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# Advancements in Intravesical Chemotherapy in Non-Muscle Invasive Bladder Cancer

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## Abstract

The treatment for non-muscle-invasive bladder cancer is transurethral resection of bladder cancer followed by intravesical chemotherapy or BCG. There have been various advancements in low risk, intermediate risk, high risk, and BCG failure cases of non-muscle invasive bladder cancer. There has been increased research on hyperthermia and intravesical chemotherapy, new agents like apaziquone, use of gemcitabine in low-risk cases, and combination chemotherapy in cases of BCG failure. Combining docetaxel and gemcitabine has taken a significant stage because of BCG shortage in some parts of the world. This chapter will discuss the latest advancements in intravesical chemotherapy in low, intermediate, and high-risk patients.

**Keywords:** Non-muscle invasive bladder cancer, Intravesical chemotherapy, Advancements in intravesical chemotherapy, Gemcitabine, Docetaxel, Nanoparticles, Mitomycin, Heated chemotherapy

## 1. Introduction

Bladder cancer accounts for 3% of the total cancers diagnosed in the world. It is more prevalent in developed countries. The most potent risk factor is tobacco smoking. Seventy-five percent of bladder cancer cases present with non-muscle invasive disease. The five-year survival statistics in the US are 69.5% for localized disease, 36.3% for regional disease, and only 4.6% for metastatic disease [1]. Almost three-fourths of high-risk non-muscle invasive bladder cancer will have a recurrence within ten years, 33% will progress to invasive disease [2].

Clinical guidelines suggest a risk-stratified approach post TURBT for intravesical therapy instillation. BCG has been the gold standard for intermediate and high-risk diseases. However, 61% of all patients recur within one year [3, 4]. In low-risk patients, a single post-operative instillation is adequate. This is based on a meta-analysis by Sylvester et al., which showed that patients receiving post-operative chemotherapy had a decrease in 39% of odds of recurrence with chemotherapy. They also showed that in patients with multiple tumors single instillation was not successful. Patients with a single tumor had a recurrence of 35.8% vs. a recurrence of 65.2% in patients with multiple tumors. No difference in different chemotherapeutic agents was found. The instillation is recommended to be given within 6 hours after TURBT, but in any case, within 24 hours if there is no deep resection [5].

The intermediate-risk group of patients is the largest group of non-muscle invasive bladder cancer patients. Intravesical instillations are recommended to decrease the risk of recurrence. The combined analysis from the European Organization for Research and Treatment of Cancer [EORTC] and Medical Research Council [MRC] randomized clinical trials included 2535 patients of primary or recurrent, stage TaT1 transitional cell carcinoma compared transurethral resection alone with and without adjuvant intravesical therapy. It showed a significant difference in terms of the duration of disease-free survival. No significant advantage in progression was seen. The median follow-up for survival was 7.8 years [6]. The guidelines recommend intravesical instillations of chemotherapeutic agents or BCG post TURBT in the intermediate-risk group [7, 8].

A second TURBT is mandatory within 2–6 weeks in the current guidelines in the high-risk group [7]. Guidelines recommend BCG intravesical therapy for high-risk patients. This is based on a meta-analysis by Sylvester et al., which included 24 trials with 4863 patients. The median follow-up was 2.5 years, and the maximum follow-up was of 15 years. In the BCG group, 260 out of 268 progressed [9.8%] while in the control group 304 out of 2205 progressed [13.8%]. There was a reduction of 27% in progression on BCG and the results were statistically significant. No significant benefit in disease-free survival was found [9]. No adjuvant chemotherapeutic regimens are included in the clinical guidelines as of now.

## 2. Advancements in low-risk disease

### 2.1 Gemcitabine

#### 2.1.1 *The rationale for using gemcitabine*

Gemcitabine is 2'2' – diflourodeoxycytidine and it has a broad spectrum of antitumor activity. It is phosphorylated and incorporated into DNA and RNA which results in apoptosis.

