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REVIEW

Experimental and New Approaches for Bladder Preservation in Intermediate and High-Risk Non-Muscle-Invasive Bladder Cancer (NMIBC)

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Abstract: About 75% of bladder cancers are detected as non-muscle invasive. High-risk patients have high progression risk. Although the standard is transurethral resection of bladder tumor plus full dose intravesical BCG for one to 3 years, due to the high risk of progression, radical cystectomy may be considered in specific cases. Although radical cystectomy is still the best approach for high-grade NMIBC from an oncological perspective, its high morbidity and impact on quality of life motivate studies of new strategies that may reduce the need for cystectomy. We carried out a mini-review whose objectives were: 1 - to identify bladder-sparing alternatives that are being studied as possible treatment for patients with intermediate and high-risk NMIBC; 2 - understand the evidence that exists regarding success rate, follow-up, and side effects of different strategies. Several studies have sought alternatives for bladder preservation, including immunotherapy, intravesical chemotherapy, chemo-hyperthermia, antibody-drug conjugates, viral genetic therapy, and others with promising results. The selection of an optimal therapy for high-risk NMIBC that can reduce the need for cystectomy, with low toxicity and high efficacy, is of paramount importance and remains an issue, however, several known medications are being tested as bladder-preserving alternatives in this scenario and have shown promise in studies.

Keywords: high-grade, non-muscle-invasive bladder cancer, unfavorable, bladder preservation

Introduction

Bladder cancer (BC) is the tenth most reported cancer worldwide when both sexes are considered, and the standardized death rate (per 100,000 person-years) is 3.3 for men versus 0.86 for women.[1]

Approximately 75% of bladder cancers are detected as non-muscle invasive (NMIBCs).[2] The European Urological Association (EAU) guidelines classify NMIBCs as low, intermediate, high, and very high risk based on the World Health Organization (WHO) 2004/2016 or WHO 1973 classification systems (Table 1). Patients diagnosed with high-risk NMIBC recurred in 2.6% to 5.7% in one year and 10% to 19% in ten years, while very high-risk patients experienced recurrence in 12% to 32% and 39% to 79% in one and ten years, respectively.[3]

Standard treatment varies by risk. Low-risk NMIBCs are treated with transurethral resection of bladder tumor (TURBT) alone, while intermediate- and high-risk NMIBCs should be treated with TURBT plus full-dose intravesical BCG for 1 to 3 years. Due to the high risk of progression, immediate radical cystectomy (RC) should be discussed with patients, mainly in the very high-risk group. Early RC is strongly recommended in patients with tumors that are not BCG-responsive and should be considered in recurrent high-grade tumors.[4]

Although RC is the best approach from an oncological point of view, its high morbidity and impact on quality of life motivate studies of new strategies that may reduce the need for cystectomy.

The only conservative alternative treatment approved by the Food and Drug Administration (FDA) for BCG-unresponsive disease is pembrolizumab, but toxicity and durability of response are concerns. Other conservative treatments are being studied and may be a future alternative to bladder preservation.

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Table 1 EAU Risk Classification According to WHO 2004/2016/WHO 1973 Grading Classification Systems

Low Risk	- Primary single TaT1 LG/G1 tumor <3 cm in diameter without CIS in a patient ≤70 years - Primary Ta LG/G1 tumor without CIS with at most one of the additional clinical risk factors*
Intermediate Risk	- Patients without CIS who are not included in either the low, high, or very high-risk groups
High Risk	- All T1 HG/G3 without CIS, except those included in the very high-risk group - All CIS patients, except those included in the very high-risk group - Stage, grade with additional clinical risk factors*: Ta LG/G2 or T1G1, no CIS with all 3 risk factors* Ta HG/G3 or T1LG, no CIS with at least 2 risk factors* T1G2 no CIS with at least 1 risk factor*
Very High Risk	- Stage grade with additional clinical risk factors*: T1 HG/G3 and CIS with all 3 risk factors* T1G2 and CIS with at least 2 risk factors* T1 HG/G3 and CID with at least 1 risk factor* T1 HG/G3 no CIS with all 3 risk factors*

Notes: *Risk factors: age > 70; multiple papillary tumors; tumor diameter > 3 cm.
Abbreviations: LG, Low grade; HG, High grade; G1, grade 1; G2, grade 2; G3, grade 3; CIS, carcinoma in situ.

New Strategies to Reduce the Need for Cystectomy

Immunotherapy

Recent studies found that intradermal BCG priming, prior to intravesical instillations, can be a promising alternative, as it has demonstrated the ability to expedite the migration of T lymphocytes into the bladder, thereby enhancing the local immune response.[5] Table 2 summarizes the main studies.

Another immunotherapy that also has its role proven are PD-1/PD-L1 inhibitors, which are already included in the guidelines for metastatic and locally advanced bladder cancer. Recent studies have shown the role of this immune checkpoint blockade (ICB) also in NMIBC, showing it to be an important therapeutic target in BCG-unresponsive NMIBC.

One notable breakthrough has been the approval of Pembrolizumab by the FDA for treating BCG-unresponsive Carcinoma In Situ (CIS), based on the KEYNOTE-057 study. This study evaluated the efficacy of the PD-1 inhibitor Pembrolizumab in high-risk, BCG-unresponsive NMIBC and yielded impressive results, with a complete response in 40% of patients within three months, and 42% achieving complete response. Serious treatment-related adverse events occurred in eight (8%) patients.[8] Another study evaluated the combination of BCG and intravesical pembrolizumab, the 1-year recurrence-free rates was 22% and 5 of 9 patients had progressed to muscle invasive bladder cancer (MIBC), one death occurred from myasthenia gravis that was deemed potentially related to treatment.[6]

The SWOG S1605 study examined the use of Atezolizumab in patients with CIS unresponsive to BCG, with promising results with 37.6% of complete response at 6 months. Despite the promising results of ICB, its systemic administration presents significant adverse effects, the most frequent AEs were fatigue (49.3%) and 12.3% patients presented grade 3–5 adverse effects including one treatment-related death.[9] Intravesical administration of Durvalumab was also studied in patients with pT1 or higher (BCG-naïve) bladder cancer with modest reported activity.[7]

CD40 is another immune checkpoint under investigation expressed by several cell types in the myeloid cell lineage, such as dendritic cells, macrophages, monocytes, and B cells, that can be targeted for agonistic antibody treatment in bladder cancer.[11] CD40 ligand stimulation produces a robust antitumor response, including activation of dendritic cells to engulf, process, and present tumor antigen to T cells and can initiate programmed cell death.[12] However, systemic CD40 therapy was associated with immune-related adverse events such as cytokine release syndrome, thrombocytopenia, and liver toxicity.[10]

Intravesical Chemotherapy

Chemotherapy is another modality that has already proven its role in metastatic and muscle invasive bladder cancer and intravesical administration has been studied for NMIBC (summarized in Table 3). Several studies have been carried out

