European Journal of Pharmacology 926 (2022) 175024

Contents lists available at ScienceDirect

European Journal of Pharmacology

journal homepage: www.elsevier.com/locate/ejphar

Intravesical combination therapies for non-muscle invasive bladder cancer: Recent advances and future directions

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ARTICLE INFO

Keywords:
Bladder cancer
Combination therapies
Intravesical drug delivery
Non-muscle invasive bladder cancer
BCG
Formulation

ABSTRACT

Bladder cancer is the 10th most frequently diagnosed cancer worldwide with 5-year survival rate around 70%. The current first-line treatment for non-muscle invasive bladder cancer is transurethral resection of bladder tumours followed by intravesical *Mycobacterium Bovis* Bacillus Calmette-Guérin (BCG) immunotherapy. However, tumor recurrence rate is still high ranging from 31% to 78% within five years. To avoid radical cystectomy, intravesical combination therapies have been developed as salvage treatments to overcome BCG failure. Recent advances in diagnostics thanks to tumor molecular profiling and in treatment such as development of immunotherapies provides more treatment options beyond BCG treatment. This also goes hand-in hand with formulation advances to deliver these new therapies where traditional drug delivery systems might not be suitable, which in turn is completed by challenges to deliver drugs via the intravesical route.

In this article the aim was to provide an in-depth analysis of the current developments of intravesical combination therapies, ranging from relatively simple combinations of mixing existed intravesical therapeutic agents (immunotherapies and chemotherapies) to the combined formulations containing advanced gene therapies and targeted therapies, with special focus on therapies that have made it to the clinical trial stage. In addition, recent attempts to utilize device-assisted treatments and novel drug delivery platforms are included. This review also highlights the limitations that still need to be overcome such as the inadequate studies on newly explored drug carriers and proposes potential directions for future work to overcome BCG-failure.

1. Introduction

As a severe genitourinary cancer, bladder cancer is induced by the abnormal cell proliferation in the urothelial lining of urinary bladders. In 2020, bladder cancer became the 10th most commonly diagnosed cancer in the whole world, which occupied about 3% of new cancer cases and led to over 200,000 deaths (Sung et al., 2021). The 5-year survival rate of bladder cancer is around 70%. The disease is more common in men that it has become one of the five leading causes of cancer death among men over 80 (Marcos-Gragera et al., 2015; Yoon et al., 2020). The prevalence of bladder cancer can be regarded as the reflection of the popularity of tobacco since smoking is one of the leading risk factors of bladder cancer (Sung et al., 2021). Other risk factors include being exposed to industrial pollution and family history, which may explain the increased number of cases in high-income countries (Wong et al., 2018).

Bladder cancer can be classified into muscle invasive bladder cancer (MIBC) or non-muscle invasive bladder cancer (NMIBC) (Matulewicz and Steinberg, 2020). Theoretically, the prognosis of bladder cancer should be good, and the mortality rate should be low since majority of cases are NMIBC (approximately 75%) (Kamat et al., 2016a; Sung et al., 2021). But unexpectedly, the lifetime treatment cost of bladder cancer is ranking top of all cancers and should be responsible for a financial burden of about $3.98 billion in the US and €4.9 billion in Europe per year (Leal et al., 2016; Mossanen and Gore, 2014). These might result from the expensive cost owing to the difficulty of treating this cancer, and the high recurrence rate within five years (ranging from 31% to 78%) (Sylvester et al., 2006).

As a temporary storage site of urine, it is crucial for the bladder to strictly isolate urine from blood, and hence urothelium acts as

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https://doi.org/10.1016/j.ejphar.2022.175024
Received 20 February 2022; Received in revised form 30 April 2022; Accepted 9 May 2022
Available online 14 May 2022

impermeable barrier (Lewis, 2000). The special protein arrays and the tightly knitted superficial umbrella cells in the surface of urothelium prevent the permeability of urine into the underlying tissue of bladder and thus inhibit the development of inflammation, fibrosis, and bladder detrusor muscle over-activity (Akkad et al., 2007; Wan et al., 2018; Zacchè et al., 2015). On the other hand, urothelium hinders drug delivery through systemic administrations (Lewis, 2000; Moch et al., 2014). Therefore, the intravesical drug delivery systems have become the focus of bladder cancer treatments to overcome the bladder permeability barrier (BPB).

Compared to the systemic delivery routes, intravesical drug delivery is safer and can increase the bioavailability of drugs by sending lower doses directly into the bladders (Yoon et al., 2020). Certainly, there are also some drawbacks awaiting to be overcome. For instance, maintaining the expected drug concentration in the bladder is challenging because drug concentration can be easily changed by the continuous emptying of urine (Joice et al., 2019). And the drug absorption through the urothelium still needs to be further improved. Repeated intravesical instillations can be adopted to maintain the needed drug concentration but this would influence patient compliance. These challenges have attracted research aiming at finding solutions.

After being firstly approved for treatment of bladder cancer by US FDA in 1990, the intravesical *Mycobacterium Bovis* Bacillus Calmette-Guérin (BCG) immunotherapy following transurethral resection of bladder tumours (TURBT) remains the gold standard for treating NMIBC (Lamm, 1995). The mechanism of action of BCG in bladder cancer is still under investigation, but it is suggested that internalization of BCG in cancer cells leads to secretion of cytokines and activation of the immune system against the tumor (Redelman-Sidi et al., 2014). However, the classic BCG treatment still has some non-negligible drawbacks. During the latest decade, the shortage of BCG supply has become a latent problem. Merck has declined the supply of the Tice strain of BCG since the announcement of insufficiency in 2014, while Sanofi declared the shortage of the Connaught strain in 2012 and shut the production permanently in 2017 (Messing, 2017).

The adverse effects of BCG are also urgently awaiting to be handled. Up to 90% of patients may undergo at least one adverse event when receiving intravesical BCG therapy, and about 8% of them may have to exit the treatment when encountering severe complications (Decaestecker and Oosterlinck, 2015; Koch et al., 2021). Local side effects including cystitis, hematuria, urinary frequency, granulomatous prostatitis, epididymitis, ureteral obstruction, and contracted bladder are more common, which can influence 62.8–75.2% of patients, while systemic complications such as general malaise, fever, sepsis, and allergic reactions (skin rash, arthralgia, and arthritis) usually occur in a lower proportion (30–40%) of patients (Brausi et al., 2014; Decaestecker and Oosterlinck, 2015; Koch et al., 2021). Life-threatening adverse events are rarely reported, but they still need to get more attention as BCG-induced infections or immune reactions have been observed in multiple organs including prostate, epididymis, testicles, glans penis, liver, kidney, and lungs (Decaestecker and Oosterlinck, 2015; Koch et al., 2021). Among all the extant shortcomings of BCG treatment, the problem which keeps attracting more attention is the existence of BCG failure. Although BCG therapy has shown great advantage by arousing an initial complete response rate of nearly 80%, there are still 30–40% of patients who cannot receive the optimal therapeutic effect (Sylvester et al., 2006). A repeated course of intravesical BCG treatment might benefit a certain number of patients, but for those who are unresponsive or intolerant to BCG, failing to find an appropriate salvage treatment can lead to recurrence and progression into MIBC and could eventually result in fatal consequences (van Rhijn et al., 2009).