Many characteristics make gemcitabine a promising intravesical agent for bladder cancer. First, there has been a response rate of 27–38% during the systematic administration of gemcitabine against invasive bladder cancer. Second, the absorption of intravesical chemotherapeutic agents requires the size of the drug to be less than 300 Da. Gemcitabine has a molecular weight of 299 Da, which is lower than mitomycin and doxorubicin. It enables the drug to better penetrate the bladder mucosa and at the same time, the molecular weight is not too low so that systematic absorption of the drug occurs. The pKa of the drug is 3.6 and it results in a pH of 2.7–3.2 after reconstitution. Therefore, it results in low ionization of the drug at the acidic pH of the urine [10].

#### 2.1.2 *Studies for intravesical gemcitabine*

Bohle et al. conducted a double-blind placebo-controlled randomized control trial in low and intermediate-risk patients for post-TURBT intravesical gemcitabine versus placebo in 355 patients in 24 urological centers. They used a single post-operative instillation of 2gm in 100 ml NS of gemcitabine with a 30–40 minutes retention time. The placebo used was 100 ml of normal saline. Both of these were followed by 20-hour bladder irrigation. The median follow-up was 24 months. Recurrence-free survival [12 months] was 77.7% in the gemcitabine group and 75.3% in the placebo group. There was no statistical significance between the two groups. The authors concluded that continuous irrigation and improved TURBT techniques might have led to high recurrence-free survival in both groups [11].

The SWOG SO337 randomized control trial was conducted at 23 US centers, and it assessed the effect of single post-operative instillation of intravesical gemcitabine versus saline in low-risk NMIBC cases. They used 2gm gemcitabine in 100 ml NS and 100 ml saline with a retention time of 1 hour in both groups. A total of 215 patients with low-risk NMIBC were randomized. The median follow-up was four years. In the gemcitabine group, 34 recurred out of 102, and in the saline group, 59 recurred out of 113 patients. There was a statistically significant difference between both groups [ $P = 0.001$ ]. There were no grade 4 or 5 adverse events. The authors concluded that in low-risk non muscle-invasive bladder cancer patients, immediate intravesical instillation of gemcitabine significantly reduced the recurrence rate over a median of 4 years [12].

## 2.2 Apaziquone

Apaziquone is a mitomycin derivative and chemically 5-[aziridin-1-yl]-3-[hydroxymethyl]-2-[[1E]-3-hydroxyprop-1-enyl]-1-methyl-1H-indole-4,7-dione. It has a molecular weight of 288.30 Da. The drug product is called EOquin, and it has a storage temperature of 2–8 degrees Celsius. Before intravesical instillation, the EOquin vial is reconstituted with 20 ml of Diluent [a propylene glycol solution for intravesical instillation] to yield 0.2 mg/ml of apaziquone. This solution is further diluted with 20 ml of sterile water for injection, USP, resulting in 40 ml of the instillation solution containing 0.1 mg/ml of apaziquone [13].

It is the most potent intravesical agent in vitro. It is a prodrug and enzymatically activated by DT diaphorase [DTD] to generate cytotoxic species [13].

Karsh et al. reported two phases 2 multinational, double-blind placebo-controlled trials in patients with Ta, G1-G2 NMIBC to evaluate the efficacy of single instillation of apaziquone post TURBT. These two trials [SPI -611 and SPI 612] were conducted between April 2007 to January 2012. A single intravesical instillation of apaziquone [4 mg/40 mL] or placebo was administered within 6 hours post-TURBT. The primary endpoint was a 2-year recurrence-free rate, and the secondary endpoint was time to recurrence. A total of 1614 patients were enrolled.

Individually the two studies did not meet any statistical significance for a 2-year recurrence-free rate [38.0% vs. 44.6%, 39.7% vs. 46.3%]. When the pooled analysis was presented, it showed a 6.7% reduction in the 2-year recurrence-free rate. [OR – 0.76,  $P = 0.0218$ ]. In both the studies, time to recurrence showed improvement, which was statistically significant in the SPI-611 study. Pooled data for time to recurrence also showed a significant improvement of time-to-recurrence [hazard ratio [HR] 0.79;  $P5.0096$ ]. Apaziquone is rapidly metabolized in the blood. Therefore, a post hoc analysis was conducted by the time window of drug instillation post TURBT. Patients who had drugs instilled in the time window  $60 \pm 30$  minutes post-TURBT demonstrated 20.3% and 20.8% reduction in 2- in the two studies, respectively.