Table 2 Immunotherapy Studies

Author, Year	Patients Number	Study Design	Treatment	Regimen	Effects of Treatment	Main Findings
Khyati Meghani et al, 2022[6]	09	Phase I	Pembrolizumab	Pembrolizumab intravesical (1–5 mg/kg for 2 hours) beginning 2 weeks prior to BCG induction until recurrence.	Works by inhibiting lymphocytes PD-1 receptors, blocking the ligands that would deactivate it and prevent an immune response. This allows the immune system to target and destroy cancer cells, but also blocks a key mechanism preventing the immune system from attacking the body itself	- The maximum tolerated dose was not reached; however, one dose-limiting toxicity was reported (grade 2 diarrhea) in the only patient who reached 52-weeks without recurrence - One death occurred from myasthenia gravis that was deemed potentially related to treatment - The 6-month and 1-year recurrence-free rates were 67% (95% CI: 42–100%) and 22% (95% CI: 6.5–75%) respectively
Andrew Moe et al, 2022[7]	09	Phase Ib	Durvalumab	Intravesical injection of durvalumab will be performed a minimum of 2 weeks prior to cystectomy, utilising a 3+3 dose escalation design (25mg, 75mg, 150mg).	Works to promote the antitumour responses mediated by immune cells. By blocking the action of PD-L1, durvalumab exerts its anticancer effects by increasing T-cell activation, enhancing detection and ablation of tumor cells	- Durvalumab was safe at all 3 dose levels without any drug-related adverse events (25/75/150mg) - All patients underwent planned cystectomy - Visible tumour was present in only 4 patients limiting interpretation of RCI. RCI varied significantly between cell types (p=0.008) - RCI numerically increased by dose but did not reach statistical significance (p=0.076) - A numeric increase in monocytes was seen at 150mg dose
Arjun V Balar et al, 2021[8]	101	Phase II	Pembrolizumab	Pembrolizumab 200 mg intravenously every 3 weeks for up to 24 months	Works by inhibiting lymphocytes PD-1 receptors, blocking the ligands that would deactivate it and prevent an immune response. This allows the immune system to target and destroy cancer cells, but also blocks a key mechanism preventing the immune system from attacking the body itself	- Pembrolizumab monotherapy was tolerable and showed promising antitumor activity in patients - Grade 3 or 4 treatment-related adverse events occurred in 13 (13%) patients - Serious treatment-related adverse events occurred in eight (8%) patients. There were no deaths that were considered treatment related

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Table 2 (Continued).

Author, Year	Patients Number	Study Design	Treatment	Regimen	Effects of Treatment	Main Findings
Peter C. Black et al, 2020[9]	73	Phase II	Atezolizumab	Atezolizumab (1200 mg IV) every 3 weeks for one year.	Binds PD-L1, preventing its interaction with PD-1 and B7-1. Preventing the interaction of PD-L1 and PD-1 removes inhibition of immune responses such as the anti-tumor immune response but not antibody dependent cellular cytotoxicity	- A complete response was observed in 30 (41.1%; 95% CI 29.7%, 53.2%) patients at 3 months and 19 (26.0%; 95% CI 16.5%, 37.6%) at 6 months - The most frequent adverse effects were fatigue 36 (49.3%), pruritus 8 (11.0%), hypothyroidism 8 (11.0%), and nausea 8 (11.0%). CDC 3–5 adverse effects occurred in 9 (12.3%) patients and there was one treatment-related death (myasthenia gravis with respiratory failure and sepsis)
Robert H Vonderheide et al, 2007[10]	29 (advanced solid tumors)	Phase I	CD40 agonist mAb CP-870,893	Dose-escalation (0.01 to 0.3 mg/kg) intravenously	The mechanism of tumor regression may involve an indirect effect of immune activation, a direct cytotoxic against CD40+ tumor cells, or both	- Maximum-tolerated dose was estimated as 0.2 mg/kg - Dose-limiting toxicity was observed in two of seven patients at the 0.3 mg/kg dose level (venous thromboembolism and grade 3 headache) - The most common adverse event was cytokine release syndrome (grade 1 to 2) which included chills, rigors, and fever - The mAb was well tolerated and biologically active, and was associated with antitumor activity - Transient laboratory abnormalities affecting lymphocytes, monocytes, platelets, D-dimer, and liver function tests were observed 24 to 48 hours after infusion

Abbreviations: CI, confidence interval; RCI, reliable confidence interval.

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Table 3 Intravesical Chemotherapy Studies

Author, Year	Patients Number	Study Design	Treatment	Regimen	Effects of Treatment	Main Findings
Phani T. Chevuru et al, 2022[28]	97	Retrospective	Gemcitabine and Docetaxel	6 weekly with monthly maintenance for 2 years.	Gemcitabine acts as a deoxycytidine nucleoside analog, thereby inhibiting deoxyribonucleic acid (DNA) synthesis, resulting in cell apoptosis. Docetaxel is an anti-mitotic chemotherapeutic agent which inhibits tubulin disassembly, thereby stopping cell division	- 75% 5-year bladder preservation rate and a 91% 5-year CSS rate - 20 patients underwent cystectomy, 15 patients experienced disease progression - Five-year PFS, CFS, CSS, and OS were 82%, 75%, 91%, and 64%, respectively, 74% Complete response at 3-month surveillance, 25 months of median duration of response - Considering just high-grade tumors: at 1, 2, and 5 years, RFS was 60%, 50%, and 30%, respectively - RFS was similar among BCG-unresponsive patients and the overall cohort
Ryan L Steinberg et al, 2020[29]	276	Retrospective	Gemcitabine and Docetaxel	Intravesical gemcitabine and docetaxel	Gemcitabine is a non-vesicant chemotherapeutic agent that acts as a deoxycytidine nucleoside analog, thereby inhibiting deoxyribonucleic acid (DNA) synthesis, resulting in cell apoptosis Docetaxel is an anti-mitotic chemotherapeutic agent which inhibits tubulin disassembly, thereby stopping cell division	- 9 patients were unable to tolerate a full induction course - One- and 2-year recurrence-free survival rates were 60% and 46%, and high-grade RFS rates were 65% and 52%, respectively - 10 patients (3.6%) had disease progression on transurethral resection - 43 patients (15.6%) went on to cystectomy (median 11.3 months from induction), of whom 11 (4.0%) had progression to muscle invasion
Guarionex J. DeCastro et al, 2020[30]	18	Phase I	Cabazitaxel, Gemcitabine and Cisplatin	6 weekly	Cabazitaxel is a semisynthetic microtubule inhibitor that induces cell death by microtubule stabilization Gemcitabine acts as a deoxycytidine nucleoside analog, thereby inhibiting deoxyribonucleic acid (DNA) synthesis, resulting in cell apoptosis Cisplatin promotes the crosslink with the purine bases on the DNA; interfering with DNA repair mechanisms, causing DNA damage, and subsequently inducing apoptosis	- Initial partial and complete response rates were 94% and 89%, respectively - At 1-year RFS was 0.83 (range 0.57 to 0.94) and at 2 years estimated RFS was 0.64 (0.32 to 0.84)

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Table 3 (Continued).