At present, radical cystectomy is widely recommended to patients failing BCG treatments (Kamat et al., 2016b; van Rhijn et al., 2009). Early cystectomy, just after BCG failure, for BCG unresponsive patients has several advantages (Kikuchi et al., 2020). It improves the chances for cure as the disease-free survival rate is 80–90% before progression to MIBC (Klaassen et al., 2018). Furthermore, as lymphadenectomy is a part of cystectomy procedure, occult lymph node metastasis can be treated and evaluated for proper management (Stein et al., 2001). In addition, cystectomy eliminates the need for subsequent intravesical treatment and makes follow-up regimen easier (Kikuchi et al., 2020). But evidently, surgery is not suitable for all patients. The cost of surgery is usually high and elderly patients cannot endure the comorbidities and complications associated with cystectomy. In addition, it is associated with high risk of mortality and morbidity, where it is shown in long term study that mortality rate was 2.7% at 30 days and 7.2% at 90 days (Nielsen et al., 2014). Also, it may result in unwanted side-effects as it is highly invasive surgical procedures (Kikuchi et al., 2020). Intravesical drug delivery is still an option to preserve their bladders using new strategies of different therapeutic agents or device-assisted treatments. However, evidence showed that inducing regulated cell death by a single treatment can hardly kill bladder cancer cells completely as it can lead to high tumour heterogeneity by pushing the cancer cells to progress more rapidly and soon acquire resistance with the help of gene mutation (Guo et al., 2020). Hence, combination therapies are expected to delay the development of resistance and be more effective since a more complicated therapeutic mechanism might hinder cancer cells from adapting. Recent studies have already demonstrated that combination therapies can successfully increase anti-cancer response and reduce toxicity by putting multiple therapeutic agents together or blending chemotherapies with device-assisted therapies (Peng et al., 2021).

During the last decade, a variety of published reviews have focused on the intravesical therapies for treating bladder cancer, and different strategies for managing BCG failure have been investigated. However, there has been a limited focus on the use of intravesical combination therapies for BCG failure. Therefore, the aim of this review is to fill this gap with an emphasis on the current state of the advanced intravesical combination treatments, and combined formulations with the aid of device-assisted therapies or novel drug delivery systems. Thus, this holistic review is organized in three key steps:

- Providing a brief interlocution into the complexity of the classification of bladder cancer and its impact on guiding choice of treatment
- Investigating the current landscape of intravesical bladder cancer treatments within the last ten years and critically evaluating the potential of the available intravesical combination treatments for solving BCG failure
- Offering several novel approaches that can potentially be used in the future.

This review is based on surveying and interrogating related articles reporting original experimental results or other previous reviews on intravesical combination therapies from two electronic databases - PubMed and Web of Science. Keywords and Boolean Operators used for restricting the range of searching were ‘intravesical’ as a fixed keyword connected with a combination of the following Boolean Operators; ‘Bladder Cancer’, ‘Combination Therapies’, ‘Non-Muscle Invasive Bladder Cancer’, ‘BCG failure’ and ‘Drug Delivery Systems’ Information about the current clinical trials that has not been published was gathered from ClinicalTrials.gov. Inclusion and exclusion criteria to further narrow down the search outcomes were used. Abstracts of articles published between January 2010 and July 2021 were screened while papers published before 2010 were not included in this study unless they refer to the landmarks of fields or have specific connections with the current research progresses. Only papers written in English were chosen for further analysis, and articles investigating MIBC or treatments other than intravesical therapies were excluded.

2. Staging, grading, and the risk stratification of NMIBC

Finding a correlation between the past studies and the present trials,

and thus making further comparisons, requires an appropriate classification of bladder cancer patients. After been divided into NMIBC and MIBC, the staging, grading, and risk stratification of NMIBC are of great prognostic value. Depending on the acceptance of BCG and the following results, patients with NMIBC can be roughly classified into three groups: BCG naive, BCG exposed, and BCG failure.

Patients with NMIBC but have never received BCG treatment can be termed as BCG naïve (Packiam et al., 2019) while under most situations, NMIBC patients who have already received BCG therapies but not reached the delimiting of BCG failure can be described as BCG exposed. On the other hand, deciding the optimal therapeutic regime for patients undergoing BCG failure can be difficult as the definition and classification of BCG failure keep changing. BCG failure can be used to represent patients with any recurrence or progression during or after BCG treatments. In 2016, the International Bladder Cancer Group (IBCG) suggested a standard classification system for BCG failure into four categories, which are summarized in Table 1 (Kamat et al., 2017). This classification system has been accepted by the European Association of Urology (EAU) including the same four categories as IBCG classification and updated in the latest guidelines on NMIBC (Babjuk et al., 2019). However, in the guidelines from the Canadian Urological Association (CUA), BCG unresponsive is replaced by BCG resistance which represents the recurrence that happens 3 months after BCG therapies but vanishes subsequently by 6 months (Kassouf et al., 2015). No specific classification of BCG failure can be found in the guidelines from the American Urological Association (AUA), but the FDA has adopted the concept of BCG unresponsive disease and correlative clinical trials have been permitted (Chang et al., 2016). As demonstrated by the definition in Table 1, the category BCG unresponsive encompasses diverse groups of patients, which could add more challenges in the clinical setting. Nonetheless, the FDA provides a detailed guidance on stratification of patients in this category to assist in the development of new treatments.

On the other hand, staging of tumour is mainly based on the tumour, node, metastasis (TNM) classification system, and the depth of tumour invasion (T stage) plays the most important role in determining the stage of NMIBC as the regional lymph nodes (N stage) and the distant metastases (M stage) are absent (Matulewicz and Steinberg, 2020). The Union for International Cancer Control (UICC) updated the TNM classification system in 2017 and suggested that bladder tumours in the stage of Tis, Ta, or T1 can be put under the title of NMIBC (Tis refers to "carcinoma in situ (CIS)", Ta refers to "non-invasive papillary carcinoma', and T1 refers to "tumour invades subepithelial connective tissue") (Brierley et al., 2017).

The situation becomes a bit complicated when coming to the histological grading of NMIBC. In 1973, the World Health Organization (WHO) published the grading system based on the cellular anaplasia of urothelial carcinoma, and NMIBC could be stratified into Grade 1 (G1, well differentiated), Grade 2 (G2, moderately differentiated), and Grade 3 (G3, poorly differentiated) (Mostofi et al., 2012). In 2004, WHO updated the grading standard with the new categories of papillary urothelial neoplasm of low malignant potential (PUNLMP), Low grade papillary urothelial carcinoma (LG), and High grade papillary urothelial carcinoma (HG) (Eble et al., 2004). However, the 2004/2016 grading system failed to show distinct advantages when helping to predict the recurrence and progression of tumours, so it has been recommended that both the 1973 system and the 2004/2016 system should be taken into consideration when grading the NMIBC patients (Babjuk et al., 2019; Soukup et al., 2017).

The risk stratification of NMIBC can influence the diagnosis, design of the therapeutic regimen, and prognostication. To date, the most widely accepted method to determine the risk stratification is to use the European Organisation for Research and Treatment of Cancer (EORTC) risk tables, which adopt the grade, stage, tumour size, prior recurrence rate, presence of concomitant CIS, and number of tumours as parameters to predict the probability of recurrence and progression (Sylvester et al., 2006). Based on this system, NMIBC can be classified into low-risk, high-risk and intermediate-risk NMIBC (between the categories of low and high-risk) (Babjuk et al., 2019). Recurrence after BCG treatments or BCG failure usually occurs to intermediate- and high-risk NMIBC. It has been suggested that low-risk NMIBC can be handled by single intravesical instillation of chemotherapy or immunotherapy, but high-risk NMIBC might need repeated instillations and maintenance treatments with a duration of 3 years, and the management of intermediate-risk NMIBC should be varied relying on specific situations, both of single-dose treatment and induction intravesical therapy can be options, and maintenance treatments can also be considered, with a shorter duration of several months (Bree et al., 2021).

Earlier reviews mentioning intravesical therapies are summarized in Table S1 and show a discussion of the situation of adopting intravesical combination therapies for handling BCG failure. They also demonstrated that utilizing intravesical therapies for handling NMIBC patients with BCG failure has lately stimulated higher concern since more reviews have been published during recent years (2019–2021). Among all those research directions, the combinations of therapeutic agents have attracted the most attention. Beginning with the existing BCG therapy, a wide range of combined formulations with or without BCG have been attempted. Based on the foundation of the existed therapeutic drugs, device-assisted treatments have also been investigated for their capability of enhancing therapeutic efficacy. The utilization of novel intravesical drug delivery systems are also under development, and some of these attempts can be regarded as combination treatments, which predicts the future trend of dealing with BCG failure.