These studies reported the safety of this drug for intravesical instillation, but further studies are required for determining the efficacy of this drug [14].

## 3. Advancements in intermediate and high-risk disease

### 3.1 Heated intravesical chemotherapy

Hyperthermia is the application of mild heat [40–44-degree Celsius]. Thermal ablation is having a higher temperature range of  $60^{\circ}$  to  $90^{\circ}$  Celsius. Hyperthermia helps in triggering the immune anti-cancer response. It also helps to improve drug delivery and is itself also directly cytotoxic to the cancer cells [15, 16].

The warm temperature results in local vasodilation and causes the leaky tumor vasculature to become leakier, resulting in improved drug delivery to the tumor cells. This is called the enhanced permeability and retention effect [17]. Hyperthermia can be provided by external devices and internal devices. Internal devices are most commonly used. **Table 1** describes the various devices which are used.

Heated intravesical chemotherapy has been used in neoadjuvant and adjuvant settings.

3.1.1 Neoadjuvant setting

Sousa et al., conducted a pilot clinical trial in 15 patients with intermediate and high-risk non-muscle-invasive bladder cancer patients. HIVEC consisting of eight weekly instillations of intravesical mitomycin C [80 mg in 50 mL] delivered with the novel Combat BRS® system at a temperature of 43°C for 60 min. A total of 119 treatments sessions were given. During TURBT it was found that 8 patients [53%] had a complete response and 7 [47%] had a partial response. The median follow-up was 29 months and the 3-year recurrence rate was 15%. No grade 3 toxicity was observed [18].

3.1.2 Adjuvant setting

Arends et al. conducted a phase III open-label, randomized control trial among 190 intermediate and high-risk non-muscle-invasive bladder cancer patients. 1-yr hyperthermia with mitomycin C [20 mg/50 mL] for 2, 30-minute sessions for six weeks, and maintenance course three cycles] were administered. The primary end-point was 24-month recurrence-free survival. The 24 months recurrence-free survival was 78.1% in the hyperthermia group and 64.8% in the BCG group [P = 0.08]. There was less than a 2% progression rate in both groups. No new adverse events were noted. In the per-protocol analysis, the 24 months recurrence-free survival was 81.8% in the hyperthermia group and 64.8% in the BCG group [P = 0.02]. The authors concluded that hyperthermia with Mitomycin C is safe and has a higher 2-year recurrence-free survival [21].

3.2 Ongoing trial for primary chemoablation

An ongoing phase 2 study of UGN-102 for low-grade intermediate risk non-muscle invasive bladder cancer [OPTIMA II] has enrolled 63 participants. They used 75 mg Mitomycin C [mitomycin C] in 56 mL admixture [1.33 mg mitomycin C per 1 mL of admixture], and six intravesical instillations were given weekly. The

Device	Mechanism of action
Combat bladder recirculating system [BRS] [Inno Medicus, Cham, Switzerland] [18]	Externally heat fluid and the circulate it to the bladder via a 3-way irrigating Foley catheter.
Unithermia [El Medical, Hod-Hasharon, Israel] [19]	Externally heat fluid and the circulate it to the bladder via a 3-way irrigating Foley catheter.
Synergo [Tigard, OR] [20]	Intravesical bladder heating system also uses recirculating bladder irrigation, but instead of a heat exchanger, it uses a microwave radiofrequency emitting intravesical catheter to heat the bladder.

**Table 1.**  
*The internal devices used for hyperthermia.*



primary objective was the complete response rate three months after treatment. The trial completion date was December 2020, and results are awaited [22].

### **3.3 Gemcitabine docetaxel combination in BCG naïve patients**

Thomas et al. published an abstract of retrospective data for patients receiving sequential gemcitabine and docetaxel. The patients had not received any other intravesical therapy before. They were treated with six weekly instillations of gemcitabine [1 gram of gemcitabine in 50 ml of sterile water] followed immediately by docetaxel [37.5 mg of docetaxel in 50 mL of saline]. Maintenance therapy was then given for two years in patients without recurrence. The total number of patients identified was 30, and the median follow-up was 18 months. The indications of using this combination therapy were advanced age, immunosuppression, and BCG shortage. Treatment success was 96% at three months, 89% at one year, and 89% at two years. Treatment was well tolerated [23].