Author, Year	Patients Number	Study Design	Treatment	Regimen	Effects of Treatment	Main Findings
Rodolfo Hurle et al, 2020[34]	36	Phase II	Gemcitabine	6 weekly and once a month for 12 months	Gemcitabine acts as a deoxycytidine nucleoside analog, thereby inhibiting deoxyribonucleic acid (DNA) synthesis, resulting in cell apoptosis	- The DFS was 68.75% at the end of the induction phase and 44.44% and 31.66% at 12 and 24 months, respectively. - The PFS was 43.75%. The OS and CSS were 77.9% (95% CI 58.78%–88.92%) and 80.68% (95% CI 61.49%–90.96%), respectively - The most common mild and moderate adverse events reported were urinary symptoms and fatigue (CDC 1 and 2)
Nayan Kumar Mohanty et al, 2018[23]	35	Prospective	Intravesical Gemcitabine	6 weekly	Gemcitabine acts as a deoxycytidine nucleoside analog, thereby inhibiting deoxyribonucleic acid (DNA) synthesis, resulting in cell apoptosis	- 21 patients (60%) showed no recurrences - 11 patients (31.4%) had superficial recurrences - 3 patients (8.75%) progressed to muscle invasive
Guido Dalbagni et al, 2017[31]	56	Phase I/II	Everolimus and Gemcitabine	One dose of everolimus and gemcitabine / Continuous everolimus daily with gemcitabine followed by everolimus maintenance	Everolimus is a rapamycin analog (rapalog), suppress hypoxia induced and increases in hypoxia inducible factor-1α (HIF-1α), and inhibit the response of vascular endothelial cells to stimulation by vascular endothelial growth factor (VEGF)Gemcitabine acts as a deoxycytidine nucleoside analog, thereby inhibiting deoxyribonucleic acid (DNA) synthesis, resulting in cell apoptosis	- 16% were disease free at 1 yr (95% - CI: 3%–40%). The probability of RFS was 20% (95% - CI 5%–42%) at 12 months - 4 patients withdrew consent prior to treatment initiation, 10 patients out of 19 had grade 3 or greater toxicity events, 7 withdrew consent or were taken off study (21 patients) - Continuous oral everolimus plus intravesical gemcitabine was not well tolerated in this patient population
Niv Milbar et al, 2017[35]	33	Retrospective	Gemcitabine and Docetaxel	6 weekly	Gemcitabine acts as a deoxycytidine nucleoside analog, thereby inhibiting deoxyribonucleic acid (DNA) synthesis, resulting in cell apoptosis. Docetaxel is an anti-mitotic chemotherapeutic agent which inhibits tubulin disassembly, thereby stopping cell division	- DFS was 6.5 months, 42% 1-year, and 24% 2-year DFS - Regarding high grade: RFS was 17.1 months with 56% 1-year and 42% 2-year - 5 low grade and 16 high-grade recurrences, with 5 progressions and 8 cystectomies among these

Dennis J. Robins et al, 2017[36]	28	Phase II	Intravesical Nanoparticle Albumin bound Paclitaxel	6 weekly	Paclitaxel is an antimicrotubule agent, replication becomes inhibited and may also distort mitotic spindles causing the chromosomes to break	- 10 patients (36%) achieved complete response. - 6 patients remain cancer free, with a recurrence-free survival rate of 18% - Five-year overall and CSS rates were 56% and 91%, respectively - Radical cystectomy occurred in 11 patients (39%), of - Whom 2 out of 11 (18%) had pT2 or greater disease
Patrick A Cockerill et al, 2016[32]	27	Retrospective	Gemcitabine / Mitomycin C	Weekly for 6–8 weeks	Gemcitabine acts as a deoxycytidine nucleoside analog, thereby inhibiting deoxyribonucleic acid (DNA) synthesis, resulting in cell apoptosisMitomycin C inhibits DNA synthesis and cross-links DNA	- Disease-free survival of all patients was 15.2 (1.7–39.3) months - 63% developed recurrent bladder cancer, a median of 15.2 months after therapy - 1 patient progressed to muscle-invasive disease 5 months after treatment - 1 patient developed metastatic disease 22 months after treatment - 3 patients went on to cystectomy - 10 patients (37%) had no evidence of disease at last follow-up (22.1 months)
Andrew J Lightfoot et al, 2014[33]	47	Retrospective	Intravesical Gemcitabine and Mitomycin C (MMC)	6 weekly	Gemcitabine acts as a deoxycytidine nucleoside analog, thereby inhibiting deoxyribonucleic acid (DNA) synthesis, resulting in cell apoptosis Mitomycin C inhibits DNA synthesis and cross-links DNA	- Complete response, 1-year, and 2-year recurrence-free survival rates for all patients were 68%, 48%, and 38%, respectively - Median recurrence-free survival for all patients was 9 months (range 1–80) - 14 patients (30%) remained free of recurrence with a median time to follow-up of 26 months (range 6–80 months) - 10 patients required cystectomy
Eila C Skinner et al, 2013[13]	47	Phase II	Gemcitabine	6 weekly for 12 months	Gemcitabine acts as a deoxycytidine nucleoside analog, thereby inhibiting deoxyribonucleic acid (DNA) synthesis, resulting in cell apoptosis Mitomycin C inhibits DNA synthesis and cross-links DNA	- At the initial 3-month evaluation 47% of patients were free of disease - At 1-year disease had not recurred in 28% of the 47 patients, all except 2 from the high-risk group - At 2 years disease had not recurred in 21%

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Table 3 (Continued).

Author, Year	Patients Number	Study Design	Treatment	Regimen	Effects of Treatment	Main Findings
Itay A Sternberg et al, 2013[14]	69	Retrospective	Intravesical Gemcitabine	2 courses twice weekly for 3 weeks	Gemcitabine acts as a deoxycytidine nucleoside analog, thereby inhibiting deoxyribonucleic acid (DNA) synthesis, resulting in cell apoptosis	- 27 patients experienced a complete response. PFS, CSS and OSI did not differ significantly between patients with and without a complete response - Cystectomy was subsequently performed in 20 patients - PFS and CSSI were similar in patients with refractory disease and those with other types of BCG failure
LaMont J. Barlow et al, 2013[37]	54	Retrospective	Intravesical Docetaxel	6 weekly	Docetaxel is an anti-mitotic chemotherapeutic agent which inhibits tubulin disassembly, thereby stopping cell division	- 32 patients (59%) had a complete initial response after induction therapy, including 18 who received additional monthly maintenance treatments. - Median time to recurrence in initial responders treated with vs without docetaxel maintenance was 39.3 vs 19.0 months - One- and 3-year RFS rates for the entire cohort were 40% and 25%, respectively - 17 patients (24%) underwent radical cystectomy at a median of 24 months of follow-up - Five-year DFS and OS rates were 85% and 71%, respectively
Gary D Steinberg et al, 2011[15]	82	Phase III	Valrubicin	6 weekly	Valrubicin mediates formation of DNA cleavable complexes and inhibit topoisomerase II activity leading to defects in DNA replication and transcription	- 18 patients demonstrated a complete response - 64 patients demonstrated partial or no response
James M McKiernan et al, 2011[16]	18	Phase I	Intravesical nanoparticle albumin-bound paclitaxel	6 weekly	Paclitaxel is an antimicrotubule agent, replication becomes inhibited and may also distort mitotic spindles causing the chromosomes to break	- 5 patients (28%) had no evidence of disease at posttreatment evaluation - 10 patients (56%) had CDC I local toxicities and no grades 2, 3 or 4 drug related local toxicities were encountered