Table 1
The International Bladder Cancer Group (IBCG) classification system for BCG failure (Kamat et al., 2017; Food and Drug administration, 2018).

Category	Definition
BCG refractory	patients fail to reach the recovery status by 6 months after the maintaining or repeating BCG treatments
BCG relapsing	recurrence happens to patients by 6 months after the disease-free status has once been achieved
BCG unresponsive	patients who can hardly benefit from BCG therapies in most circumstances According to FDA patients with either - Persistent or recurrent CIS alone or with Ta/T1 within 12 month of therapy completion. - Recurrent high-grade Ta/T1 within 6 months of therapy completion. - T1 high-grade disease at first evaluation following induction of course of treatment
BCG intolerant	patients who cannot bear the BCG treatments because of the severe adverse events or toxicity

Cis carcinoma in situ, Ta non-invasive papillary carcinoma, T1 tumor invades subepithelial connective tissues.

3. Recent developments in intravesical combination therapies

Various intravesical combinations for treating BCG failure have been investigated over the last few decades and made it to the clinical trial stage. The following section will introduce them under their corresponding categories, as summarized in Fig. 1.

3.1. Combinations of multiple therapeutic agents

Combining different therapeutic agents should be the most comprehensively investigated strategy to manage BCG unresponsiveness, and the present drug combinations can be sorted depending on the mechanisms and varieties of the components. A summary of clinical trials assessing this therapeutic combination for NMIBC is shown in Table 2.

3.1.1. BCG augmented immunotherapies

Although the intravesical BCG treatment has remained the front-line

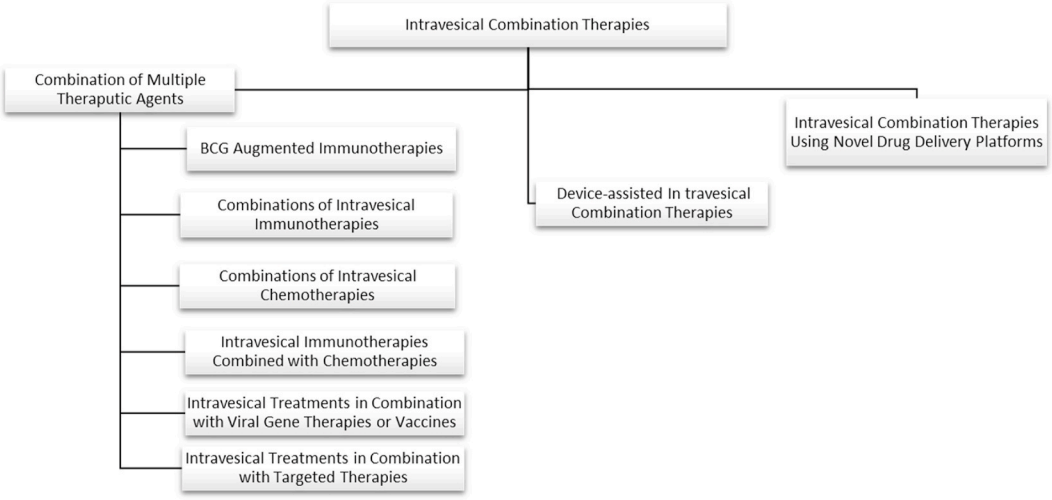

Fig. 1. Overview of intravesical combination therapies according to type and mechanism of the therapeutic agents.

therapy for NMIBC for years, its therapeutic mechanism still cannot be fully understood. Currently, the widely accepted assumption is that after being instilled into human bladders, BCG can interact with the urothelial cells directly and promote the release of cytokines as well as stimulate the inflammation-mediated non-specific tumor response, and finally the adaptive immune response would be activated and the killing of cancer cells would be accelerated by inducing the T-cell mediated cytotoxic reactions (Patard et al., 1993; Sapre and Corcoran, 2013). It has also been proposed that BCG is capable of modulating gene expression which might have a certain effect on the therapeutic efficacy of killing cancer cells (Rahmat et al., 2018). For the BCG unresponsive patients who are insensitive to the intravesical BCG monotherapies, one promising strategy is combining BCG with different immunomodulators. These immunomodulators have found to augment the innate immune response activity of BCG.

One of the most intensively studied agents is the interferon-alpha (IFN-α), especially the IFN-α2b. In the 1990s, IFN-α2b was expected to become a single intravesical therapeutic agent for treating superficial bladder cancer, but this project was terminated as IFN-α2b failed to induce a satisfying tumour-free response (Glashan, 1990; Hudson and Ratliff, 1995). Afterwards, other researches investigating IFN as a single therapeutic agent are still ongoing, but more efforts have been paid on evaluating the anti-tumour efficacy of combining IFN-α2b with BCG (Joudi et al., 2006). Results showed that the combination of IFN-α2b and BCG could help about 45% of patients with BCG failure to become disease-free by 24 months after treatments (Joudi et al., 2006). Nonetheless, the patients with BCG failure have not been further classified in the present trials, and thus the therapeutic efficacy of the BCG plus IFN-α2b combination on BCG unresponsive patients still needs to be further investigated (Packiam et al., 2021).

Another promising formulation is the quadruple immunotherapy (QIT), which refers to the combination of BCG, IFN, interleukin-2 (IL-2), and granulocyte colony stimulating factor (GM-CSF). The design of such combination therapy was based on previous evidence which proved that apart from IFN, IL-2 and GM-CSF can also synergize with BCG and enhance the cytotoxic T-cell response (Luo et al., 2003). Since GM-CSF is usually sold as injections under the commercial name of Leukine (sargramostim), this regimen needs to be administrated through both the intravesical route and the system route. Results showed that the treatment success was 53–55% for up to two years, about quarter of patients needed to eventually receive radical cystectomy because of disease progression (Steinberg et al., 2017). But it needs to be noticed that high percentage of patients reporting side effects (Steinberg et al., 2017). Overall, the results were not so impressive, but QIT still becomes an option for patients with BCG failure, although further subclassification of BCG failure has not been studied yet.

More recently, another immunomodulatory agent which has great expectations is the N-803 (ALT-803/Anktiva). N-803 is a super-agonist of IL-15, which can stimulate both innate and adaptive immune responses by promoting the proliferation and activation of natural killer (NK) cells and $CD8^+$ T cells (Chamie et al., 2021). Using N-803 as a mono-treatment is also under investigation, but more emphasis has been laid on combining N-803 with BCG (Furuya et al., 2019). The latest results of phase II and III clinical trials (NCT03022825)(ImmunityBio, 2022) demonstrated that the mixed formulation of N-803 and BCG has achieved a complete response rate at any time of 72% in the BCG unresponsive NMIBC patient group, and the possibility of maintaining this complete response rate for at least 1 year was high (Chamie et al., 2021). Together, these promising data illustrate the potential of N-803 becoming a favorable augmenting agent for BCG unresponsive patients.

3.1.2. *Combinations of intravesical immunotherapies*

Besides immunotherapeutic agents which augments the BCG effect, others have been emerging during the past few decades for treating NMIBC. They include humanized antibodies pembrolizumab, atezolizumab, durvalumab, avelumab, and nivolumab. By blocking certain immune checkpoints and up regulating the immune responses, immunotherapies are considered to be more bearable and thus have better patient compliance (Peng et al., 2021). Although these agents may not be able to augment BCG, combining them with each other is still a practical approach to enhance efficacy and address drug resistance, and therefore overcome the BCG failure.

