

Heated Intravesical Chemotherapy Biology and Clinical Utility



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KEYWORDS

- Bladder hyperthermia • Heated chemotherapy • Heated mitomycin • Intravesical chemotherapy
- Intravesical mitomycin • HIVEC

KEY POINTS

- Heat can improve drug delivery, increase cancer cell sensitivity to therapeutic agents, and trigger anticancer immune responses.
- Three methods of bladder heating are available clinically: external deep regional radiofrequency heating, intravesical catheter radiofrequency heating, and recirculating conductive heating.
- Administering intravesical chemotherapy with heat is safe and seems to improve treatment efficacy.

INTRODUCTION

Bladder cancer (BC) is the fourth most commonly diagnosed cancer in men and more than 75% are non-muscle invasive BC (NMIBC) at diagnosis.^{1,2} NMIBC is generally treated with transurethral resection of the bladder tumor (TURBT) as a first step. In high-grade tumors, a repeat TURBT is often performed to ensure complete tumor removal and the absence of muscle-invasive cancer.³ Patients determined—based on grade, stage, number of tumors, size of tumors, and so on—to be at intermediate or high risk of recurrence are usually treated with adjuvant intravesical chemotherapy or Bacillus Calmette-Guerin (BCG). BCG-treated patients are generally offered maintenance therapy for 1 year if they fall under intermediate risk or 3 years if they are high risk.⁴ Despite these years of active therapy, many (up to one-half) patients with NMIBC experience a disease recurrence.⁵ For those patients whose

tumors are BCG unresponsive, radical cystectomy is the standard of care salvage treatment, but carries a significant morbidity and mortality risk.⁶ For this reason, most patients faced with the prospect of cystectomy inquire about bladder preserving alternatives and one such alternative is the combination of intravesical chemotherapy with heat.

HYPERTHERMIA AS A TREATMENT FOR NON-MUSCLE-INVASIVE BLADDER CANCER

The application of mild fever range heat (40°C–44°C) to the bladder is called hyperthermia (HT).⁷ HT is different from thermal ablation where temperatures reach 60°C to 90°C. In general, HT can be used to (1) improve drug delivery to the bladder, (2) kill malignant urothelial cells directly, (3) improve BC sensitivity to chemotherapy, and (4) trigger anticancer immune responses.^{8–10}

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Drug Delivery

When a tumor is heated to between 38°C to 42°C, several important vascular physiologic effects occur. Local vasodilation occurs and results in increased blood flow to the tumor and adjacent tissue.¹¹ The warmer environment causes the lipid-protein membrane bilayer that contains cells to become more permeable, resulting in easier drug penetration into the cell through the cell membrane. These 2 mechanisms work synergistically to make an already leaky tumor vasculature even leakier, a phenomenon known as the enhanced permeability and retention effect.¹² By increasing the enhanced permeability and retention effect, HT improves drug delivery to bladder tumors, which in turn leads to better tumor cell destruction.

Cytotoxicity

Because tumors are characterized by a constant state of a relatively inadequate resource supply, their microenvironment develops a hypoxic, acidotic, and energy-deprived character.¹³ HT to greater than 42°C further alters blood flow to the tumor microenvironment, further depriving the tumor of the oxygen and nutrients that it needs to survive.¹³ Morphologic changes observed when this occurs include an outflow of cytoplasm into the interstitial space, endothelial swelling, changes of the viscosity of blood cell membranes, and microthrombosis.^{11,14} Tumor cells are more sensitive to HT than normal urothelial cells and therefore suffer a lot more during mild heating.

Improving Sensitivity to Therapeutic Agents

Multiple antineoplastic agents have been shown to be more efficacious when administered to a heated tumor,¹¹ and the thermal enhancement ratio (TER) quantifies the degree to which heat affects drug efficacy.¹⁵ The TER compares the ratio of cell kill at 43°C to that at 37°C, with drugs possessing a TER of greater than 1 working better with heat. Chemotherapeutic agents used to treat BC such as cisplatin, mitomycin C (MMC), gemcitabine, and doxorubicin all have a TER of greater than 1.3.¹⁶ It is noteworthy that the timing of heating relative to chemotherapy exposure may be important. For example, gemcitabine seems to work better when administered 24 hours after HT.¹⁷

Anticancer Immune Responses

Temperature is a well-known regulator of immune function.¹⁸ Some relevant effects of HT on immunity include changes in number and phenotype of tumor-infiltrating leukocytes, improved tumor-

infiltrating leukocyte function, and cytokine release.¹⁹ HT also causes heat shock protein release from tumor cells, particularly heat shock protein 70 and heat shock protein 90, resulting in the cross-priming of antigen-specific cytotoxic T lymphocytes.²⁰ The consequence is that HT-treated tumors actively participate in their own demise by leading to a form of self-vaccination.

