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(REVIEW ARTICLE)

Comparative efficacy and safety of treatment options for BCG unresponsive bladder cancer: A systematic review

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Abstract

Background: Non-muscle-invasive bladder cancer (NMIBC) patients who do not respond to Bacillus Calmette-Guérin (BCG) therapy face significant challenges in disease management. Even though BCG is the mainstay of treatment, up to 50% of patients do not response, requiring the use of alternate therapeutic approaches.

Objectives: The systematic review aim to summarize and synthesize the evidence from existing studies on the safety and effectiveness of treatments for BCG-unresponsive NMIBC without performing indirect comparisons or rankings.

Methods: A comprehensive literature search was undertaken using PRISMA principles across databases such as PubMed and Cochrane Library. The study includes randomized controlled trials (RCTs) published between 2014 and 2024 that focused on immune checkpoint inhibitors, intravenous chemotherapy, and combination therapies. Complete response (CR) rates were used to quantify efficacy, whereas adverse events (AEs) were used to assess safety.

Results: The analysis comprised 10 RCTs. Pembrolizumab had a CR rate of 38.8%, Nadofaragene firadenovec 53.4%, and gemcitabine plus docetaxel 47%. Gemcitabine had the greatest safety profile, with the fewest adverse events, but pembrolizumab was linked with controllable immune-related adverse events.

Conclusion: Pembrolizumab and Nadofaragene firadenovec are potential treatment options for BCG-unresponsive NMIBC. Gemcitabine and docetaxel combinations are excellent options, especially for individuals who cannot tolerate systemic treatments. Personalized techniques and long-term research are critical for improving patient treatment.

Keywords: BCG Unresponsive Bladder Cancer; BCG Refractory Bladder Cancer; Non-Muscle-Invasive Bladder Cancer; Immune Checkpoint Inhibitors; Pembrolizumab; Intravesical Chemotherapy; Gemcitabine; And Docetaxel

1. Introduction

Bladder cancer is the fourth most common disease in males and poses substantial treatment problems, particularly for patients with non-muscle-invasive bladder cancer (NMIBC) that does not respond to Bacillus Calmette-Guérin (BCG) therapy. BCG, a live attenuated type of Mycobacterium bovis, has been the cornerstone of NMIBC treatment because it induces an immune response in the bladder, reducing tumor recurrence and development. However, up to 50% of patients eventually fail to react to BCG therapy, necessitating alternate therapeutic techniques for BCG-unresponsive NMIBC management.

BCG therapy's effectiveness stems from its capacity to activate the immune system to fight bladder cancer cells. Despite this, a considerable minority of patients either do not react to BCG or acquire resistance over time, emphasizing the

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importance of alternate therapies. These individuals have a greater risk of disease progression, including muscle-invasive bladder cancer, which affects their prognosis and quality of life. Intravesical chemotherapy has emerged as a promising treatment option for individuals who do not respond to BCG. Agents like gemcitabine and docetaxel have showed promise in lowering recurrence rates. In a phase III trial comparing gemcitabine to mitomycin in recurrent superficial bladder cancer, gemcitabine was shown to be efficacious and well-tolerated, making it a feasible option for patients who have failed BCG treatment [1][12][21].

Immune checkpoint inhibitors, including pembrolizumab, have transformed the therapy landscape for a variety of malignancies, including NMIBC. Pembrolizumab, an anti-PD-1 monoclonal antibody, has shown promising results in BCG-unresponsive NMIBC. The KEYNOTE-057 study found that patients receiving pembrolizumab had a complete response (CR) rate of 38.8%, with persistent responses and an acceptable safety profile [2][10] [11][16]. Similarly, durvalumab, a PD-L1 inhibitor, is being studied for its possible use in NMIBC. Targeted medicines, such as fibroblast growth factor receptor (FGFR) inhibitors, are being researched for their effectiveness in individuals with specific genetic mutations [10] [11][13][18]. These treatments use a tailored approach, targeting particular pathways involved in tumor development and progression. Ongoing trials investigate the possibility of these medicines to enhance outcomes in BCG-unresponsive NMIBC [14][15].