Pembrolizumab, an immune checkpoint inhibitor that can activate the anti-tumour immune response by blocking the Programmed Death-1 (PD-1), has been studied for years and finally be approved for treating NMIBC patients with BCG failure by the FDA in 2020 (Bree et al., 2021). But before that, scientists have already put forward the suggestion of uniting pembrolizumab with other drugs. The study of the combination of intravenous pembrolizumab and intravesical BCG has already proceeded into a phase III clinical trial (KEYNOTE-676/NCT03711032) (Merck Sharp & Dohme Corp, 2022) since the results of the phase I trial are quite promising (with a disease-free survival rate of 78%)(Alanee et al., 2019). Meanwhile (from February 2017), a phase I clinical trial of examining the possibility of administrating both of the pembrolizumab and BCG intravesically for treating high-risk and BCG refractory NMIBC is also ongoing (NCT02808143) (Meeks, 2020) among a small group of patients) and results of both experiments are still waiting to be released.

Another PD-1 inhibitor expected to become an NMIBC treatment is

Table 2
A summary of the current clinical trials assessing combinational intravesical therapy for NMIBC patients with BCG failure.

	Treatments	Patient population	Results	Reference
BCG Augmented-Immunotherapies	- Reduced dose or the standard dose (50 mg) of intravesical BCG directly mixed with 50 million units of IFN-α2b - The maintenance treatments included another 3 courses of 3-week BCG (reduced dose) plus IFN-α2b intravesical instillations at 3, 9, and 15 months after the induction completion	1106 patients were enrolled into either the BCG failure group or the BCG naive group	The combination of IFN-α2b and BCG could help about 45% of patients with BCG failure to become disease-free by 24 months after treatments	Joudi, Smith, and O'Donnell (2006)
	- Quadruple immunotherapy (QIT) which is combination of BCG, IFN, interleukin-2 (IL-2), and granulocyte colony stimulating factor (GM-CSF) - Treatment was 6 QIT, once a week. The therapies included weekly intravesical instillations containing one-third of the standard dose of BCG, 50 million units of IFN, and 22 million units of IL-2, followed by a 250 μg GM-CSF - Maintenance treatments should be arranged at 3, 9, and 15 months after the completion of induction.	52 patients (45 of whom had accepted one BCG treatment and 7 of whom had accepted multiple BCG therapies before)	The treatment success was 55% after 1 year and 53% after two years, about 25% of patients needed to eventually receive radical cystectomy because of disease progression. But it needs to be noticed that 90% of patients reported side effects, and 6% of them failed to tolerate the full treatments	(R. L. Steinberg et al., 2017)
	- Combination with N-803 (ALT-803/Anktiva) which is immunomodulatory agent acting as a super-agonist of IL-15, which can stimulate both innate and adaptive immune responses. - Intravesical solutions of N-803 mixed with BCG and saline every week for 6 consecutive weeks, whether followed by a 3-week maintenance treatment or a 6-week re-induction course would be decided by the first disease assessment - The rest of the maintenance courses would be set at month 6, 9, 12, and 18 (the third period) and month 24, 30, and 36 (the fourth period).	180 high grade NMIBC patients	Phase II and III clinical trials demonstrated that the mixed formulation of N-803 and BCG has achieved a complete response rate at any time of 72% in the BCG unresponsive NMIBC patient group, and the possibility of maintaining this complete response rate for at least 12 months is around 59%.	ImmunityBio (2022)
Combinations of Intravesical Immunotherapies	- Combination of intravenous pembrolizumab and intravesical BCG. - intravesical instillations containing 50 mg BCG once a week for 6 weeks, combining with intravenous infusions having 200 mg pembrolizumab every three weeks (or 400 mg pembrolizumab every 6 weeks for BCG naive patients) - The following maintenance therapies would be set at month 3, 6, 12, 18, 24, 30, and 36, once a week for 3 weeks.	1525 high-risk NMIBC patients who are BCG unresponsive	Phase I trial results were promising with a disease-free survival rate of 78%	(Kamat et al., 2020; Merck Sharp & Dohme Corp, 2022)
	- Combination of both pembrolizumab and BCG intravesically	9 patients with high-risk and BCG refractory NMIBC	Results are still waiting to be released	Meeks (2020)
	- Combination of BCG and atezolizumab - Weekly BCG intravesical instillations combined with intravenous infusions containing 1200 mg atezolizumab once every 3 weeks for 12 weeks in total	24 high-risk NMIBC patients who were either BCG unresponsive or BCG relapsing	Results have not been published yet	(Hoffmann-La Roche, 2021)
	- Combination of BCG and APL-1202 (methionine aminopeptidase 2 inhibitor) - Oral administrations of 250 mg APL-1202 three times a day (750 mg in total) for 5–7 days before the first instillation of BCG, and the daily dosing of APL-1202 and weekly dosing of BCG would be given in parallel for another 11 weeks.	6 Patients who were resistant to BCG monotherapy	Results have not been published yet	AsierisPharma (2020)
	-Combination of Nivolumab (the PD-1 inhibitor) plus BMS-986205 (the IDO1 inhibitor) plus intravesical BCG -The doses are flexible and would be altered under specific conditions.	69 high-risk NMIBC patients who are BCG unresponsive	Results have not been published yet	(Bristol-Myers Squibb, 2022)
Combinations of Intravesical Chemotherapies	- Combination of gemcitabine and mitomycin C. - 1000 mg gemcitabine was first given and stayed for 90 min and then drained, immediately followed by 40 mg mitomycin C which stayed for another 90 min.	47 high grade NMIBC patients with BCG failure	complete response rate of 68%, and the 1-year and 2-year recurrence-free survival were 48% and 38%, respectively.	Lightfoot et al. (2014)
	- Combination of gemcitabine with docetaxel	45 BCG failure patients		(R. L. Steinberg et al., 2015)

(*continued on next page*)

Table 2 (*continued*)

	Treatments	Patient population	Results	Reference
	- First received intravesical instillations of 1000 mg gemcitabine for 90 min, followed by 37.5 mg docetaxel for another 120 min.		Treatment success of 66% at the beginning, and 54% for 1 year, 34% for 2 years after the initial induction.	
	- Combination of cabazitaxel, gemcitabine, and cisplatin. - Cabazitaxel on Monday, gemcitabine on Wednesdays, and cisplatin every other Friday for 6 weeks. - The dose of gemcitabine has been fixed to be 2000 mg, while the doses of cabazitaxel and cisplatin kept changing, and the intravesical solutions should be retained in bladders for 1–2 h.	18 patients who were BCG unresponsive or BCG relapsing	The complete response rate was estimated to be 89%, and the recurrence-free survival rate was 0.83 at 1 year, and 0.64 at 2 years.	(Decastro et al., 2020; James M. McKiernan, 2022)
Intravesical Immunotherapies Combined with Chemotherapies	- Combination of gemcitabine and BCG. - Twice-weekly gemcitabine at week 1, 4, 7, and 10 (the dose is decided by specified assessments) while BCG would be given once a week at week 2, 3, 5, 6, 8, and 9 (50 mg for each dose)	68 high grade NMIBC patients who are BCG relapsing	The results are still pending	Memorial Sloan Kettering Cancer Center (2021)
	- Combination of gemcitabine and pembrolizumab. - 4 cycles of treatments (3 weeks for each cycle), intravenous infusions of pembrolizumab would be given on day 1 of cycle 1 to 4, and intravesical instillations of gemcitabine hydrochloride would be received on day 1, 8, and 15 of cycle 1 and 2. - During the stage of maintenance, pembrolizumab and gemcitabine would be given once every 3 weeks for 12 cycles.	161 BCG unresponsive NMIBC patients	The results are still pending	National Cancer Institute (2022b)
	- Combination of cetrelimab with TAR-200, a gemcitabine-releasing intravesical system. - TAR-200 is inserted by catheter into the bladder on Day 0 and dosed every 21 days up to the first 24 weeks, then every 12 weeks through Week 99. - Cetrelimab dosed every 3 weeks through Week 78 (18 months). - Combination of both or either TAR-200 or Cetrelimab alone were studied	200 high-risk BCG unresponsive NMIBC patients	The results are still pending	(Janseen Research and Development, 2022)
Intravesical Treatments in Combination with Viral Gene Therapies or Vaccines	- Combination of pembrolizumab and CG0070. - 6 weekly intravesical instillations of CG0070, followed by bladder washes with dodecyl maltoside (DDM, the enhancer). From week 12, patients who show complete response to the treatment would receive another 3 weekly treatments, or otherwise, 6 weekly treatments. - From week 24 to week 48, patients would get 3 weekly treatments every 3 months, and then every 24 weeks thereafter. Meanwhile, pembrolizumab would be given intravenously since day 1, every 3 weeks, and continue for no more than 2 years.	37 participants who had failed previous BCG treatment	The results might be released in 2022.	CG Oncology (2022)
	- Combination of PANVAC and BCG - As the treatment started at week 3, participants in the combination therapy group were given 6 weekly intravesical administrations of BCG in total, while the subcutaneous injections of PANVAC were given at week 3, 7, 11, and 15.	32 high grade NMIBC patients who had failed in at least 1 BCG treating course	Results have not been published yet	(Vladimir Valera Romero, 02020)
Intravesical Treatments in Combination with Targeted Therapies	- Combination of vicinium and durvalumab - Intravenous injections of 1500 mg durvalumab once every 4 weeks for 12 months, while 30 mg vicinuim would be received intravesically weekly for 12 weeks. - During the maintenance treating course, the same doses of durvalumab and vicinium would be administrated once every 3 months or every other week, respectively, for up to 2 years.	40 high grade NMIBC patients	Trial might last until the coming of 2024.	(National Cancer Institute (NCI), 2022a)
	- Combination of everolimus and gemcitabine		such combination failed to demonstrate an improved efficacy as most participants withdrew during the	(Dalbagni et al., 2017; Memorial Sloan Kettering Cancer, 2018)