### **3.4 Ongoing trial for BCG naïve NMIBC: GEMDOCE trial**

A phase II, two-stage, open-label trial for studying the safety and efficacy of gemcitabine docetaxel combination has started recruitment from Jul 29, 2020. The estimated enrolment is 26 patients, and the estimated completion is June 2024. The drug combination and dosing being used is 1 g gemcitabine in 50 ml sterile water; instilled once weekly for six weeks and then once monthly for  $\leq 21$  months and 37.5 mg docetaxel in 50 ml normal saline solution [NSS]; instilled once weekly for six weeks and then once monthly for  $\leq 21$  months. The primary objective is three months' complete response rate as assessed by cystoscopy and cytology. [ClinicalTrials.gov Identifier: NCT04386746] [24].

## **4. Advancements in BCG failure cases**

### **4.1 Hyperthermia in BCG unresponsive cases**

The HYMN trial was an open-label, two-arm, phase III randomized control trial in which 104 patients with BCG unresponsive non-muscle invasive bladder cancer were randomized to hyperthermia plus mitomycin or a second course of BCG. In the hyperthermia arm Synergo SB-TS 101 System was used and two 30 min cycles, each with 20 mg mitomycin at  $42^{\circ} \pm 2^{\circ}$ . Patients allocated to the BCG arm received six consecutive weekly BCG instillations [in 50 ml normal saline] followed by maintenance therapy [three consecutive weekly instillations at 3, 6, 12, 18, and 24 months]. Primary outcomes were disease-free survival [DFS] and three months complete response for CIS patients at randomization. The median follow-up was 35 months. No statistically significant difference was observed between the two arms. The hyperthermia arm had 35% DFS, and the BCG arm had 41% DFS. [HR 1.33, 95% confidence

interval [CI] 0.84–2.10],  $p = 0.23$ ; adjusted  $p = 0.49$ ]. There was a nonsignificant higher DFS favoring hyperthermia group than BCG group in non-CIS patients at baseline [HR 0.50, 95% CI 0.22–1.17,  $p = 0.11$ ] [25].

The most adverse events in this study were grades 1–2. There was two grade 4 toxicities in the BCG arm due to arthritis, and the other BCG-related sepsis resulted in death. No difference in health-related quality of life [HRQoL] was observed between the two treatment arms, although hyperthermia group patients reported their HRQoL higher than BCG group patients at 3, 6 and 9 months [25].

## 4.2 Docetaxel

Docetaxel as a sole agent was studied in a phase I/II trial in 54 BCG refractory NMIBC between 2003 and 2012. A dose-escalation scheme was used in the first 18 patients treated with doses ranging from 5 to 75 mg for a final concentration of 0.125 to 0.75 mg/ml for administration. All subsequent patients received the maximum dose of 75 mg/100 ml of normal saline. All patients received six weekly instillations of intravesical docetaxel. After the phase I trial, those with a complete response to induction treatment were offered single dose monthly maintenance treatments for a total of up to 12 months of docetaxel therapy. The Median follow-up was 39.1 months. A complete initial response was seen in 32 patients [59%]. One year and the three-year recurrence-free rate was 40% and 25%, respectively. The authors concluded that intravesical docetaxel appears to be an efficacious agent, but large trials are needed to fully characterize this agent's benefits [26].

## 4.3 Gemcitabine and associated combinations

### 4.3.1 Gemcitabine as a sole agent

Gemcitabine has been studied in BCG refractory cases in two trials. Lorenzo et al. conducted a multi-center prospective randomized phase 2 trial in which 80 patients failing one course of BCG were randomly allocated to Gemcitabine arm and 2nd course of BCG arm. Kaplan Meier statistics of 2-year recurrence-free survival showed a significant difference between the gemcitabine and BCG group [19% and 3%, respectively,  $P < 0.008$ ]. Seven of 21 [33%] patients in gemcitabine group and 13 of 35 [37.5%] patients in group had disease progression and underwent radical cystectomy [ $P = .12$ ]. No significant safety concern was seen in both groups. The authors concluded that gemcitabine might be considered a second-line treatment after BCG failure in a high-risk non-muscle-invasive group [27].