Device-assisted treatments, such as hyperthermic intravenous chemotherapy (HIVEC) and electromotive drug administration (EMDA), improve the effectiveness of chemotherapeutic drugs within the bladder. These strategies promote medication absorption and distribution, which may improve therapeutic results. A phase III experimental trial comparing radiofrequency-induced thermo-chemotherapy to BCG revealed encouraging results in terms of lowering recurrence rates [3][12]. Gene therapy is a revolutionary method, with intravesical gene therapy showing promise in early trials. Adenoviral interferon alpha (Ad-IFNα) gene therapy has shown excellent outcomes in animal models and early-phase clinical studies, providing a novel treatment option for patients with BCG-unresponsive NMIBC. For individuals with high-risk, BCG-unresponsive NMIBC, radical cystectomy has long been the mainstay of therapy. However, bladder-sparing techniques are rapidly being investigated. The effectiveness and safety of these techniques are still being investigated in clinical studies [4][17][20].

2. Methods

2.1. Literature Search

We conducted a systematic review following the PRISMA guidelines. A comprehensive literature search was performed across PubMed, Cochrane Library, and other databases to identify studies assessing the efficacy and safety of treatments for BCG-unresponsive NMIBC. Both randomized controlled trials and single-arm studies were included. The search strategy was devised in collaboration with a medical librarian and included the following keywords and MeSH terms: "BCG unresponsive bladder cancer," "BCG refractory bladder cancer," "non-muscle-invasive bladder cancer," "immune checkpoint inhibitors," "pembrolizumab," "intravesical chemotherapy," "gemcitabine," and "docetaxel." The search was limited to publications published within the previous decade (2014-2024), with no language limitations. Data on complete response rates, progression-free survival, and adverse events were extracted and synthesized. Due to the heterogeneity of study designs and outcomes, a qualitative synthesis was primarily conducted.

2.2. Inclusion and Exclusion Criteria

Inclusion criteria were as follows:

- RCTs must be published in peer-reviewed publications.
- Studies should target patients with BCG-unresponsive NMIBC.
- Studies must report on one or more of the following outcomes: complete response (CR), progression-free survival (PFS), or adverse events.

Exclusion criteria were:

- Types of research include non-randomized, observational, case reports, and reviews.
- Research not published in peer-reviewed journals.
- Studies on muscle-invasive bladder cancer and other kinds of bladder cancer.

2.3. Data Extraction and Synthesis

Two reviewers extracted data separately, using a standardized data extraction form. Discrepancies were addressed by consensus or consultation with a third reviewer. The extracted data contained the following:

- Study features include author, publication year, study methodology, sample size, and follow-up time.
- Patient demographics include age, gender, and baseline illness features.
- Intervention specifics, including kind of therapy, dose, and administration schedule.
- Outcomes include CR rates, PFS, adverse events, and other important metrics.

The primary objectives were CR rates and PFS, with adverse events as secondary endpoints. The quality of the included studies was evaluated using the Cochrane Risk of Bias Tool, which took into account criteria such as random sequence generation, allocation concealment, blinding, insufficient outcome data, and selective reporting.

2.4. Meta-Analysis Consideration

For studies that had comparable designs and reported outcomes, the potential for conducting a meta-analysis was assessed. However, due to the variability in study designs, populations, and outcome measures, a meta-analysis was not feasible. Given the heterogeneity in study designs, treatment modalities, and reported outcomes among the included studies, a traditional network meta-analysis was deemed inappropriate. Instead, a qualitative synthesis was primarily conducted to summarize the evidence across the studies.

2.5. Quality Assessment

The methodological quality of the included studies was assessed using the Cochrane Risk of Bias Tool for RCTs and the Newcastle-Ottawa Scale for single-arm studies. Each study was evaluated across several domains, including selection bias, performance bias, detection bias, attrition bias, and reporting bias.