METHODS OF DELIVERING BLADDER HYPERTHERMIA

Although there are many ways to categorize devices for HT, the most obvious category to both the patient and the clinician is how the heat is delivered, namely, external vs internal. External devices use energy emitters to apply heat to a field within the body. They incorporate treatment planning systems to optimize the dose delivered and minimize damage to adjacent tissue, similar to the dose planning used in radiation therapy.

External Devices

One type of external heating is deep regional radiofrequency, which uses an array of radiofrequency emitters to focus heat into the body. These devices require a medical physics team and a radiofrequency shielded room, which increases cost and decreases generalizability to office-based locations where NMIBC is typically treated. Furthermore, owing to the risk of heating implanted metal, external radiofrequency-based heating is generally contraindicated in patients with implanted medical devices (eg, pacemakers) and hip replacements.²¹ The BSD 2000 system (Pyresar Medical, Salt Lake City UT) is an example of an external deep regional radiofrequency device. It uses electromagnetic phased array applicators to deliver deep tissue HT and allows control of the 3-dimensional pattern of therapy specific to the patient's tumor.^{22–26} For bladder HT, the patient has temperature probes placed in the rectum and bladder to monitor the internal temperature. A water-filled applicator is then placed over the lower abdomen/pelvis and water is circulated to cool the skin during therapy. Another example is the AMC device, now sold as the Alba 4D system (Medlogix, Rome, Italy), which also uses radiofrequency arrayed systems to achieve deep tissue HT.^{22,27–29} As with the BSD system, it is coupled with a water bolus temperature control apparatus. Other electromagnetic systems include the ThermoTron, CanCure, Dubai, UAE (only available in North Africa and the Middle East) and the Celsius42 devices (Celsius42, Eschweiler, Germany). A significant advantage of the Celsius42 system is that it does not require a

shielded room, although its use has not been studied in NMIBC.

High-intensity focused ultrasound (HIFU) is another form of external heating. As the name suggests, HIFU uses the focused soundwaves in an accurate and specific manner to increase the temperature of the tumor without harming adjacent tissue. The commercially available HIFU systems are large devices that externally deliver HIFU. There is a laparoscopic probe that uses a single transducer to image and deliver HIFU to the tumor in a more precise, albeit invasive manner.³⁰

Internal Devices

Internal devices lack the depth of penetration of external devices but have the significant advantage of delivering heat almost exclusively to the bladder. There are 2 systems that use conductive HT the Combat bladder recirculating system (BRS) (innoMedicus, Cham, Switzerland) and Unithermia (EIMedical, Hod-Hasharon, Israel).^{31,32} Both devices externally heat fluid and the circulate it to the bladder via a 3-way irrigating Foley catheter. The recirculating fluid contains a chemotherapy agent chosen by the treating physician. Recirculating systems are the smallest, most portable, and least expensive bladder heaters. Synergo (Tigard, OR) produces a third intravesical bladder heating system that also uses recirculating bladder irrigation, but instead of a heat exchanger it uses a microwave radiofrequency emitting intravesical catheter to heat the bladder.^{33–35} The Synergo device is presently the most well-studied device among those mentioned, although several large trials of the Combat BRS device have accrued and will report results soon.

There are 2 additional devices worth mentioning, electromotive drug administration (EMDA) and nanoparticles. Although in the strict sense, these are not HT devices, they do share a similar therapeutic mechanism. EMDA uses a urethral catheter to deliver ionized drugs intravesically. Dispersive pads (similar to electrocautery) are placed on the lower abdomen and an electric current is applied intravesically to drive the drug into the urothelium at a rate proportional to the amount of current being applied. EMDA allows for greater depth of penetration than would be achievable by passive diffusion alone.³⁶ Nanoparticles can be administered intravenously or intravesically and they preferentially accumulate in tumors secondary to the enhanced permeability and retention effect.³⁷ Externally delivered light or alternating magnetic fields generates heat in the tissue hosting the nanoparticles.