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Table 2 (*continued*)

	Treatments	Patient population	Results	Reference
			treating course because of the insufferable toxicity	
Intravesical Combination Therapies Using Novel Drug Delivery Platforms	- Combining albumin-bound rapamycin nanoparticles (ABI-009) with gemcitabine - treating course of 6 weeks, patients would have received weekly intravesical instillations of 200 mg ABI-009 for 1 h, followed with 2000 mg intravesical gemcitabine for another 1 h after eliminating the previous treatment.	29 participants	With the help of albumin, ABI-009 is expected to deliver the drug directly into tumour cells via albumin receptors across the epithelial cells and thus increase drug uptake. The results are still pending.	(Sparreboom et al., 2005; Aadi, 2021)

atezolizumab, which has also been testing for its probability of handling BCG failure by combing with BCG. During a phase Ib/II clinical trial started from June 2016, with high-risk NMIBC patients who were either BCG unresponsive or BCG relapsing received BCG intravesical instillations combined with intravenous infusions of atezolizumab (NCT02792192) (Hoffmann-La Roche, 2021). The trial should be completed in September 2020, but no results have been published yet.

APL-1202 is a methionine aminopeptidase 2 (MetAP2) inhibitor that has become the world's first oral therapy for NMIBC (Asieris Pharmaceuticals, n.d.) From November 2018 to June 2020, a phase Ib clinical trial assessed the safety of the combination of APL-1202 and BCG (NCT03672240) (AsierisPharma, 2020) with patients who were resistant to BCG monotherapy were given APL-1202 intravesical BCG and the results are still pending.

The up-regulated expressions of programmed cell death-ligand 1 (PD-L1) and indoleamine 2,3-dioxygenase 1 (IDO1) found in NMIBC tumour cells inspired researchers to combine more than one immune checkpoint inhibitor together (Witjes et al., 2019). An ongoing phase II clinical trial (began from August 2018) is evaluating the combination of Nivolumab (the PD-1 inhibitor) plus BMS-986205 (the IDO1 inhibitor) plus intravesical BCG among high-risk NMIBC patients who are BCG unresponsive (NCT03519256)(Bristol-Myers Squibb, 2022), the doses are flexible and would be altered under specific conditions.

3.1.3. Combinations of intravesical chemotherapies

Unlike immunotherapeutic agents, chemotherapeutic agents induce cytotoxicity to cancer cells directly and thus produce cell death (Yoon et al., 2020). Intravesical chemotherapies for bladder cancer have been intensively researched for at least 40 years, and the currently available drugs include valrubicin, gemcitabine, cisplatin, methotrexate, docetaxel, vinblastine, doxorubicin, and mitomycin C (Chehroudi and Black, 2020). Among all those agents, valrubicin is the only FDA-approved salvage treatment for NMIBC patients who are suffering from BCG refractory (Steinberg et al., 2000) But later research revealed that the complete response rate of valrubicin might decline to 4% at 2 years after treatment, which makes it rarely recommended (Dinney et al., 2013).

When it comes to combination therapies, putting multiple chemotherapeutic agents together can be dangerous as the enhanced tissue irritating activity can lead to severe cystitis (suggested by the earlier formulation of combining doxorubicin with mitomycin C) (Fukui et al., 1989). During the last two decades, gemcitabine, a deoxynucleotide analog that can incorporate with replicating DNA and therefore hinder further DNA synthesis, has attracted more attention because it is easier to be tolerated and more cost-effective (Messing et al., 2018). A series of related formulations has been attempted.

In 2006, gemcitabine was first reported to be combined with mitomycin C, which can also prevent DNA synthesis by cross-linking with DNA moieties (Maymi et al., 2006). Then, the following assessments of this regimen were carried out among multiple institutions. Between 2000 and 2010, a trial for high grade NMIBC patients with BCG failure received sequential combination intravesical therapies of gemcitabine and mitomycin C was conducted. Results demonstrated a complete response rate of more than two third of the patients and good 1 and 2-year recurrence-free survival (Lightfoot et al., 2014). Another more recent similar study (from 2005 to 2011) presented a disease-free rate of 37% at 22 months after treatment (Cockerill et al., 2016).

Nevertheless, the global shortage of mitomycin C hampered the foregoing therapy to be further developed (Velaer et al., 2016). Subsequently, a new sequential regimen of combining gemcitabine with docetaxel (an anti-mitotic chemotherapeutic agent which can stop cell division) has been formulated. The first trial was set between June 2009 and May 2014 for BCG failure patients (BCG refractory, relapsing, and intolerant were all covered). Intravesical gemcitabine and docetaxel were tested, and the reported results illustrated a treatment success (Steinberg et al., 2015) these results were confirmed by other researchers in 2017 with a 1-year recurrence-free survival rate of 49% and a 2-year recurrence-free survival rate of 34% among patients who were BCG unresponsive or BCG relapsing, with no serious adverse events reported (Milbar et al., 2017). The efficacy of gemcitabine plus docetaxel as maintenance therapy among BCG unresponsive patients has also been evaluated between 2013 and 2018, and the results showed that the disease-free survival rates were 81% and 32% at 12 months and 24 months, respectively (Daniels et al., 2020).

In December 2014, a phase I clinical trial started to investigate the use of intravesical cabazitaxel, gemcitabine, and cisplatin (CGC) for NMIBC patients with BCG refractory (NCT02202772) (James M. McKiernan, 2022), and the preliminary investigation suggested that the CGC triple agents' regimen can be well tolerated (DeCastro et al., 2017). The complete response rate was high with the equally encouraging recurrence-free survival rate (Decastro et al., 2020).

Recent studies have suggested a role of androgen receptors overexpression in bladder cancer and that antiandrogen can be combined with other chemotherapeutic agents. However, research is still in early stages and focuses on MIBC (Tyagi et al., 2019).

3.1.4. Intravesical immunotherapies combined with chemotherapies

As more therapeutic agents for treating NMIBC have come into practice, combining immunotherapeutic agents with chemotherapeutic agents becomes an appealing strategy. But it remains challenging as improper combinations might result in severe side effects. For instance, combining BCG with mitomycin C was supposed to reduce BCG relapsing, but turned out to be more toxic than BCG monotherapy (Solsona et al., 2015).