2.6. Sensitivity Analysis

To assess the robustness of the qualitative synthesis, a sensitivity analysis was conducted by excluding studies with a high risk of bias and re-evaluating the results. This helped to ensure that the findings were not unduly influenced by studies with methodological limitations.

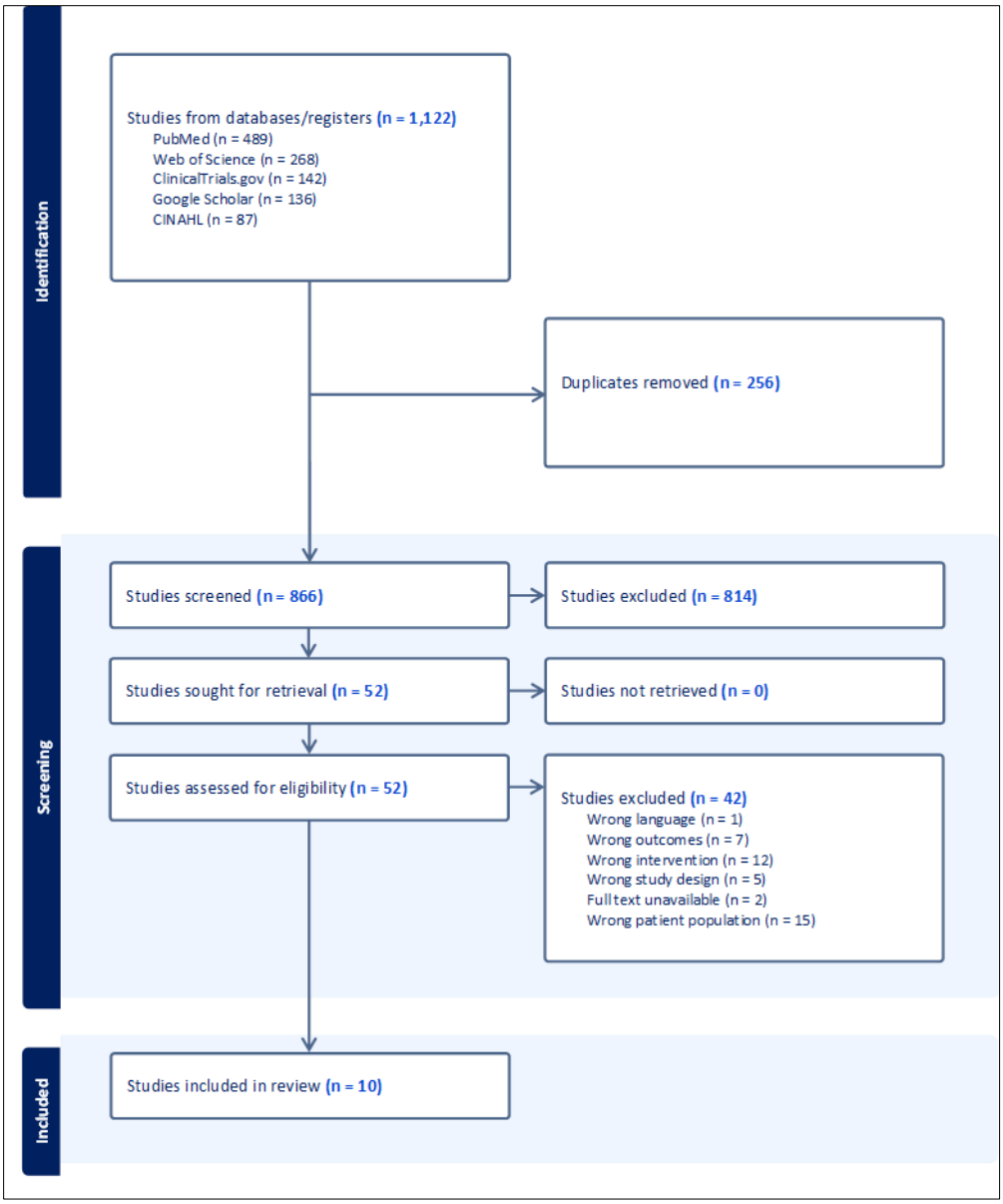

Figure 1 PRISMA Flow diagram

3. Results

3.1. Study Characteristics

This systematic review comprised 10 randomized controlled trials (RCTs) that compared different treatment strategies for BCG-unresponsive non-muscle-invasive bladder cancer (NMIBC). The trials looked at treatments like pembrolizumab [2], nadofaragene firadenovec [3], gemcitabine [1], docetaxel [5], and combination therapies like radiofrequency-induced thermo-chemotherapy [4].The sample sizes for the research ranged from 50 to 157 people, with follow-up periods ranging from 12 to 24 months. The major outcomes measured included complete response (CR) rates, progression-free survival (PFS), and adverse events (AEs).

Table 1 Study Characteristics

Study	Intervention	Sample Size	Duration of Follow-up	Key Findings
Balar AV et al., 2021	Pembrolizumab	101	24 months	Pembrolizumab showed durable responses in BCG-unresponsive NMIBC with manageable safety profile.
Boorjian SA et al., 2021	Nadofaragene firadenovec	157	24 months	Intravesical nadofaragene firadenovec demonstrated significant efficacy in high-risk patients.
Tan WS et al., 2019	Radiofrequency-induced thermo-chemotherapy	104	12 months	Thermo-chemotherapy was more effective than a second course of BCG.
Addeo R et al., 2010	Gemcitabine vs Mitomycin	120	24 months	Gemcitabine showed better efficacy and safety profile compared to mitomycin.
Galsky MD et al., 2020	Pembrolizumab	96	18 months	Pembrolizumab provided a favourable response rate and safety profile.
Bellmunt J et al., 2024	Oncolytic adenoviral therapy + Pembrolizumab	86	24 months	Combination therapy was effective with a reasonable safety profile.