Pierfrancesco Francesco Bassi et al, 2011[17]	16	Phase I	Paclitaxel - Hyaluronic Acid for Intravesical	6 weekly	Paclitaxel is an antimicrotubule agent, replication becomes inhibited and may also distort mitotic spindles causing the chromosomes to break	- 9 patients (60%) showed complete treatment response - No dose limiting toxicity occurred at any drug level evaluated
Giuseppe Di Lorenzo et al, 2010[18]	80	Phase II	Intravesical Gemcitabine	Twice weekly for 6 weeks (A) or weekly for 3 consecutive weeks at 3, 6, and 12 months (B)	Gemcitabine acts as a deoxycytidine nucleoside analog, thereby inhibiting deoxyribonucleic acid (DNA) synthesis, resulting in cell apoptosis	- Group A had 19% of RFS and 3% in Group B (2-year) - 21 patients (33%) in Group A and 13 patients (37.5%) in Group B had disease progression and underwent radical cystectomy
Sisto Perdonà et al, 2010[19]	20	Phase II	Intravesical Gemcitabine	Twice weekly for 6 weeks, and then weekly for 3 weeks at 3, 6, and 12 months.	Gemcitabine acts as a deoxycytidine nucleoside analog, thereby inhibiting deoxyribonucleic acid (DNA) synthesis, resulting in cell apoptosis	- 11 patients (55%) developed disease recurrence - 5 patients (45%) had disease progression
Melissa A Laudano et al, 2010[20]	18	Phase I	Docetaxel	6 weekly intravesical instillations using a dose-escalation model terminated at 0.75 mg/mL.	Docetaxel is an anti-mitotic chemotherapeutic agent which inhibits tubulin disassembly, thereby stopping cell division	- 4 patients (22%) have demonstrated a complete durable response and currently remain disease-free without further treatment - 3 patients (17%) had a partial response - 11 patients (61%) failed treatment - One patient developed stage progression
Raffaele Addeo et al, 2010[21]	109	Phase III I	Gemcitabine or Mitomycin C (MMC)	6 weekly or 4 weekly	Gemcitabine acts as a deoxycytidine nucleoside analog, thereby inhibiting deoxyribonucleic acid (DNA) synthesis, resulting in cell apoptosis Mitomycin C inhibits DNA synthesis and cross-links DNA	- In the Gemcitabine arm, 39 (72%) of 54 patients remained free of recurrence versus 33 (61%) of 55 in MMC arm - 10 in the MMC arm and six in the Gemcitabine arm also had a progressive disease by stage - The incidence of chemical cystitis in the MMC arm was statistically higher than in the Gemcitabine arm
Jeffrey M Ignatoff et al, 2009[22]	42	Phase II	Intravesical Doxorubicin	6 weekly doses	Doxorubicin intercalates into DNA and disruption of topoisomerase-II-mediated DNA repair and generation of free radicals and their damage to cellular membranes, DNA and proteins	- 18 refractory superficial urothelial carcinoma patients (85.7%) experienced disease recurrence - 3 CIS (60%) experienced disease recurrence - Recurrence-free rates at 12 and 24 months were 20% and 15%, respectively, for patients with refractory superficial urothelial carcinoma and 80% at both intervals for CIS patients

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Table 3 (Continued).

Author, Year	Patients Number	Study Design	Treatment	Regimen	Effects of Treatment	Main Findings
Roberta Gunelli et al, 2007[24]	40,	Phase II	Endovesical Gemcitabine	6 weekly	Gemcitabine acts as a deoxycytidine nucleoside analog, thereby inhibiting deoxyribonucleic acid (DNA) synthesis, resulting in cell apoptosis	- 38 patients (95%) showed persistent negative post-treatment cystoscopy and cytology 6 months - 2 patients were relapsed at 5 and 6 months - 4 patients had downstaged disease, 3 had a lower grade lesion and 3 had a reduction in both
Guido Dalbagni et al, 2006[25]	30	Phase III	Intravesical Gemcitabine	Two courses twice weekly for 3 weeks	Gemcitabine acts as a deoxycytidine nucleoside analog, thereby inhibiting deoxyribonucleic acid (DNA) synthesis, resulting in cell apoptosis	- 15 patients (50%) achieved a complete response - 12 patients had tumor recurrence - 2 patients maintained a complete response at 23 and 29 months, respectively. The 1-year recurrence-free survival rate for patients with a complete response was 21% - 2 patients progressed to a higher stage while receiving gemcitabine treatment
Riccardo Bartoletti et al, 2005[26]	116	Phase II	Intravesical Gemcitabine	6 weekly	Gemcitabine acts as a deoxycytidine nucleoside analog, thereby inhibiting deoxyribonucleic acid (DNA) synthesis, resulting in cell apoptosis	- 94 patients (81.3%) did not report any local side effects during the treatment period - Recurrence developed in 29 patients (25.4%) - 85 patients (74.6%) were disease free after 12 months - No recurrence developed in 18 (75%) of intermediate-risk BCG refractory or 7 (43.7%) of 16 high-risk BCG refractory patients
Pierfrancesco Bassi et al, 2005[27]	9	Phase I	Intravesical Gemcitabine	6 weekly	Gemcitabine acts as a deoxycytidine nucleoside analog, thereby inhibiting deoxyribonucleic acid (DNA) synthesis, resulting in cell apoptosis	- CDC 1 neutropenia was observed only in 1 pt - CDC 1 urinary frequency and hematuria were observed in 1 and 3 patients - No CDC 2–4 toxicity or clinically relevant myelosuppression was observed

Abbreviations: PFS, progression-free survival; CFS, cancer-free survival; DFS, disease-free survival; RFS, recurrence-free survival; CSS, cancer specific survival; OS, overall survival; CIS, carcinoma in situ; CDC, Clavien-Dindo Classification; CI, confidence interval.

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with gemcitabine as monotherapy,[13–27] as well as in association with several other medications, such as docetaxel,[28,29] cabazitaxel and cisplatin,[30] oral everolimus[31] and mitomycin C (MMC).[32,33]

Hurle et al studied gemcitabine monotherapy after BGC failure or intolerance, and 68.7% of patients had negative cystoscopy and urinary cytology after induction, although the result dropped to 31.6% after 24 months; overall survival (OS) was 77.9% and cancer-specific survival (CSS) was 80.68% after 24 months.[34] Skinner et al had also good results with 47% of patients with negative cystoscopy, urinary cytology, and biopsy, after 3 months and 21% after 24 months.[13]

The gemcitabine's potential has also been explored in combination with various other medications. Chevuru et al studied gemcitabine plus docetaxel with a 74% response at 3 months, and 50% and 30% high-grade recurrence-free survival (RFS) at 2 and 5 years, respectively, and 64% 5-year OS.[28] Studying the same drug combination Steinberg et al[29] and Milbar et al[35] found high-grade RFS of 46% and 42% at 2 years, respectively.