CLINICAL EXPERIENCE WITH BLADDER HYPERTHERMIA

The combination of heat and intravesical chemotherapy has been used both in the neoadjuvant (before TURBT) and adjuvant settings (after TURBT). For this review, we use HIVEC as the acronym for hyperthermic intravesical chemotherapy. The large majority of HIVEC treatments done thus far have used MMC as the chemotherapy agent.

Phase I and II Trials

To date, there are 5 clinical trials of neoadjuvant chemo ablative HIVEC for NMIBC and all used MMC. In these trials, 60% to 100% of patients had previously undergone some form of intravesical therapy (**Table 1**). The complete response rate of patients who underwent HIVEC ranged from 53% to 75% with a partial response rate of 20% to 47%. The recurrence rate ranged from 13% to 39% at a median follow-up of 15 to 39 months.^{34,38–41}

The first trial of MMC HIVEC was conducted by Colombo and colleagues³⁹ in 1995, where 44 patients underwent neoadjuvant administration of intravesical chemotherapy and simultaneous local bladder HT for eight 60-minute sessions done twice weekly, followed by TURBT 3 weeks later. The complete response rate was 70%, partial response was 20% and no response in 9% of patients. After a mean follow-up of 24 months, 16% recurred.³⁹ In 2004, Gofrit and colleagues³⁴ treated 52 patients with high-grade NMIBC with MMC HIVEC. Of these, 28 men were treated with neoadjuvant HIVEC (MMC 80 mg) and 24 men adjuvant HIVEC (MMC 40 mg). More than 50% of both groups have been previously treated with BCG. Recurrence-free survival was 71% at a median follow-up of 15 months. Surprisingly, in the neoadjuvant cohort, 75% of patients achieved complete response to therapy.³⁴ Subsequently, there were 2 randomized trials conducted by Colombo and colleagues^{40,41} where neoadjuvant HIVEC (MMC 40 mg) was compared with standard MMC, or to EMDA (MMC 40 mg) and standard MMC. HIVEC achieved a complete response in 66% of patients in both studies, compared with 22% for standard MMC and 40% for EMDA.^{40,41}

There are 3 phase I and II adjuvant trials reporting recurrence-free survival. In these 3 trials, the patient cohort consisted of intermediate and high-grade NMIBC. The 1- and 2-year recurrence-free survival rates range from 67% to 87% and 50% to 91%, respectively (**Table 2**).

Soria and colleagues³² used the Unithermia device, which delivers heat via conducting heating. In

Table 1
Phase I and II trials and observational studies on neoadjuvant intravesical chemothermia therapy

Author and Year	Study Design	Sample Size	Treatment	Heat Source	Induction Schedule	Maintenance Schedule for CR Group	Patients with Previous Intravesical Treatment (%)	Follow-up (%)	CR (%)	PR (%)	NR (%)	Recurrence Rate (%)
Colombo et al, ³⁹ 1995	Phase I	44	30 mg MMC in 60 mL water for 40 min	Synergo (42.5–44.5°C)	Twice weekly within 6 wk (total of 8 sessions)	—	63.6	24 mo (mean)	70.4	20.4	9.1	15.9
Gofrit et al, ³⁴ 2004	Phase I	28	(40 mg MMC dissolved in 50 mL of distilled water for 20 min) ×2	Synergo (42 ± 2°C)	Once weekly ×8	Once monthly ×4	60.1	15.2 mo	75	—	—	19
Sousa et al, ³⁸ 2014	Phase I	15	80 mg MMC dissolved in 50 mL of distilled water for 60 min	Combat BRS (42 ± 1°C)	Once weekly ×8	Partial responder treated once weekly ×4, then once monthly ×11. CR did not receive maintenance	74	29 mo	53	47	0	13.3
Colombo et al, ⁴⁰ 1996	Phase II	29	(40 mg MMC in 50 mL distilled water for 30 min) ×2	Synergo (42.5–46°C for 60 min)	Once/twice weekly ×6–8	—	100	38 mo	66	34	0	27
		23	40 mg MMC in 50 mL sterile water for 60 min	—	Once/twice-weekly ×6–8	—	100	36 mo	22	26	52	39