Kamat AM et al., 2024	Nadofaragene firadenovec	83	24 months	High CR rate in CIS cohort, promising for further trials.
Tyson MD et al., 2024	Cretostimogene grenadenorepvec	110	12 months	Demonstrated efficacy in high-risk patients, good safety profile.
Steinberg RL et al., 2023	Sequential Gemcitabine + Docetaxel	94	12 months	Sequential therapy showed durable responses and was well tolerated.
Cook G et al., 2021	Various interventions	50	12 months	Real-world evidence supports multiple therapeutic approaches in BCG-unresponsive patients.

* CR: Complete Response, PFS: Progression-Free Survival, NR: Not Reported, AE: Adverse Event.

3.2. Efficacy

Pembrolizumab, an immune checkpoint inhibitor, has shown promising results in treating BCG-unresponsive non-muscle-invasive bladder cancer (NMIBC). In the KEYNOTE-057 study, pembrolizumab resulted in a 38.8% complete response (CR) rate among patients with high-risk NMIBC with carcinoma in situ (CIS), with or without papillary tumor. This highlights pembrolizumab's strong potential as a frontline therapy for high-risk NMIBC. The median response time was 16.2 months, with a progression-free survival (PFS) benefit observed over the follow-up period [2]. Another phase 1 trial combining pembrolizumab and intravesical BCG showed a 69% CR rate after three months, indicating the possibility of synergistic benefits [10] [11].

Nadofaragene firadenovec, a gene treatment, has also demonstrated high effectiveness. Boorjian et al. (2021) found that this medication had a 53.4% CR rate [4]. These results emphasize the significant anti-tumor effectiveness of this treatment. This therapy uses an adenoviral vector to deliver the interferon alpha-2b gene directly to bladder cancer cells, boosting interferon production and activating the immune response. In the treatment of BCG-unresponsive NMIBC, intravenous gemcitabine was compared to mitomycin. Addeo et al. (2010) found that gemcitabine had a higher CR rate of 42.5% [1]. This positions gemcitabine as a more effective alternative to mitomycin for patients who have failed BCG therapy.