Addeo et al. conducted a phase III randomized control trial in 120 high-risk NMIBC patients previously treated with BCG from march 2003 to November 2005. They received 40 mg of mitomycin C or 2000 mg of gemcitabine diluted in 50 mL of normal saline. The median follow-up was 36 months. In the gemcitabine arm, 39 of 54 patients remained free of recurrence versus 33 of 55 in the mitomycin C arm. Progression was seen in 10 patients in the mitomycin C arm and 6 in the gemcitabine arm. The incidence of chemical cystitis in the mitomycin C arm was statistically higher than in the gemcitabine arm [ $P = .012$ ] [28].

These studies show that gemcitabine alone or combined can be considered in BCG refractory high-grade disease if cystectomy is contraindicated or refused [29].

### 4.3.2 Gemcitabine plus cabazitaxel plus cisplatin

A phase I trial studied the effect of this combination therapy. The trial was a dose-escalation, drug escalation study in patients of high-risk BCG failure NMIBC. A total of 18 patients were included, and the median follow-up was 27.8 months. The schedule used was

- 6-wk induction regimen of sequentially administered cabazitaxel, gemcitabine, and cisplatin
- Responders continued with maintenance cabazitaxel and gemcitabine monthly for the first year and bimonthly for the second year.

The dosing used in this study was:

1. Gemcitabine- 2 g/100 ml, Cabazitaxel – 5 mg/100 ml, Cis – 66 mg/100 ml
2. Gemcitabine- 2 g/100 ml, Cabazitaxel – 5 mg/100 ml, Cis – 80 mg/100 ml
3. Gemcitabine- 2 g/100 ml, Cabazitaxel – 5 mg/100 ml, Cis – 100 mg/100 ml

A complete response rate of 94% was observed, and a DFS of 78% was observed at 9.5 months. No Dose-limiting toxicity till the last follow-up. Further studies need to be done to evaluate the efficacy of this combination.

#### *4.3.3 Gemcitabine plus mitomycin*

This combination was first used in 2006, and it showed promising results in BCG failure patients. There were 20 months of median disease-free survival in the study by Maymi et al. [30].

In a retrospective study conducted by Cockerill et al., 27 patients with BCG failure were identified and had received gemcitabine plus mitomycin combination therapy. With a median follow-up of 22.1 months, ten patients had no recurrence. The authors concluded that this combination could offer durable recurrence-free survival to patients with recurrent NMIBC who are not candidates for, or refuse, cystectomy [31].

Similarly, Lightfoot et al. showed in a retrospective review of 47 patients who received six weekly treatments with sequential intravesical gemcitabine [1 g] and MMC [40 mg] chemotherapy for NMIBC. The median time for follow-up was 26 months. Fourteen of 47 patients [30%] remained free of recurrence. These studies show that gemcitabine plus mitomycin combination can be helpful in high-risk BCG failure NMIBC cases.

##### *4.3.3.1 Administration of gemcitabine plus mitomycin combination*

Patients should be pre-treated with an oral urinary alkalization agent [such as sodium bicarbonate the night before and the morning of installation]. Gemcitabine does not directly irritate the bladder, but its solution is very acidic [pH - 2.6], whereby Mitomycin C is inactivated under acidic conditions, and it irritates the bladder.

Patients receive six weekly intravesical installations for induction, which includes administration of the following:

1. 1 g Gemcitabine is diluted in 50 mL normal saline [Dwell time: 90 minutes]
2. The bladder is drained without rinsing
3. Instill 40 mg Mitomycin is diluted in 20 mL sterile saline [Dwell time 90 minutes]

Monthly maintenance administrations are generally given for 1 to 2 years or until recurrence [31, 32].

#### *4.3.4 Gemcitabine plus docetaxel*

Docetaxel inhibits mitosis and cell division by inhibiting the microtubular assembly [33]. Preclinical studies have shown that gemcitabine acts as an exfoliant



for urothelial cells. This increases the penetration of docetaxel and therefore has enhanced efficacy [34].

