NMIBC (Table 2). However, with the exception of one phase 3 study on durvalumab, the other studies on immune checkpoint inhibitors are small phase 1 studies and larger studies with reliable study designs are necessary for validating the effects of immunotherapy on BCG naive NMIBC, on the basis of these phase 1 studies. Additionally, other types of immunotherapeutic agents are also being tested for the treatment of BCG naive NMIBC, and the results of a phase 1b/2b ALT-803 study on 596 patients are awaited. In addition, gene therapy could be another novel stream treatment method for BCG unresponsive NMIBC, as mentioned above, although optimal selection strategies for each patient are remained to be developed. These studies could mark the beginning of massive alterations and a number of studies on immunotherapeutic agents are expected to be performed within a few years the treatment of BCG naive NMIBC, and it is necessary for clinicians to be concerned with these aspects.

In near future, vaccine might be an effective preventing...
method for bladder cancer, in addition to treatment methods for BCG naive NMIBC because of the lifelong prevention of bladder cancer as mentioned above. Currently, two ongoing phase 1 clinical trials using vaccine, including Ty21a, and RUTIVAC-1 is on the way and the results are awaited. If these studies showed promising results, not only treatment landscape for NMIBC, but also preventing strategies for bladder cancer expected to change significantly.

**Conclusions**

At present, the treatment of BCG unresponsive NMIBC is challenging, and novel treatment options for BCG unresponsive NMIBC awaited. A number of immunotherapeutic agents have been recently developed, which showed satisfactory oncological outcomes for the treatment of MIBC and are rapidly progressing towards the treatment of BCG unresponsive NMIBC. A large number of clinical trials are ongoing and the preliminary results of some of these trials have been promising, which might alter the treatment strategies for BCG unresponsive NMIBC in a few years. Additionally, the treatment landscape for BCG unresponsive NMIBC, and also for NMIBC in general, could undergo slight alterations in a few years. In addition, due to the worldwide shortage of the BCG the development of novel agents for not only for BCG unresponsive NMIBC, but also for BCG naive NMIBC. In this regard, clinicians need to continue studying clinical trials on the use of immunotherapy in treating BCG unresponsive NMIBC.

**Acknowledgments**

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<table>
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<tr>
<th>Identifier</th>
<th>Agents</th>
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<th>Intervention model</th>
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<td>March, 2023</td>
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</table>

BCG, Bacillus Calmette-Guérin; NMIBC, non-muscle invasive bladder cancer.

**Footnote**

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