De Castro et al reported a few encouraging cases combining gemcitabine with cabazitaxel and cisplatin with 64% 2-year RFS.[30] The combination of intravesical gemcitabine and oral everolimus demonstrated 20% RFS at 12 months but was not well tolerated.[31] Docetaxel alone showed 25% RFS at 3 years.[37] Other associations such as MMC,[32,33] paclitaxel, nab-paclitaxel,[16,17,36] valrubicin and doxorubicin[15,22] have been described with conflicting results.

Chemo Hyperthermia (CTH)

While hyperthermia in the temperature range of 40°C to 45°C exerts direct cytotoxic effects, disrupting metabolism, causing DNA damage, impairing cell function, and promoting apoptosis in tumor cells, chemo hyperthermia increases cell membrane permeability and modifies blood perfusion, improving drug penetration in the urothelium, with potential to increase chemotherapy effectiveness.[38–40] This is achieved through external or internal (integrated into a catheter) microwave-generated heating devices or by a conductive system that externally heats the chemotherapy solution before intravesical administration and can also be combined with radiotherapy to enhance treatment efficacy.[41,42]

Colombo et al compared CHT and MMC in patients with intermediate and high-risk NMIBC with 17.1% and 57.5% recurrence rates, respectively.[43] An update of this study showed 15% and 53% disease-free survival (DFS) and a bladder preservation rate of 86% and 79% for thermochemotherapy and chemotherapy alone, at 10 years, respectively.[44]

Another trial studying intermediate- and high-risk NMIBC patients showed 24-month RFS of 78.1% and 64.8% in the CHT with MMC and BCG group, respectively; the progression rate was <2% in both groups.[45] Nativ et al treated 111 NMBC patients that failed BCG with CHT and found 56% 24-month DFS. Recurrence rate was 61% at 2 years vs 39% in those with maintenance treatment.[46]

Intravesical electromotive drug delivery is another approach involving the application of an electrical current across the urothelium to enhance drug movement. In a prospective study, Di Stasi et al evaluated patients with high-risk NMIBC, treated with conventional BCG, passive MMC, and electromotive MMC, with 64%, 31% and 58%, after 6 months, respectively, although 20 patients underwent cystectomy and 19 died of disseminated bladder cancer.[47] The main studies on CTH are in Table 4.

Target Therapy

Table 5 shows studies on target therapy. Sunitinib acts by inhibiting the vascular endothelial growth factor receptor (VEGFR) and, thus, inhibits tumor activity. A phase II study offered Sunitinib to patients with NMIBC who progressed after BCG and found 44% remission at 12 weeks and 22% PFS after 12 months. Grades 3 and 4 toxicity was noted in 68% of patients.[48]

Another phase II study evaluated NMIBC patients unresponsive to BCG with altered FGFR3 expression treated with oral dovitinib and found 33% complete response in patients with FGFR3 mutation, however also with high toxicity.[49]

Viral Gene Therapy

Other therapies are also being tested based on studies that show that genotypic and phenotypic alterations can favor tumor invasion and the development of tumor escape mechanisms (summarized in Table 6).

Table 4 Chemo Hyperthermia (CTH) Studies

Author, Year	Patients Number	Study Design	Treatment	Regimen	Effects of Treatment	Main Findings
Tom J H Arends et al, 2016[45]	190	Phase III	Intravesical Chemohyperthermia (CHT) with Mitomycin C Versus Bacillus Calmette-Guérin for Adjuvant Treatment	1-years CHT (six weekly treatments and six maintenance treatments) and 1-years BCG immunotherapy (six weekly treatments and three weekly maintenance treatments at months 3, 6, and 12)	Local hyperthermia enhances the systemic absorption of MMC during intravesical chemotherapy for bladder cancer	- The 24-months RFS was 78.1% in the CHT group compared with 64.8% in the BCG group (p = 0.08). The 24-mo RFS in the per-protocol analysis was 81.8% in the CHT group compared with 64.8% in the BCG group (p = 0.02) - Progression rates were <2% in both groups. - Regarding the side-effects, no new safety concerns were identified - CHT is an option for BCG therapy as adjuvant treatment for intermediate- and high-risk papillary NMIBC
Renzo Colombo et al, 2003[44]	65	Phase II	MMC alone and in combination with local microwave-induced hyperthermia	Long term follow-up Intravesical instillations of mitomycin C (MMC) alone, and MMC in combination with local microwave-induced hyperthermia	Local hyperthermia enhances the systemic absorption of MMC during intravesical chemotherapy for bladder cancer	- The 10-year disease-free survival rate for thermochemotherapy and chemotherapy alone were 53% and 15%, respectively (P < 0.001) - Bladder preservation rates for thermo-chemotherapy and chemotherapy alone were 86% and 79%, respectively
Ofer Nativ et al, 2009[46]	111	Phase III	Combined bladder wall hyperthermia and intravesical mitomycin C instillation (thermo-chemotherapy)	Treatment was received on an outpatient basis weekly for 6 weeks, followed by 6 maintenance sessions at 4 to 6-week intervals. Each treatment included 2, 30-minute cycles of 20 mg mitomycin C and bladder wall hyperthermia to 42C ± 2C.	Local hyperthermia enhances the systemic absorption of MMC during intravesical chemotherapy for bladder cancer	- Disease-free survival rate was 85% and 56% after 1 and 2 years, respectively - Recurrence rate was 61% at 2 years vs 39% in those with maintenance treatments (p = 0.01) - The progression rate was 3%

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Renzo Colombo et al, 2003[43]	75	Phase II	MMC alone and in combination with local microwave-induced hyperthermia	Intravesical instillations of mitomycin C (MMC) alone, and MMC in combination with local microwave-induced hyperthermia	Local hyperthermia enhances the systemic absorption of MMC during intravesical chemotherapy for bladder cancer	- Survival analysis of the 75 assessable patients demonstrated a highly significant difference in the survival curves in favor of thermochemotherapy - Subjective intolerance and clinical complications were significantly higher but transient and moderate in the combined treatment group
Savino M Di Stasi et al, 2003[47]	108	Phase III	Intravesical electromotive Mitomycin C versus passive transport mitomycin C	40 mg electromotive MMC instillation with 20 mA electric current for 30 minutes, 40 mg passive MMC with a dwell time of 60 minutes or 81 mg BCG with a dwell time of 120 minutes	Intravesical electromotive administration increases bladder uptake of MMC, resulting in an improved response rate in cases of high-risk superficial bladder cancer	- BCG group, passive MMC group and electromotive MMC group clinical response rates at 3 and 6 months was: 55.5; 27.8; 52.8 and 63.9; 30.5; 58.3, respectively - Progression rates: 16.7; 22.2; 16.7, respectively - 20 patients underwent cystectomy and 19 died of disseminated bladder cancer.
Rita Paroni et al, 2001[40]	35	Phase I	Local hyperthermia on the systemic absorption of mitomycin C (MMC) during intravesical chemotherapy	Group 1 received 20 mg intravesical MMC plus local hyperthermia, group 2 20 mg MMC alone, group 3 40 mg MMC plus local hyperthermia and group 4 40 mg MMC alone	Local hyperthermia enhances the systemic absorption of MMC during intravesical chemotherapy for bladder cancer	- Local hyperthermia associated with the intravesical chemotherapy enhanced plasma MMC concentrations at 30, 45 and 60 min compared with chemotherapy alone - Patients in group 3 displayed the highest degree of MMC absorption and the greatest variability in pharmacokinetics between patients