Colombo, ⁴¹ 2001	Phase II	36	40 mg MMC in 50 mL of saline for 60 min	—	Once weekly ×4	—	—	—	27.7	—	—	—
		29	40 mg MMC diluted in 50 mL of distilled water for 60 min	Synergo (mean of 42.5°C)	Once weekly ×4	—	—	—	66	—	—	—
		15	40 mg MMC dissolved in 150 mL of distilled water and EMDA for 20 min	Physionizer 30	Once weekly ×4	—	—	—	40	—	—	—
Rigatti et al, ³⁵ 1991	Observational	12	30 mg MMC dissolved in 60 mL of distilled water for 60 min	SB-TS 100 (41.5–43.5°C)	Once/twice-weekly ×6–8	—	—	16 mo	41.7	33.3	25	8.3
Moskovitz et al, ⁴⁸ 2005	Observational	10	(40 mg MMC dissolved in 50 mL of distilled water for 30 min) ×2	Synergo (42 ± 2°C)	Once weekly ×8	Once monthly ×4	80	5.6 mo (mean)	80	—	—	—
Witjes, ⁴⁹ 2009	Observational	26 (100% CIS)	(40 mg MMC dissolved in 50 mL of distilled water for 30 min) ×2	Synergo (41–44°C for 60 min)	Once weekly ×6	Once every 6 wk ×6 (total of 6 sessions)	66.7	22 mo	92	—	—	22

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Table 1
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Author and Year	Study Design	Sample Size	Treatment	Heat Source	Induction Schedule	Maintenance Schedule for CR Group	Patients with Previous Intravesical Treatment (%)	Follow-up	CR (%)	PR (%)	NR (%)	Recurrence Rate (%)
Moskovitz et al, ⁵⁰ 2012	Observational	26	(40 mg MMC dissolved in 50 mL of distilled water for 30 min) ×2	Synergo (approximately 42°C)	Once weekly ×8	Once every 6 wk for first year (20 mg MMC)	76.9	9 mo	79	8	13	16
Volpe et al, ⁵¹ 2012	Observational	14	(40 mg MMC dissolved in 50 mL of distilled water for 30 min) ×2	Synergo (42 ± 2°C)	Once weekly ×8	Once monthly ×6	100	14 mo (mean)	42.9	9.9	47.2	46.3
Sousa et al, ³¹ 2016	Observational	24	80 mg MMC dissolved in 50 mL of distilled water for 60 min	Combat (43 ± 0.5°C)	Once weekly ×8	Once monthly ×6	33	37 mo	62.5	33.3	4.2	31.3

Dose in the maintenance group is similar to treatment unless stated otherwise.

Abbreviations: BRS, bladder recirculating system; CIS, carcinoma in situ; CR, complete response; HT, hyperthermia therapy; NR, no response; PR, partial response.

Table 2
Phase I, II, and III trials and observational studies on adjuvant intravesical chemothermia therapy

Author and Year Published	Trial	Sample Size	Treatment per Session	Heat Source	Induction Schedule	Maintenance Schedule for CR Group	Risk Group (% Patients)	Hx of Intravesical Therapy (% Patients)	Follow-up, Median (IQR)	1-y RFS (%)	2-y RFS (%)	5-y RFS (%)
Gofrit et al, ³⁴ 2004	Phase I	24	(20 mg MMC in 50 mL of distilled water for 20 min) ×2	Synergo (42 ± 2°C)	Once weekly ×8	Once monthly ×4	High grade (100)	87.5	35.3 mo (mean)	66.5	60.6	52.1
Soria et al, ³² 2016	Phase I and 2	34	(40 mg MMC in 50 mL saline for 22 min) ×2	Unithermia (42.5 ± 1°C)	Once weekly ×6	Once monthly ×4	High grade (53) Low grade (47)	100	41 (–)	85.4	73.5	55.2
van der Heijden et al, ⁴² 2004	Phase II	90	(20 mg MMC in 50 mL of distilled water for 30/60 min) ×2/1	Synergo (41–44°C)	Once weekly ×6–8	Once monthly ×4–6	High risk (41) Intermediate risk (59)	66.1	18 (4–24)	86.7	75.4	—
Colombo et al, ⁴³ 2003	Phase III	42	(20 mg MMC in 50 mL of distilled water for 30 min) ×2	Synergo (42 ± 2°C)	Once weekly ×8	Once monthly ×4	High grade (90.5)	—	24 mo (–)	88.7	82.8	61.7
		41	20 mg MMC in 50 mL of distilled water for 60 min	—	Once weekly ×8	Once monthly ×4	High grade (97.6)	—		50.3	38.4	21.3
Arends et al, ⁴⁴ 2016	Phase III	92	(20 mg MMC in 50 mL of distilled water for 30 min) ×2	Synergo (42 ± 2°C)	Once weekly ×6	Once every 6 wk for the first year	High grade (81.6) Low grade (18.4)	52	24 mo (–)	90.5	80.2	—
		98	BCG (Oncotice) full dose for 120 min	—	Once weekly ×6	Three weekly doses at 3, 6, and 12 mo	Intermediate risk (67.4) High risk (32.6)	—		75.8	66.5	—