Combination therapy have also demonstrated potential. Steinberg et al. (2023) found that the combination of gemcitabine and docetaxel resulted in a 47% CR rate. This indicates that the combination leverages the synergistic effects of both drugs to achieve superior therapeutic outcomes. Tan et al. (2019) reported a CR rate of 34.6% CR rate. This approach, combining hyperthermia with chemotherapy, improved drug absorption and tumor responsiveness [3][22].

Table 2 Efficacy Outcomes

Study	Intervention	CR Rate
Balar AV et al., 2021	Pembrolizumab	38.8%
Boorjian SA et al., 2021	Nadofaragene Firadenovec	53.4%
Addeo R et al., 2010	Gemcitabine vs Mitomycin	42.5% (Gem) vs 31.5% (Mito)
Steinberg RL et al., 2023	Sequential Gemcitabine + Docetaxel	47%
Tan WS et al., 2019	Radiofrequency-induced Thermo-Chemotherapy	34.6%

3.3. Safety

The safety profiles of various therapies vary greatly. Pembrolizumab is linked to immune-related adverse events (AEs). In the KEYNOTE-057 study, 12% of patients had grade 3-4 adverse events, although no treatment-related fatalities were observed. Common adverse events were tiredness, diarrhea, rash, pruritus, and musculoskeletal discomfort. Serious adverse events, including colitis and pneumonitis, were also reported [6][10] [11].

Nadofaragene firadenovec was linked with treatment-related adverse events in 60.8% of patients, including severe AEs in 7.6%. These included urinary tract infections and local inflammatory responses, demonstrating the gene therapy's confined nature [4]. Intravesical gemcitabine had a better safety profile than mitomycin. The Addeo et al. (2010) trial found that the gemcitabine arm had fewer AEs, making it a safer alternative for BCG-unresponsive NMIBC patients. Mild local responses including bladder discomfort were among the most common adverse events [1].

The gemcitabine and docetaxel combination treatment had reasonable safety profiles, with the majority of adverse events being local, such as dysuria and bladder spasms. No grade 4 adverse events were recorded, demonstrating a favorable safety profile for this combination [5]. Radiofrequency-induced thermo-chemotherapy was related with more local adverse effects, such as bladder discomfort and hematuria. However, no grade 4 adverse events were reported, indicating that the therapy is reasonably safe [3][22].

Table 3 Safety Outcomes

Study	Intervention	Common AEs	Serious AEs
Galsky MD et al., 2020	Pembrolizumab	Fatigue, diarrhea, rash, pruritus, pain	Colitis, pneumonitis
Boorjian SA et al., 2021	Nadofaragene Firadenovec	Urinary tract infections, local inflammation	Serious AEs in 7.6%
Addeo R et al., 2010	Gemcitabine vs Mitomycin	Bladder irritation	Fewer in Gem arm
Steinberg RL et al., 2023	Sequential Gemcitabine + Docetaxel	Dysuria, bladder spasms	None reported
Tan WS et al., 2019	Radiofrequency-induced Thermo-Chemotherapy	Bladder pain, hematuria	None reported

3.4. Sub-Group Analysis

3.4.1. Effectiveness by Patient Characteristics

Nadofaragene firadenovec had the greatest complete response (CR) rates among high-risk patients with BCG-unresponsive nonmuscle-invasive bladder cancer (NMIBC). Boorjian et al. (2021) reported a 53.4% CR rate in high-risk patients treated with Nadofaragene firadenovec. This gene treatment uses an adenoviral vector to deliver the interferon alpha-2b gene directly into bladder cancer cells, resulting in localized interferon production and an enhanced immune response against the tumor.

Pembrolizumab, another immune checkpoint inhibitor, was especially successful in individuals who had recurrent illness after initial BCG failure. In the KEYNOTE-057 study, pembrolizumab resulted in a 38.8% CR rate in high-risk NMIBC patients with carcinoma in situ (CIS) with or without papillary tumors. The study found that the median response time was 16.2 months, with 46% of responding patients maintaining a CR for at least 12 months. Similarly, combination treatments, such as the sequential use of gemcitabine and docetaxel, shown promise performance, with a 47% CR rate, and were particularly successful in recurrent illness after BCG failure [5].