In recent years, more intravesical chemoimmunotherapies have been explored to deal with the situation of BCG failure. So far, a number of formulations have progressed into phase I or II clinical trials. One is a combination of intravesical gemcitabine and BCG (NCT04179162) (Memorial Sloan Kettering Cancer Center, 2021) which began in November 2019 with high grade NMIBC patients who are BCG relapsing. The other potential chemoimmunotherapy refers to combining intravesical gemcitabine with intravenous pembrolizumab (NCT04164082) (National Cancer Institute, 2022a). Started from January 2020 with BCG unresponsive NMIBC patients. The results of both trials are still pending and might be released around 2023. The most recent clinical trial (SunRISe-1) has studied the combination of cetrelimab with TAR-200, a gemcitabine-releasing intravesical system. The study started in

December 2020 in 200 participants with high-risk BCG-unresponsive NMIBC and primary study completion is expected in 2024 (NCT04640623) (Janseen Research and Development, 2022).

Studies have also found that knockdown of androgen receptors increases intracellular BCG quantity resulting in a higher cytotoxicity, which means that combining antiandrogenic drugs and BCG could be a possible treatment to enhance the efficacy of BCG (Fanghong et al., 2003; Ide and Miyamoto, 2021; Mizushima et al., 2020; Shang et al., 2015).

3.1.5. Intravesical treatments in combination with viral gene therapies or vaccines

Gene therapy has been attracting great interest, especially for treating cancer. It can act upon tumor cells directly or induce anti-tumor immune responses by delivering and integrating the transferred genetic material into the host genome (Narayan and Dinney, 2020). Intravesical gene therapies for NMIBC are still under development, and two potential representatives are rAd–IFN–α/Syn3 (also known as nadofaragene firadenovec or Instiladrin, a replication-deficient recombinant adenovirus encoding the IFN-αab complementary DNA (cDNA), along with the enhancer Syn3) and CG0070 (a replication-competent oncolytic adenovirus expressing GM-CSF), both have exhibited promising anti-tumor efficacy in clinical trials and are expected to be approved by the FDA soon (Bree et al., 2021; Khaled et al., 2020).

Similarly, intravesical gene therapeutic agents have got involved in combination therapies, as well. The combination of intravesical CG0070 and intravenous pembrolizumab is being investigated in a phase II clinical trial for its capability of managing BCG unresponsive NMIBC (NCT04387461) (CG Oncology, 2022).

The cancer vaccine is also a popular concept awaiting further development. PANVAC is a pox viral vector-based vaccine containing genes that have been demonstrated to be capable of inducing CD4 and CD8 antigen-specific immune response against two common cancer-associated antigens: carcinoembryonic antigen and mucin-1, and also three human T cell co-stimulatory molecules helping to augment immune response (Brancato et al., 2014). The phase II clinical trial for comparing the efficacy of the combination of PANVAC and BCG to BCG monotherapy was conducted from December 2013 to May 2019, 32 with high grade NMIBC patients but the final findings have not been released yet.

3.1.6. Intravesical treatments in combination with targeted therapies

Targeted cancer therapies are expected to cause less harm to normal cells by aiming at specific targets on cancer. A variety of targeted therapeutic agents have been explored as salvage treatments for NMIBC, those include vicinium, rapamycin, tamoxifen, metformin, pemagitinib, sunitinib, and lenalidomide (Packiam et al., 2019). Still, some combination therapies involving targeted therapies for handling BCG failure have emerged. Vicinium (oportuzumab Monatox, or VB4-845), the most intensively studied intravesical targeted therapeutic agent for BCG unresponsive NMIBC, is a recombinant fusion protein with a fragment of humanized anti-epithelial cell adhesion molecule (EpCAM) antibody fused with Pseudomonas exotoxin A (Biggers and Scheinfeld, 2008). By targeting the EpCAM surface marker overexpressed in urothelial carcinoma, vicinium can be selectively internalised by cancer cells and lead to cell death (Biggers and Scheinfeld, 2008). An ongoing phase I clinical trial began in June 2018 is assessing the combination of vicinium and durvalumab among high grade NMIBC patients who failed in the prior BCG therapies (NCT03258593). Durvalumab is given by intravenous injections while vicinuim is received intravesically and this trial might last until the coming of 2024.

There was another attempt of combining oral everolimus (a mammalian target of rapamycin (mTOR) inhibitor) with intravesical gemcitabine as an alternative therapy for BCG refractory NMIBC patients (Dalbagni et al., 2017). However, during the phase I/II clinical study which was set between December 2010 and June 2017 (NCT01259063) (Memorial Sloan Kettering Cancer, 2018), such combination failed to demonstrate an improved efficacy as most participants withdrew during the treating course because of the insufferable toxicity (Dalbagni et al., 2017), and no further study has been carried out.

3.2. Using novel drug delivery platforms for intravesical combination therapies

To overcome the shortcomings of intravesical therapies, new drug delivery systems have been explored. Nanoparticles with their surfaces modification and hydrogels have demonstrated to be capable of prolonging retention time and enhancing cell penetration (Yoon et al., 2020). However, limited reports on intravesical combination therapies delivered by novel platforms can be found when it comes to managing NMIBC with BCG failure, probably because the studies of most of such combinations are still in the preclinical stage.

Currently, there is one phase II clinical trial assessing the therapeutic effect of combining albumin-bound rapamycin nanoparticles (ABI-009) with gemcitabine among BCG refractory patients (NCT02009332) (Aadi, 2021) given intravesically. The nanoparticles are expected to deliver the drug directly into tumour cells via albumin receptors increasing drug uptake (Sparreboom et al., 2005). The trial started in April 2014, but results are still pending.

3.3. Device-assisted intravesical combination therapies

Device-assisted therapies intend to improve the efficacy of drugs with an external or internal devices. The probability of integrating device-assisted therapies with the existed therapeutic agents for NMIBC has been explored for several years, and currently utilized techniques include hyperthermia, photodynamic therapy, electromotive drug administration, and radiotherapy. However, studies investigating the efficacy of those therapies among patients undergoing BCG failure are not common.

Combining hyperthermia with intravesical chemotherapy (chemohyperthermia) has drawn the most attention and is probably the only devices-assisted intravesical combination therapy for managing BCG failure to date. By controlling the temperature of the solution within the bladder to be in the range of 40–44 °C, intravesical hyperthermia can boost the efficacy and uptake of drugs by raising blood perfusion and cause DNA damage and cell apoptosis by changing intracellular metabolism instead of inducing direct tumor tissue ablation (Liem et al., 2016). Various methods have been adopted for developing heating devices, which include microwave-induced heating (Synergo), conductive-based heating (Combat BRS/HIVEC, and Unithermia), and local/regional heating (BSD-2000, and AMC 70 MHz system) (Liem et al., 2016). Capacitive hyperthermia systems are also common heating devices but have not been used for treating NMIBC yet (Liem et al., 2016). Clinical trials comparing the efficacy of combining Synergo with mitomycin C or epirubicin to other monotherapies among patients with BCG failure started from the beginning of the 21st century, but the results kept varying between different trials. In recent years, more combinations such as putting Unithermia, Combat BRS, or BSD-2000 with mitomycin C together have also been attempted, suggesting new options for managing BCG failure. Nonetheless, it needs to be noticed that mitomycin C was demonstrated to have higher toxicity and thus lead to severer side effects when under increased temperature, so there are still various uncertainties with the future of chemohyperthermia (Kiss et al., 2015). A summary of the current clinical trials assessing chemohyperthermia as an alternative treatment for NMIBC patients with BCG failure is shown in Table 3.

4. Limitation of current approaches to intravesical combination therapies

In general, the process of developing intravesical combination

Table 3
A summary of the current clinical trials assessing chemohyperthermia as an alternative treatment for NMIBC patients with BCG failure.