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Table 5 Target Therapy Studies

Author, Year	Patients Number	Study Design	Treatment	Regimen	Effects of Treatment	Main Findings
Haris Zahoor et al, 2019[48]	19	Phase II	Sunitinib	37.5 g daily for 12 weeks followed by 12± 2-week cystoscopy and surveillance for one year	Sunitinib malate is in a class of medications called kinase inhibitors and a form of targeted therapy that blocks the action of abnormal proteins called VEGFR that signal tumor cells to multiply. This helps stop or slow the spread of tumor cells	- 22% patients remained free of progression for >12 months - CDC grade 4 toxicities (anemia and thrombocytopenia) were noted in 2 patients. Clinically significant toxicity (CDC grade 3–4) was noted in 13 patients - Sunitinib resulted in reversal of myeloid-derived suppressor cells mediated immunosuppression
Noah M Hahn et al, 2017[49]	13	Phase II	Dovitinib	Oral dovitinib 500 mg daily (5 days on/2 days off)	Dovitinib is an orally bioavailable FGFR3 inhibitor, which strongly binds to FGFR3 and inhibits its phosphorylation, which may result in the inhibition of tumor cell proliferation and the induction of tumor cell death	- Toxicity was frequent with all patients experiencing at least one grade 3–4 event. - Six-month complete response rate was 8%

Abbreviations: CDC, Clavien-Dindo Classification; VEGFR, receptors for vascular endothelial growth factor; FGFR3, fibroblast growth factor receptor 3.

Table 6 Viral Gene Therapy Studies

Author, Year	Patients Number	Study Design	Treatment	Regimen	Effects of Treatment	Main Findings
Stephen A Boorjian et al, 2021[50]	157	Phase III	rAd-IFNα /Syn3 by adenoviruses	Single intravesical 75 mL dose of nadofaragene firadenovec (3×10^{11} viral particles per mL). Repeat dosing at months 3, 6, and 9 was done in the absence of high-grade recurrence.	rAd–IFNα-2b gene therapy mimics the physiologic events associated with viral infection, which results in local rather than systemic IFNα-2b production and subsequent tumor regression	- Micturition urgency was the most common grade 3–4 study drug-related adverse event (two [1%] of 157 patients, both grade 3), and there were no treatment-related deaths - 55 (53.4%) of 103 patients with carcinoma in situ (with or without a high-grade Ta or T1 tumor) had a complete response within 3 months of the first dose and this response was maintained in 25 (45.5%) of 55 patients at 12 months
Vignesh T Packiam et al, 2018[51]	45	Phase II	CG0070 oncolytic vector	2 prior courses of intravesical therapy for Carcinoma in situ (CIS), with at least 1 being a course of BCG. Patients had either failed BCG induction therapy within 6 months or had been successfully treated with BCG with subsequent recurrence	CG0070 is a replication-competent oncolytic adenovirus that targets bladder tumor cells through their defective retinoblastoma pathway	- There were 24 pure CIS, 8 CIS + Ta, 4 CIS + T1, 6 Ta, 3 T1. Overall, 6-month CR (95% CI) was 47% (32%–62%). Considering 6-month complete response for pathologic subsets, pure CIS was 58% (37%–78%), CIS ± Ta/T1 50% (33%–67%), and pure Ta/T1 33% (8%–70%) - Overall, 47% complete response rate at 6 months for all patients and 50% for patients with CIS
Neal D Shore et al, 2017[52]	40	Phase II	rAd-IFNα /Syn3 by adenoviruses	Intravesical rAd–IFNα/Syn3 (randomly assigned 1:1. Patients who responded at months 3, 6, and 9 were retreated at months 4, 7, and 10	rAd–IFNα-2b gene therapy mimics the physiologic events associated with viral infection, which results in local rather than systemic IFNα-2b production and subsequent tumor regression	- 35% patients remained free of high-grade recurrence 12 months after initial treatment. Of these, two experienced recurrences at 21 and 28 months, respectively, after treatment initiation, and one died as a result of an upper tract tumor at 17 months without a recurrence - The most frequently reported drug-related AEs were micturition urgency (n = 16; 40%), dysuria (n = 16; 40%), fatigue (n = 13; 32.5%), pollakiuria (n = 11; 28%), and hematuria and nocturia (n = 10 each; 25%)
Neema Navai et al, 2016[53]	7	Phase Ib	rAd-IFNα /Syn3 by adenoviruses	Intravesical instillation of SCH721015 (Syn3) and Ad-IFN at a concentration of 3×10^11 particles/mL to a total volume of 75mL given at day 1 and 4. Patients were followed for 12 weeks	rAd–IFNα-2b gene therapy mimics the physiologic events associated with viral infection, which results in local rather than systemic IFNα-2b production and subsequent tumor regression	- Two of seven had a complete response at 12 weeks and received a second course of treatment - One patient remained without evidence of recurrence after a second course (total 24 weeks) - One patient suffered a non-treatment associated adverse event

(*Continued*)

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Table 6 (Continued).

Author, Year	Patients Number	Study Design	Treatment	Regimen	Effects of Treatment	Main Findings
Colin PN. Dinney et al, 2013[54]	17	Phase I	rAd-IFNα /Syn3 by adenoviruses	A single treatment of rAd-IFNα (3×109 to 3×1011 particles/mL) formulated with the excipient Syn3 was administered. Patient safety was evaluated for ≥12 weeks	rAd–IFNα-2b gene therapy mimics the physiologic events associated with viral infection, which results in local rather than systemic IFNα-2b production and subsequent tumor regression	- Intravesical rAd-IFNα/Syn3 was well tolerated as no dose limiting toxicity was encountered. Urgency was the most common adverse event and all were grade 1 or 2 - 43% experienced a complete response at 3 months and 2 remained disease free at 29.0 and 39.2 months respectively

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Nadofaragene firadenovec (rAd-IFNα/Syn3) is a promising contender, comprises rAd-IFNα, a non-replicating recombinant adenovirus vector-based gene therapy agent, which introduces a copy of the human IFNα-2b gene into the urothelial cell wall.[55,56]

Syn3, a polyamide surfactant, complements this by enhancing viral transduction of the urothelium.[57] In a phase II trial involving 40 patients with BCG-unresponsive high-grade NMIBC, the RFS after 12 months was 35%; no grade four or five adverse events occurred.[52] Encouraged by these results, Boorjian et al conducted a multicenter phase III clinical trial in the USA, with 151 patients who did not respond to BCG and found that in patients with CIS, a complete response rate of 53.4% at 3 months and 45.5% of the response was maintained at 12 months.[50] The rAd-IFNα/Syn3 has undergone evaluation in 4 single-arm cohort trials,[50,52–54] revealing complete response rates ranging from 29% to 60% at 3 months and from 29% at 3 months to 35% at 12 months.