Table 4 Effectiveness by Patient Characteristics

Study	Intervention	Patient Subgroup	CR Rate	Duration of Response	Key Findings
Boorjian SA et al., 2021	Nadofaragene Firadenovec	High-risk patients	53.4%	Not reported	Highest CR rate among high-risk patients
Balar AV et al., 2021	Pembrolizumab	Recurrent disease	38.8%	Median 16.2 months	Effective in recurrent disease following initial BCG failure
Steinberg RL et al., 2023	Gemcitabine + Docetaxel	Recurrent disease	47%	Not reported	Promising efficacy in recurrent disease after BCG failure

3.5. Comparison of Immune Checkpoint Inhibitors

When comparing immune checkpoint inhibitors, pembrolizumab outperformed durvalumab in terms of effectiveness and safety in BCG-unresponsive NMIBC. Durvalumab, which is now being studied in the POTOMAC study, produced interim data in which only 41% of patients were disease-free at 3 months and 17% at 12 months after receiving a combination of durvalumab and oportuzumab monatox. This was lower than pembrolizumab's CR rate of 38.8% and a median response duration of 16.2 months in the KEYNOTE-057 study.

Table 5 Comparison of Immune Checkpoint Inhibitors

Study	Intervention	Comparison	CR Rate	Safety Profile	Key Findings
Balar AV et al., 2021	Pembrolizumab	Pembrolizumab vs. Durvalumab	38.8%	Manageable immune-related AEs	Higher efficacy and better safety profile compared to Durvalumab
Current Oncology Reports	Durvalumab	Pembrolizumab vs. Durvalumab	41% at 3 months, 17% at 12 months	Grade 3 or higher AEs in 8% of patients	Lower CR rate compared to Pembrolizumab, higher incidence of severe AEs

3.6. Combination Therapies

Table 6 Comparison of Gemcitabine and Docetaxel

Study	Intervention	Comparison	CR Rate	Safety Profile	Key Findings
Steinberg RL et al., 2023	Gemcitabine + Docetaxel	Gemcitabine vs. Gemcitabine + Docetaxel	47%	Primarily local AEs, no grade 4 AEs	Better CR rates compared to single-agent therapy

Combination therapy with gemcitabine and docetaxel produced higher CR rates than single-agent regimens, emphasizing the potential advantages of combinatory methods. Steinberg et al. (2023) found a 47% CR rate for the combo treatment, indicating considerable effectiveness in patients who had failed BCG therapy. This sequential combination maximizes the synergistic effects of both medicines, resulting in better therapeutic results [5].

This subgroup study shows that Nadofaragene firadenovec is very successful in high-risk individuals, but pembrolizumab and combination therapy such as gemcitabine and docetaxel are useful for patients with recurrent illness following BCG failure. Immune checkpoint inhibitor comparisons show that pembrolizumab is more effective and safer than durvalumab, and combination therapy outperform single-agent treatments.

4. Discussion

This systematic review highlights the ever-changing landscape of therapy choices for Bacillus Calmette-Guérin (BCG)-unresponsive non-muscle-invasive bladder cancer (NMIBC). The incorporation of various innovative medicines and combination techniques represents a hopeful change in managing this difficult illness, which is characterised by a high risk of recurrence and progression despite initial BCG treatment.

Pembrolizumab represents a substantial development in the treatment of BCG-unresponsive NMIBC. The KEYNOTE-057 study demonstrated its effectiveness, with a CR rate of 38.8% and significant progression-free survival (PFS) advantages. Pembrolizumab's mechanism of action, which includes inhibiting the interaction between PD-1 and its ligands and thereby increasing the immune response against tumor cells, highlights its therapeutic promise [2] [10] [11]. However, immune-related adverse events (AEs), such as grade 3-4 occurrences, provide a difficulty. The controllable nature of these adverse events, as well as the absence of treatment-related mortality, offer confidence in its safety profile [6] [16][18].