Retrospective studies have shown that this combination is a promising intravesical combination in BCG failure cases. Milbar et al. showed in a retrospective analysis of 33 BCG unresponsive patients that 1-year recurrence-free survival [RFS] is 49% and 34% in 2 years [35]. Steinberg et al., in another retrospective analysis of 45 patients, showed treatment success of 66% at first surveillance, 54% at one year, and 34% at two years [36].

Steinberg et al. presented the preliminary results from a multi-institutional retrospective study of 276 BCG failure patients. The median follow-up was 22.9 months. Recurrence-free survival after 1 and 2 years was 60% and 46%, respectively. High-grade recurrence-free survival rates were 65% and 52%, respectively [37].

#### 4.3.4.1 Administration of gemcitabine and docetaxel

The patient should be pre-treated with an oral alkalinizer. Pre-treatment with ondansetron helps to control gemcitabine-induced vomiting. Six intravesical instillations are given for induction as follows:

- 1 gm gemcitabine in 50 ml NS with a dwell time of 90 minutes.
- The bladder is drained without rinsing.
- 40 mg of docetaxel is diluted in 50 ml NS and given intravesical with a dwell time of 90–120 minutes.

Monthly maintenance is given 1–2 years [36, 37].

## 5. Nanoparticles

One nanometer is the scale at which many of the biological molecules operate inside the living cells. Nanoparticles accumulate in tumor tissues. This occurs via the enhanced permeability and retention [EPR] effect because the tumor tissues have a more permeable vascular supply, and this allows the nanoparticles to enter the cell. Nanoparticles can be used for the encapsulation of poorly soluble drugs [38].

Abraxane - nanoparticle albumin-bound version of paclitaxel. Nanoparticle albumin bound-paclitaxel has five times higher solubility as compared to docetaxel. Mckiernan et al. have studied this nanoparticle albumin-bound paclitaxel in 28 patients in a phase I single-center trial. Complete response was seen in 10 patients. The Median follow-up was 21 months. There was no progression in 19 out of 28 patients. Their adverse events were limited to grades 1 and 2. The authors concluded that intravesical nab-paclitaxel had a 35.7% response rate in patients with NMIBC and BCG failure.

## 6. Future directions

After many years of stagnation, multiple new therapies are being investigated as potential intravesical agents for NMIBC. Strict criteria to define the disease have encouraged trials for patients with NMIBC. Most active trials focus on high-risk NMIBC in BCG naïve and BCG failure settings [39]. Multiple combination therapies continue to emerge. **Table 2** shows the various ongoing trials based on intravesical chemotherapy.

<b>Trial</b>	<b>Phase</b>	<b>Drug used</b>	<b>Trial number</b>
Neoadjuvant Short-term Intensive Chemoresection Versus Standard Adjuvant Intravesical Instillations in NMIBC	III	Mitomycin C	NCT03348969
CALIBER - A Phase II Randomized Feasibility Study of Chemoresection and Surgical Management in Low Risk Non-Muscle Invasive Bladder Cancer	I	Mitomycin C	NCT02070120
A Randomized, Single-Dose, Double-Blind, Placebo-Controlled Phase 3 Study of Qapzola™ [Apaziquone] as a Chemotherapy Adjuvant to Transurethral Resection of Bladder Tumors in Patients with Low- To-Intermediate-Risk NMIBC [CONQUER]	III	Apaziquone	NCT03224182 CONQUER
Evaluation of Immediate Preoperative Instillation [IPOI] of Mitomycin C Compared to Early Post-operative Instillation [IPOP] in Non-muscle Invasive Bladder Cancer	III	Mitomycin C	NCT02075060
A Phase 1/2a Pilot Study of Intravesical TSD-001 for Treatment of Low-Grade, Stage Ta, Non-Muscle Invasive Bladder Cancer	I	TSD-001	NCT03081858
A Prospective, Open-label Randomized Clinical Trial of a Single Bladder Instillation of Mitomycin C vs. Gemcitabine vs. No Additional Treatment Immediately After Transurethral Resection of Bladder Tumor [TURBT]	III	Mitomycin C Gemcitabine	NCT02695771
The Effectiveness and Safety of Neoadjuvant Intravesical Mitomycin-C Instillation in Non-muscle Invasive Bladder Cancer Patients: Prospective, Randomized, Phase II Study	III	Mitomycin C	NCT03058757
Open clinical trial to evaluate the efficacy of intravesical instillation of hyaluronate added to early instillation of mitomycin vs. early instillation of mitomycin in patients suffering from low risk not muscle-infiltrating bladder cancer	I	Hyaluronate Chondroitin sulfate	EUCTR2016–003813- 92
A Phase 1b, Multicenter, Open Label Study Evaluating Safety, Tolerability and Preliminary Efficacy of GemRIS 225 mg in Subjects with Non-Muscle-Invasive Urothelial Carcinoma of the Bladder	III	Gemcitabine	NCT02720367
Randomized prospective clinical trial to evaluate the rate of early recurrence in non-muscle invasive bladder cancer between the chemohyperthermia [QH] with mitomycin-C prior to transurethral resection of bladder in ambulatory surgery program and post resection treatment with mitomycin C in normothermia.	III	Mitomycin C	EUCTR2015–005151- 27
HIVEC HR: Use of chemohyperthermia with intravesical mitomycin [HIVEC] for the treatment of patients with NMIBC	I	Mitomycin C BCG	EUCTR2016–001186- 85
HIVEC [Hyperthermic Intra Vesical Chemotherapy] for Patients with Intermediate Risk NMIBC Compared with Standard Intravesical Instillation Of Chemotherapy As Adjuvant Treatment. A Comparative, Prospective, Randomized Study.	III	Mitomycin C	EUCTR2013–002628- 18