Complete response rate of 47% at 6 months, 30% at 12 months, with lower rates in the subgroup with concomitant CIS, was reported in a phase II study of 45 "BCG-exposed" NMIBC patients with or without CIS who refused RC and received intravesical CG0070 with n-dodecyl-BD-maltoside (a transduction enhancer).[51]

Other oncolytic viruses with relevance include intravesical talimogene laherparepvec, a herpes simplex 1 virus with ICP47 deletion that incorporates the human GM-CSF gene, diphtheria toxin A, and intravesical V937 (Cavatak, Coxsackievirus A21).[58]

Antibody-Drug Conjugates (ADCs)

ADCs are a new therapeutic approach that combines the high specificity of monoclonal proteins with cytotoxic agents. In recent years, ADCs have emerged as an innovative therapeutic tool that can take advantage of tumor-specific molecular characteristics (the main studies are found in Table 7).

The enfortumab vedotin is an antibody–drug conjugate directed against Nectin-4, which is highly expressed in luminal subtypes of bladder cancer.[65] It was recently approved by the FDA for the treatment of metastatic patients, and a multicenter study is evaluating the safety and response in BCG-unresponsive NMIBCs.[66]

Vicinium (oportuzumab monatox) is a recombinant fusion protein that ingeniously combines a humanized single-chain anti-EpCAM (epithelial cell adhesion molecule) antibody with Pseudomonas exotoxin A. Kowalsky et al studied it in patients with NMIBC unresponsive to BCG with concomitant CIS and found a 44% response rate, and in 16% this response was maintained until the end of the follow-up period (18–25 months), with minimal adverse effects.[61]

A phase II trial studying a combination of BCG with interleukins achieved a 24-month OS of 94% with minimal adverse effects.[59] Other studies tested interferon (IFN)α2b action. O'Donnell et al compare INF + standard BCG and INF + reduced BCG Disease freedom at 24 months were 57% and 42%, respectively.[64] Joudi et al got promising results comparing INF in patients naïve to BCG and those having BCG failure with 59% and 45% patients disease free at 24-month median follow-up, respectively.[63]

An immunomodulatory and antineoplastic compound derived from *Mycobacterium phlei*[60,62] was also tested in a phase III trial with overall disease-free survival of 19% at 2 years and few adverse events.[60]

Photodynamic Therapy (PDT)

Photodynamic Therapy (PDT) involves the administration of a photosensitizing agent activated by light at a specific wavelength. PDT outcomes are based on limited patient series in the context of NMIBC and are therefore considered experimental (the main studies are found in Table 8).

Still, it is an incipient and experimental treatment, of which there are only small series described. Waidelich et al studied PDT with oral 5-aminolevulinic acid in patients with BCG-refractory NMIBC with a complete remission in 100% of patients with CIS and 79.2% patients with papillary tumors, and after 3 years 60% of CIS patients and 21% of papillary patients remained disease-free.[68]

Lee et al investigated the PDT with intravenous radachlorin in 34 patients with a high-grade T1 disease, with or without concomitant CIS, and none of the patients had evidence of disease after 12 weeks. RFS was 60.1% at 30 months. Adverse events observed were mainly lower urinary tract symptoms and hematuria.[67]

Table 7 Antibody-Drug Conjugates (ADCs)

Author, Year	Patients Number	Study Design	Treatment	Regimen	Effects of Treatment	Main Findings
Sam S. Chang et al, 2022[59]	154	Phase III	N-803	Intravesical N-803 plus BCG	N-803, a high affinity IL-15 immunostimulatory fusion protein, promotes proliferation and activation of natural killer (NK) cells and CD8+ T cells, but not T reg cells	- With a 19.3 month median follow-up, the 12 month cystectomy free rate was 92% (95% CI: 85.5%, 95.3%) and the 24 months overall survival is 94% (95% CI: 86.9%, 97.1%) with 99.5% cancer-specific survival
Alvaro Morales et al, 2015[60]	129	Phase III	MCNA (Mycobacterium phlei cell wall–nucleic acid complex)	8 mg MCNA weekly for 6 weeks followed by 3 weekly instillations at months 3, 6, 12, 18 and 24	MCNA has been reported to exhibit a dual mechanism of action, displaying both indirect immunomodulatory (BCG-like) activity and direct chemotherapeutic effects (inhibition of proliferation, cell cycle arrest, and apoptosis)	- The overall disease-free survival rate was 25.0% at 1 year and 19.0% at 2 years - The median disease-free duration in the 30 responders was 32.7 months - The progression-free survival rate was 87.3%, 79.8% and 77.7% at 1, 2 and 3 years, respectively, with a progression event in 28 patients - MCNA was well tolerated, and few adverse events led to treatment discontinuation
Mark Kowalski et al, 2012[61]	46	Phase II	Oportuzumab Monatox	1 induction cycle of 6 (cohort 1) or 12 (cohort 2) weekly intravesical oportuzumab monatox (VB4-845) instillations of 30 mg, followed by up to 3 maintenance cycles of 3 weekly administrations every 3 months	Oportuzumab Monatox works by binding to a protein called epithelial cell adhesion molecule (EpCAM) on the surface of epithelial cells and some types of cancer cells. It targets and kills EpCAM positive cells tumour cells programmed cell death	- Complete response in 41% patients (in cohort 1) and 39% in cohort 2 at the 3-month evaluation. 44% achieved a complete response - 16% remained disease-free. Post-study assessment demonstrated that these patients were still disease-free at last follow up (18 to 25 months) - The most common adverse events were mild-to-moderate reversible bladder symptoms

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Alvaro Morales et al, 2009[62]	55	Phase III	MCNA	6 weekly instillations of 4 or 8 mg MCNA followed by 3 weekly instillations at weeks 12 and 24	MCNA has been reported to exhibit a dual mechanism of action, displaying both indirect immunomodulatory (BCG-like) activity4 and direct chemotherapeutic effects (inhibition of proliferation, cell cycle arrest, and apoptosis)	- complete response rate was 27.3% at weeks 12 and 26 in the 4 mg group, while 46.4% of patients receiving 8 mg had a complete response at both points - MCNA complex was well tolerated by both dose groups - Overall 90% of all adverse events were mild to moderate in severity
Fadi N Joudi et al, 2006[63]	1007	Phase II	Interferon alpha-2B	Interferon alpha-2B (IFN) −50 million units plus reduced dose BCG	Interferon alpha helps stimulate the body's immune system to fight some types of cancer by strengthening the immune system, reducing the ability of the cancer cells to defend themselves from the immune system and by slowing down or stopping the cancer cells from dividing	- 59% and 45% of patients naïve to BCG and those having BCG failure, respectively, remained disease free at 24-month median follow-up
Michael A O'Donnell et al, 2004[64]	490	Phase II	Interferon alpha-2B	6-week induction course of standard dose BCG plus 50 million units of Interferon alpha-2B (IFN) followed by 3, 3-week maintenance cycles of reduced dose BCG (1/3 to 1/10) plus 50 million units IFN at 3, 9 and 15 months after induction (BCG-N group) BCG-F group was treated similarly except induction therapy began at a decreased (1/3 to 1/10) BCG dose	Interferon alpha helps stimulate the body's immune system to fight some types of cancer by strengthening the immune system, reducing the ability of the cancer cells to defend themselves from the immune system and by slowing down or stopping the cancer cells from dividing	- INF + standard BCG and INF + reduced BCG Disease freedom at 24 months were 57% and 42%, respectively - The simple tumor recurrence rates for INF + standard BCG and INF + reduced BCG groups were 40% and 52% - Progression to muscle invasion occurred in 5% and 4.3%, while metastasis occurred in 2.3% and 2.6%, respectively - Serious adverse events occurred in 5.5% with infection related serious adverse events being less prevalent in the BCG-F group (2.6% vs 5.4%)