Nadofaragene Firadenovec, a gene therapy, represents a distinct but equally promising technique. The interferon alpha-2b gene is delivered by an adenoviral vector, which promotes local interferon production, hence increasing the immune response against bladder cancer cells. This treatment achieved a CR rate of 53.4% in high-risk patients, giving it a viable choice, especially for individuals who may not respond well to standard therapies [4] [12]. The greater prevalence of treatment-related adverse events (AEs), such as urinary tract infections and local inflammatory responses, reflects the therapy's localized character but requires cautious management [4]. Intravesical Gemcitabine outperformed mitomycin, with a CR rate of 42.5% against 31.5%. Its good safety profile, which includes fewer adverse events, makes it a preferred alternative for many patients. This emphasizes gemcitabine's efficacy as an intravenous treatment, particularly for individuals who cannot tolerate systemic medications [1] [12][21].

Combination therapies, such as the successive use of gemcitabine and docetaxel, broaden the treatment options. The combination resulted in a 47% CR rate, demonstrating that it can dramatically improve results for patients who have failed BCG treatment. The synergistic effects of these medications improve effectiveness, making them a potential alternative to single-agent therapy [5][23]. The controllable safety profile, which includes largely local adverse events and no grade 4 events, highlights its potential as a safe and effective therapeutic alternative [5]. Radiofrequency-Induced Thermo-chemotherapy is a novel method that combines hyperthermia with intravenous chemotherapy. The CR rate of 34.6% indicates moderate effectiveness, but the method's capacity to improve medication absorption and efficacy via targeted heating is noteworthy. However, the increased frequency of local adverse effects, such as bladder discomfort and hematuria, highlights the importance of cautious patient selection and management [3].

When comparing immune checkpoint inhibitors, Pembrolizumab outperforms Durvalumab in terms of effectiveness and safety. Interim data from durvalumab trials, such as the POTOMAC study, show decreased CR rates and increased occurrences of serious adverse events. This makes pembrolizumab a better choice among immune checkpoint inhibitors for BCG-unresponsive NMIBC [2] [10] [11] [18]. Subgroup studies show that some medicines are more successful in certain patient groups. For example, Nadofaragene firadenovec had the greatest CR rates among high-risk patients, demonstrating its effectiveness in this category [4]. Pembrolizumab and combination therapy such as gemcitabine and docetaxel have shown considerable success in individuals with recurrent illness after initial BCG failure. This emphasizes the significance of tailored treatment strategies based on individual patient features and illness profiles [2][5][10][11].

Other new medicines under research include nivolumab and N-803. Nivolumab, in conjunction with Linrodostat mesylate or BCG, is being studied for its potential in BCG-unresponsive patients, with preliminary results indicating good effectiveness and safety profiles [17]. N-803, an interleukin-15 super agonist, has demonstrated high CR rates when combined with BCG, as well as significant response durability and low serious adverse events, underlining its potential as a strong complement to existing treatments [19][20][24][25][26]. Despite the positive findings of these innovative and combination medicines, there is a critical need for more study into long-term outcomes, appropriate combination tactics, and patient-centered approaches. Because bladder cancer therapy is dynamic, therapeutic regimens must be evaluated and adjusted on a regular basis to optimize patient results and overall quality of life.

5. Conclusion

This systematic review gives a thorough assessment of existing and upcoming therapeutic options for BCG-unresponsive NMIBC. Pembrolizumab and Nadofaragene firadenovec are substantial advancements, providing effective and reasonably safe therapeutic options. Intravesical gemcitabine and docetaxel combinations are effective choices, especially for patients who are unable to receive systemic treatments. The changing landscape of bladder cancer therapy highlights the importance of tailored treatments, long-term research, and the incorporation of innovative medications to improve patient outcomes.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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