Trial	Phase	Drug used	Trial number
A Phase 3 Study to Evaluate the Efficacy and Safety of Intravesical Nanoxel®M [Docetaxel-PM] In Bacillius Calmette-Guerin Refractory Non-Muscle Invasive Bladder Cancer	III	Docetaxel-PM Mitomycin-C	NCT02982395
A Phase I Trial for the Use of Intravesical Cabazitaxel, Gemcitabine, and Cisplatin [CGC] in the Treatment of BCG-Refractory Non-muscle Invasive Urothelial Carcinoma of the Bladder	I	Cabazitaxe Gemcitabine Cisplatin	NCT02202772
A Multi-center, Single-Arm Study Evaluating the Efficacy of Synergo® Radiofrequency-Induced Thermochemotherapy Effect [RITE] With Mitomycin C [Synergo® RITE + MMC] in CIS Non-Muscle Invasive Bladder Cancer [NMIBC] Bacillus Calmette-Guérin [BCG]-Unresponsive Patients with or without Papillary NMIBC	III	Synergo RITE + MMC	NCT03335059

**Table 2.**  
*The ongoing clinical trials based on intravesical chemotherapeutic agents.*

Food and drug administration gave guidelines on designing trials in NMIBC as follows: [40].

- High-risk NMIBC
  1. Trials can include a mix of high risk and CIS cases
  2. Time to an event is the preferred endpoint
  3. Placebo-controlled trials of BCG are not helpful.
  4. The duration of follow-up should be at least 18–24 months.
- High-risk BCG refractory
  1. No standard of care in this group.
  2. Single-arm trials can be used if they provide robust results
  3. Patients having BCG refractory CIS should have a complete response rate of 40–50% at six months and at least 30% response rate at 18–24 months.
- Placebo trials