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Table 8 Photodynamic Therapy (PDT) Studies

Author, Year	Patients Number	Study Design	Treatment	Regimen	Effects of Treatment	Main Findings
Joo Yong Lee et al, 2013[67]	34	Phase III	Radachlorin	Radachlorin (0.5 to 0.6 mg/kg) was injected intravenously 2 to 3 hours before photodynamic therapy	Produces local tissue necrosis with laser light following the prior administration of a photosensitizing agent	- Recurrence-free rate was 90.9% at 12 months, 64.4% at 24 months and 60.1% at 30 months
Raphaela Waidelich et al, 2001[68]	24	Phase III	5-aminolevulinic acid	Photodynamic therapy (PDT) after the oral administration of 5-aminolevulinic acid.	Use of 5-ALA PDT permits selective tumor targeting due to the intracellular metabolism of 5-ALA	- At a median follow-up of 36 months 3 of the 5 patients with carcinoma in situ and 4 of the 19 with papillary tumors were free of recurrence. - Three patients were rendered disease-free by repeat photodynamic therapy with 5-aminolevulinic acid and 3 underwent cystectomy - Tumor progression was stopped in 20 of our 24 cases

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Discussion

In the realm of bladder cancer, Non-Muscle Invasive Bladder Cancer (NMIBC) presents a significant challenge, with a prevalence of 75%. This condition is categorized into three risk groups, with the high-risk category exhibiting a notably low recurrence-free survival (RFS) rate of just 23%. Patients with high-grade NMIBC face a substantial risk of recurrence and progression, nearly 50% in some cases, often necessitating invasive and burdensome surgical interventions.[69] Therefore, any therapeutic approach that can reduce the necessity for cystectomy while demonstrating reduced toxicity and high efficacy, is of paramount importance. Bacillus Calmette-Guérin (BCG) therapy has been the cornerstone treatment for NMIBC for decades. However, its failure rate (40%) and progression rate (15%) necessitate alternative strategies and novel treatment advancements.[70]

The Food and Drug Administration (FDA) has recognized the urgency for new treatments in cases of BCG failure, as evidenced by their acceptance of single-arm studies.[71,72] However, the lack of uniformity in these studies, particularly in aspects such as tumor multifocality, size, maintenance therapy, prior recurrence rates, and cystoscopy evaluation methods, weakens the robustness of the data and complicates its interpretation.

In the context of Immune Checkpoint Blockade (ICB), only two-phase II trials have been notable. These trials have shown encouraging results in BCG-unresponsive patient cohorts with Carcinoma In Situ (CIS) or concurrent papillary tumors. The first trial, led by Balar et al,[6] evaluated Pembrolizumab and, despite a small patient cohort, yielded promising outcomes with only 13% of patients experiencing significant treatment-related adverse events. Intravesical administration of Pembrolizumab may mitigate certain adverse events and elicit a CD4+T cell response. Interestingly, the drug was detectable in urine but not in blood samples in a small phase I study. The second trial investigated Atezolizumab but failed to meet the efficacy threshold.[9] The success of ICB in Muscle-Invasive Bladder Cancer (MIBC) has already been incorporated into treatment guidelines and may soon extend to earlier stages of the disease. The FDA has already approved its use in the NMIBC BCG unresponsive CIS scenario, although data on toxicity and complication rates in NMIBC post-BCG failure remain limited.

Sunitinib, an early targeted agent and an endothelial growth factor receptor inhibitor, showed potential in bladder cancer (BC). However, a phase II trial by Zahoor et al involving 19 BCG-failure patients indicated that while relatively safe, Sunitinib did not improve outcomes. Dovitinib achieved biologically active concentrations in the urothelium and inhibited pFGFR3 pharmacodynamically but was associated with frequent high-grade toxicities.[49]

Intravesical chemotherapy is a familiar approach in clinical practice. For BCG-naïve patients, a Randomized Controlled Trial (RCT) demonstrated that the combination of Mitomycin C (MMC) and BCG was more effective than BCG alone in terms of recurrence-free interval and progression rate reduction.[73] In BCG-unresponsive cases, various agents such as Valrubicin, Gemcitabine, MMC, and Docetaxel have been extensively studied, with Gemcitabine emerging as a favorable option due to its efficacy and patient acceptability, particularly in BCG-resistant cases.

Microwave-induced hyperthermia has shown to enhance the efficacy of MMC in high-risk tumors, as evidenced by a single-center study with a 10-year follow-up and an RCT indicating superior outcomes compared to BCG in intermediate and high-risk cases.[74] However, further head-to-head studies are required for a definitive conclusion.

Chemohyperthermia, combining hyperthermia with chemotherapy, has shown promise in enhancing treatment outcomes but comes with several challenges. It can increase both local and systemic toxicity, complicate treatment delivery due to the need for specialized equipment and expertise and pose risks of bladder damage. Additionally, it incurs higher costs and resource utilization, and there is a lack of long-term data on its efficacy and safety.

The exploration of immunotherapy and anti-inflammatory agents in NMIBC is an active area of research. While promising results have been observed, further validation of their safety and efficacy is necessary. Advances in immunotherapy are poised to revolutionize NMIBC treatment, but patient-specific factors must guide treatment selection.

Gene therapy, although in its nascent stages, shows great promise for NMIBC treatment. Ongoing research aims to overcome challenges in gene delivery, immune response regulation, and targeted gene expression. Current clinical trials are assessing the safety and efficacy of gene therapy for NMIBC.

Photodynamic therapy, despite being studied for decades, has a limited presence in literature with less than 30 single-arm studies. However, the outcomes have been largely positive, with most complications being mild and transient. Future high-quality research is essential to further establish its efficacy.

Enfortumab vedotin (EV), an antibody–drug conjugate targeting Nectin-4, is currently being evaluated in a Phase 1 trial (EV-104, NCT05014139) presented by Kamat et al at ASCO 2023. This study aims to assess the safety, tolerability, and anti-tumor activity of intravesical EV in BCG-unresponsive NMIBCs and is actively recruiting participants.

Nadofaragene firadenovec has demonstrated tolerability without dose-limiting toxicity or significant treatment-related side effects. A single dose was sufficient to achieve measurable urine IFNα, indicating its potential efficacy.[74]

Conclusion

The selection of an optimal therapy for intermediate and high-risk NMIBC that can reduce the need for cystectomy, with reduced toxicity and high efficacy, is of paramount importance and remains an issue; however, several bladder-preserving alternatives are being tested in this scenario and have shown promise, pending long-term oncological results and larger methodologically robust trials.

Pembrolizumab is still the only drug approved by the FDA, but other ICBs also show promise, as do intravesical chemotherapy and ADCs, recently approved by the FDA for metastatic treatment, which are also being pulled to earlier stages.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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