Trial description	Treatments	Patient population	Results	Mean follow-up (months)	Reference
Multicentre, adjuvant	Synergo: 42 ± 2 °C Prophylactic scheme: 6 weekly instillations of 2 × 20 mg mitomycin C Maintenance: another 6 instillations of 2 × 20 mg mitomycin C every 4–6 weeks.	Recurrence after BCG treatments. (111 participants accepted therapies between 2001 and 2008)	1- year recurrence free survival rate: 85% 2- year recurrence free survival rate: 56% Progression rate: 3%	16	Nativ et al. (2009)
Single centre, prophylaxis, ablative	Synergo: 42 ± 2 °C Prophylaxis scheme: 6 weekly instillations of 2 × 20 mg mitomycin C Ablative scheme: 8 weekly instillations of 2 × 40 mg mitomycin C Maintenance: 6 monthly instillations of 2 × 40 mg mitomycin C	BCG refractory high-risk NMIBC. (30 participants accepted therapies between January 2006 and December 2009)	Recurrence free survival rates of prophylaxis scheme versus ablative scheme: 43.75% versus 42.85% Overall 12-month disease free survival rate: 77% Overall 24-month disease free survival rate: 55%	14	Volpe et al. (2012)
Single centre, prophylaxis, ablative	Synergo: 42 ± 2 °C Prophylaxis scheme: 6 to 8 weekly instillations 2 × 20 mg mitomycin C or 2 × 25 mg epirubicin Ablative scheme: 6 to 8 weekly instillations of 2 × 40 mg mitomycin C or 2 × 50 mg epirubicin Maintenance: 2 × 20 mg mitomycin C or 2 × 25 mg epirubicin, received every 6 weeks for 1 year	BCG refractory. (160 participants accepted therapies between 2002 and 2013)	1-year recurrence free survival rate: 60% 2-year recurrence free survival rate: 47% Progression rate: 4%	76	Arends et al. (2014)
Single centre, prophylaxis, ablative	Synergo: 42 ± 2 °C Prophylaxis scheme: 6 weekly instillations of 2 × 20 mg mitomycin C Curative scheme: 12 weekly instillations of 2 × 40 mg mitomycin C	Recurrence after BCG treatments. (21 participants accepted therapies between 2003 and 2009)	Disease free survival rate: 29%	50	Kiss et al. (2015)
Multicentre	Synergo: 40.5–44 °C Induction: 4 to 8 weekly instillations of 40 mg mitomycin C Maintenance: 1 instillation every 4–8 weeks	Different kinds of NMIBC patients were included. (150 participants accepted therapies between January 2000 and December 2016, 50 of them were BCG unresponsive)	6- month complete response rate of BCG unresponsive group: 46.0% 3- year recurrence rate of BCG unresponsive group: 17.4% cystectomy-free rate of BCG unresponsive group: 71.4% Overall survival rate of BCG unresponsive group: 76.0%	35.8	Van Valenberg et al. (2018)
Phase III, multicentre, comparing chemohypert-hermia to BCG monotherapy	Synergo: 42 ± 2 °C Induction: 6 weekly instillations if 2 × 20 mg mitomycin C Maintenance: 1 instillation every 6 weeks for the first year and 1 instillation every 8 weeks for the second year Control: 6 weekly 50 mg BCG instillations Maintenance: 3 consecutive weekly instillations at 3, 6, 12, 18, and 24 month	Recurrence after BCG treatments. (104 participants accepted therapies between May 2010 and July 2013)	24- month disease free survival rate of chemohymerthermia group versus control group: 35% versus 41%	36	Tan et al. (2019)
Pilot, adjuvant	BSD-2000: 42 ± 2 °C Induction: 6 weekly instillations of 40 mg mitomycin C Maintenance: 4 monthly instillations of 40 mg mitomycin C	BCG refractory. (15 participants accepted therapies between November 2008 and August 2010)	Recurrence rate: 67%	38	Inman et al. (2014)
Single centre, phase I/II,	Unithermia: 42.5 ± 1 °C		Disease free survival rate: 44.1% Recurrence rate: 35.3%	41	Soria et al. (2016)

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Table 3 (*continued*)

Trial description	Treatments	Patient population	Results	Mean follow-up (months)	Reference
adjuvant	Induction: 6 weekly instillations of 40 mg mitomycin C	Recurrence after BCG treatments. (34 participants accepted therapies between January 2009 and April 2011)	Progression rate: 23.5%		
Multicentre	Combat BRS: 42 ± 1 °C Induction: 4 to 6 weekly instillations of 80 mg mitomycin C Maintenance: 6 monthly instillations of 80 mg mitomycin C	BCG unresponsive and intermediate- or high-risk NMIBC. (55 participants accepted therapies between October 2014 and November 2017)	3-month complete response rate: 70% 1-year recurrence/progression rate: 53%	14	De Jong et al. (2018)

therapies for managing NMIBC patients with BCG failure is challenging. Several attempts have been abandoned because of failing to induce a satisfying therapeutic efficacy or insufferable adverse effects, but a variety of combinations with different working mechanisms have entered the stage of clinical practices. Hence, intravesical combination treatments has successes. However, there are still issues found in the many studies.

Regarding the patient populations of the clinical trials investigating intravesical combination treatments, it is noticed that sometimes at least one of the grading or risk stratification of NMIBC is absent, and the criteria of enrolling patients with BCG failure are varying. This can lead to the first limitation, which is the missing unified standard for registering and sorting of BCG failure patient enrollment.

From all the 17 effective intravesical combination therapies discussed above (except chemohyperthermia), six mentioned the grading of NMIBC and all of them investigated high grade NMIBC), while six mentioned about the risk stratification of NMIBC. As for the classification of BCG failure, three targeted BCG refractory, five targeted BCG unresponsive, one targeted BCG unresponsive and relapsing, one targeted BCG relapsing, one targeted multiple types of BCG failure, and six did not specifically classify BCG failure. Among all the nine thermochemotherapies discussed, two investigated high-risk NMIBC, two investigated intermediate- and high-risk NMIBC, four were intended to manage recurrence after BCG treatments, three targeted BCG refractory, one targeted BCG unresponsive, and one was evaluated in all kinds of NMIBC patients. Overall, the situation of trials neglecting or obscuring the grading or risk stratification of NMIBC exists, and the most concerned category of BCG failure is BCG unresponsive while the study field of BCG intolerance is usually unfulfilled.

Except for the trials carried out in the early years when the stratification and classification of NMIBC and BCG failure were not discussed, the confused sorting of patient population which still exists in the recent clinical trials might partly result from the inconsistent definition and classification of BCG failure among different associations. As interpreted before, the EAU accepted the classification system of BCG refractory, BCG relapsing, BCG unresponsive, and BCG intolerance from the IBCG, while the CUA substituted BCG resistance for BCG unresponsive, and the only FDA adopted category is BCG unresponsive. So, it becomes understandable to find that the terms like “resistance” or “recurrence” are being used. BCG unresponsive has produced the most research interest because it is the most widely accepted category around the world, and the absence of BCG intolerance might result from lacking certain patient population due to life-threatening adverse events induced by BCG are seldom reported, and sometimes BCG intolerant patients might be mixed with other BCG failure patients. Nonetheless, further research of developing treatment of BCG failure would be hindered and unbalanced and the comparison of one drug or combined formulation across trials carried out in different countries or regions would be difficult if the situation of lacking uniform standards for trial design and participant selection continues.