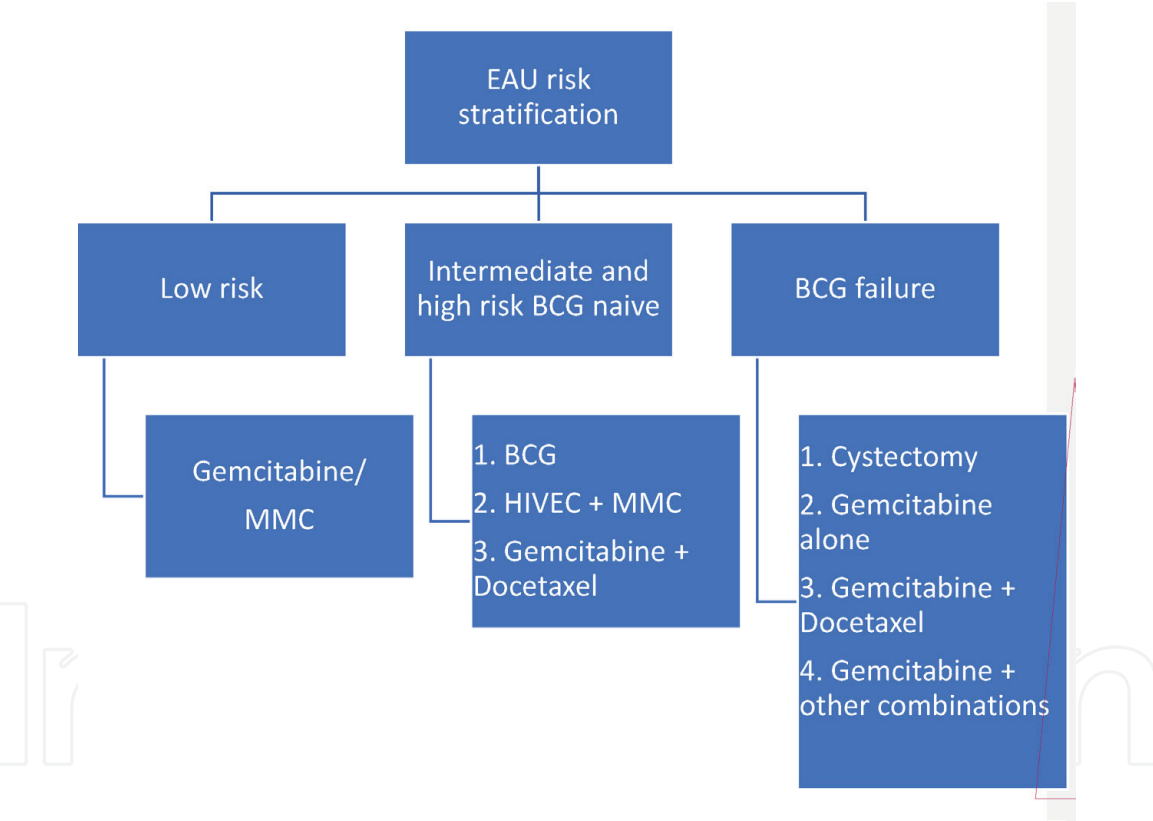
These can be used in low-risk patients.
- Perioperative intravesical instillation agents
  1. Time to event analysis should be used
  2. Follow-up of at least two years
  3. The clinically meaningful result is defined as a 15% event rate reduction or a hazard ratio of 0.7.

7. Conclusion

The **Table 3** and **Figure 1** summarizes the various advancements in intravesical chemotherapy in NMIBC and **Figure 1** also gives the intravesical chemotherapy of choice in various risk categories.

Risk	Advancement
Low risk	<ul style="list-style-type: none"><li>Gemcitabine can also be used as a 1st line agent for single instillation post TURBT</li></ul>
Intermediate and high-risk BCG naive	<ul style="list-style-type: none"><li>Single agent - HIVEC + MMC show favorable response.</li><li>Combination – Gemcitabine + Docetaxel combination is under research</li></ul>
BCG failure	<ul style="list-style-type: none"><li>Gemcitabine alone or in combination can be if cystectomy is contraindicated or refused.</li></ul>

**Table 3.**  
*Summary of the various advancements in intravesical chemotherapy in NMIBC.*



**Figure 1.**  
*EAU risk stratification based intravesical chemotherapy of choice in various risk categories.*

Conflict of interest

The authors declare no conflict of interest.

Appendices and nomenclature

European association of urology 2021 non-muscle invasive bladder cancer risk stratification:



### Risk group stratification and Characteristics

1. **Low-risk tumors** - Primary, solitary, TaG1 [PUNLMP, LG\*], < 3 cm, no CIS.

2. **Intermediate-risk tumors** - All tumors not defined in the two adjacent categories

3. **High-risk tumors** - Any of the following:

- T1 tumor
- G3 [HG\*\*] tumor
- carcinoma *in situ* [CIS]
- Multiple, recurrent and large [> 3 cm] TaG1G2/LG tumors [all features must be present]

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