Unlike other combinations like simply putting multiple drugs together or utilizing device-assisted therapies, the number of clinical trials using intravesical drug delivery platforms to aid the treating of BCG failure is extremely limited. This probably results from several problems that have been impeding the study of similar drug delivery tools for a long time. Firstly, it has to be admitted that nanoparticles and hydrogels that have been proposed for helping the treatment of bladder cancer are still newly emerged techniques even though they have been researched as drug delivery tools dealing with different diseases for quite a few years. If compared to some therapeutic agents and device-assisted therapies which have been approved to the market for decades, the treating experiences and therapeutic outcomes of using nanoparticles or hydrogels are still not enough. Also, the current *in vitro* and *in vivo* models for mimicking bladder cancer need to be further improved, the cell-based models can barely reflect the clinical realities as the stratification of human bladder cancer cells is still under discussion, and until now the most commonly used animal models for bladder cancer are xenograft tumor models using rodent species (which are also the prime animals for intravesical models), these models can hardly provide enough details to support novel drug delivery systems in heading to the clinical trials. Another problematic condition is that there are no preclinical models which can simulate BCG failure due to the inexplicable mechanisms and heterogeneity of the causes of BCG failure, which further hinders the research of BCG failure managements.

5. Future directions in intravesical combination therapies

This covers approaches that are either in the preclinical stage or shown potential in other types of bladder cancer and could be promising for NMIBC with BCG failure.

5.1. Device assisted therapies

Combined device-assisted therapies other than thermochemotherapies have been explored to treat bladder cancer. Although some of them were not described above since they might only include a single drug, or target MIBC or not to be administrated intravesically as this review especially focuses on intravesical combination treatments handling NMIBC with BCG failure. Nonetheless, the path leading to the future can still be found within them.

Photodynamic treatment involves using light to activate the tumour cells which have already been targeted by photosensitisers administrated before, and therefore induce anti-cancer efficacy (Waidelich et al., 2001). Photosensitisers 5-aminolevulinic acid (5-ALA) and its derivative hexaminolevulinate (HAL) delivered by intravesical instillations have been investigated to manage BCG refractory (Bader et al., 2013; Waidelich et al., 2001) A newly explored intravesical photosensitising agent named TLD1433 for handling BCG refractory or BCG intolerance is still under development (Theralase, 2022). Combination with these photosensitisers is envisaged to be carried out in the future. Electromotive administration refers to guiding and accelerating the delivery of drugs by applying electrical current (Racioppi et al., 2018) At present, the

electromotive administrated intravesical mitomycin C has been assessed for its effect of treating BCG refractory, which is promising for combining formulations with similar modes (Racioppi et al., 2018). Radiotherapy is a common anti-tumour strategy that can take effect by inducing radiation with high energy to the targeted tumour sites. Radiation therapies have been performed for different cancers solely or in combination with other drugs. Recently, radio-chemotherapies have been explored for handling NMIBC with BCG failure. The combination of cisplatin, fluorouracil, and mitomycin C with concurrent radiation therapy following TURBT has proceeded into a phase II clinical trial among patients undergoing BCG failure (Theralase, 2022). Although the drugs are being administrated through the intravenous route, adapting the formulation into intravesical administration can still be practical.

5.2. Novel drug delivery platforms

The exploration of utilizing novel drug delivery platforms also keeps heading forward and preclinical experiments evaluating targeting drug carriers are still processing. They may not be focusing on BCG failure yet as mimicking BCG failure in the preclinical stage is not yet possible, but their existences are suggesting the following directions and their potentials are awaiting being proved in the future. These include the following systems.

5.2.1. Nanoparticles

Intravesical nanoparticles have attracted great attention for treating bladder cancer due to their nano-scale sizes which can help them to penetrate through the BPB and their capability of being tailored to gain multiple functions when necessary. In addition to the albumin-bound nanocarriers discussed earlier, several nanoparticles carrying combined formulations for treating bladder cancer are being developed. Inspired by the difficulty of controlling the optimal ratio of the components in a combination therapy, nanoparticles have been explored to become precise ratiometric co-loading and co-delivery vehicles (Miao et al., 2014). After being loaded with gemcitabine monophosphate and cisplatin, such a system showed significant anti-cancer efficacy in an *in vivo* bladder tumour model (Miao et al., 2014). Similarly, bifunctional pH-sensitive nanovectors delivering curcumin and small interfering RNA (siRNA) have demonstrated promises in treating bladder cancer during *in vitro* and *in vivo* trials (Xing et al., 2014). With the aid of the acid-labile Zn(II)–O bond conjugated to the carriers, such formulation can target drug release in the tumour intracellular acidic environment and thus protect siRNA from enzymatic degradation (Xing et al., 2014). What is more, nanocarriers encapsulating superparamagnetic iron oxide have been designed to prolong the retention time by its mucoadhesive property with the help of an external magnetic field (Huang et al., 2012). Superparamagnetic iron oxide can also help visualise tumour sites under magnetic resonance imaging (MRI), thus assist in diagnosis (Huang et al., 2012). Since most of these formulations were applied to animal models by intravenous injections, intravesical drug delivery can be their next to be applied to.

5.2.2. Hydrogels

Hydrogels have become prospective intravesical reservoirs for carrying drugs. Relying on the anatomical features of bladders, hydrogels with various mechanisms of increasing extending retention time have been designed, which include the mucoadhesive hydrogels (such as spreading-around systems, localised-adhering systems, and magnetic systems) and the floating hydrogels (using microbubble producers) (Qiu et al., 2020). In addition, the combinations of nanoparticles and hydrogels can be more effective and promising drug delivery systems.

5.2.3. Implantable devices

To further increase the retention time and reduce the frequency of instillations and thus improve patient compliance, intravesical implantable devices has been introduced. In recent years, implantable devices have been evaluated for treating interstitial cystitis and bladder pain. Consisting of flexible shape-memory wires or tubes, such equipment can release drugs with a sustained profile for days or even weeks inside the bladder (Lee and Choy, 2016). At the end of the treatments, these devices need to be removed via the catheter again, which can be risky, but this shortcoming has been partly solved with the application of biodegradable materials (Xu et al., 2021). Currently, 3-dimensional (3D) printing has also been used for producing similar equipment, which might help to simplify the manufacturing process and offer more possibility of individualised tailoring (Xu et al., 2021). Although implantable devices have not been utilized for treating bladder cancer, they can be easily adapted by changing the loaded drugs, including the combination therapies.

Concluded from the research progresses described above, the general orientation is heading toward the development of personalised medicine. It has been widely accepted that one formulation cannot satisfy the needs of all patients. As the realisation of personalised medicine would rely on the genomic profiles of individuals and diseases, further research focusing on the genetic characteristics of bladder cancer is needed. Nonetheless, different associations have not reached the final consensus on the molecular subtypes of bladder cancer (Kamat et al., 2016a). To date, the mostly accepted categorisation of bladder cancer divides it into the basal subtype and the luminal subtype depending on the gene expression patterns, the former is distinguished by its squamous and sarcomatoid histopathological features and often results in tumour metastasis, while the latter shows papillary features and FGFR3 mutations, which also correlates to NMIBC (Kamat et al., 2016a). To further clarify the molecular characterisations of bladder cancer as well as to look for the reasons behind BCG failure more studies are needed.

6. Conclusion

Developing novel treatments for NMIBC remains to be an active research area, and the existence of BCG failure among intermediate- or high-risk NMIBC patients is still awaiting solutions. For those who are reluctant or unsuitable to accept radical cystectomy, various bladder preserving strategies are under investigation, and among all these tactics, intravesical combination therapies seem to be holding considerable promises as they are expected to overcome the BPB and hinder the progress of drug resistance. Based on the foundation paved by combining immunotherapies and chemotherapies, the current landscape of handling BCG failure has partly changed to utilizing gene therapies and targeted therapies. Moreover, device-assisted treatments and novel drug delivery platforms have shown their potential, suggesting new directions waiting for more efforts in the future. There are also some limitations that need to be solved, such as lacking realistic *in vitro* and *in vivo* models for studying the safety and efficacy of the newly emerged formulations. Nonetheless, overall, the development of intravesical combination therapies for handling BCG failure should be heading towards a promising path since the understanding of bladder cancer and correlative studies keeps moving forward.

Funding support

S.H acknowledges the funding of PhD study from the Newton Mosharafa fund.

Declaration of competing interest

The authors have no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejphar.2022.175024.

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