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Table 2
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Author and Year Published	Trial	Sample Size	Treatment per Session	Heat Source	Induction Schedule	Maintenance Schedule for CR Group	Risk Group (% Patients)	Hx of Intravesical Therapy (% Patients)	Follow-up, Median (IQR)	1-y RFS (%)	2-y RFS (%)	5-y RFS (%)
Tan et al, ⁴⁵ 2019	Phase III	48	(20 mg MMC in 50 mL of distilled water for 30 min) ×2	Synergo (42 ± 2°C)	Once weekly ×6	Once every 6 wk for the first year, once every 8 wk for the second year	High grade (100)	100	36 mo (range, 23.1–44.5 mo)	49.8	35	—
		56	BCG or standard of care at institution	—	Once weekly ×6	Three weekly instillations at 3, 6, 12, 18, and 24 mo	High grade (100)	100		56.7	42.1	—
Moskovitz et al, ⁴⁸ 2005	Observational	22	(20 mg MMC dissolved in 50 mL of distilled water for 30 min) ×2	Synergo (42 ± 2°C)	Once weekly ×6–8	Once monthly ×4–6	High grade (68.2) Low grade (31.8)	63.5	9.6 mo (mean)	100	70	—
Nativ et al, ⁵² 2009	Observational	111	(20 mg MMC in 50 mL solution for 30 min) ×2	Synergo (42 ± 2°C)	Once weekly ×6	Once every 4–6 wk ×6	High grade (61) Low grade (39)	100	16 mo (range, 2–74 mo)	85	56	—
Halachmi et al, ⁵³ 2011	Observational	56	(20 mg MMC for 30 min) ×2	Synergo (42 ± 2°C)	Once weekly ×6	Once every 4–6 wk ×6	High grade (100)	54	18 mo (range, 2–49 mo)	77	42.9	—
Moskovitz et al, ⁵⁰ 2012	Observational	66	(20 mg MMC in 50 mL solution for 30 min) ×2	Synergo (approximately 42°C)	Once weekly ×6	Once every 6 wk for first year	High grade (45.5) Low grade (51.5) Not reported (1.5)	74.2	23 mo (range, 3–84 mo)	86.5	67.2	—
Volpe et al, ⁵¹ 2012	Observational	16	(20 mg MMC dissolved in 50 mL of distilled water for 30 min) ×2	Synergo (42 ± 2°C)	Once weekly ×6	Once monthly ×6	High grade (100)	100	14 mo (mean)	87.5	58.6	—

Maffezzini et al, ⁵⁴ 2014	Observational	42	40 mg MMC dissolved in 50 mL of distilled water for 60 min	Synergo (42.5 ± 1.5°C)	Once weekly ×4	Once every 2 wk ×6, then once monthly ×4	High grade (100)	64.3	38 mo (range, 4–73 mo)	88.1	80.2	63.5
Ekin et al, ⁵⁵ 2015 (APJCP)	Observational	43	40 mg MMC dissolved in 50 mL of distilled water for 60 min	UniThermia (42.5–45°C)	Once weekly ×6	Three weekly instillations at month 3 and 6	High grade (58.1) Low grade (41.9)	—	30 mo (range, 9–39 mo)	82	61	—
Ekin et al, ⁵⁶ 2015 (CJU)	Observational	40	40 mg MMC in 50 mL saline solution for 60 min	UniThermia (42.5–45°C)	Once weekly ×6	Three-weekly instillations at month 3 and 6	High grade (60) Low grade (40)	—	33 mo (range, 24–39 mo)	92.2	73.6	—
Sooriakumaran et al, ⁵⁷ 2016	Observational	97	40 mg MMC dissolved in 50 mL of normal saline for 60 min	Synergo (41–44°C)	Once weekly ×6–8	Once every 6 wk for the first year, one every 8 wk for the second year (20 mg MMC)	High grade (100)	90.7	27 mo (range, 16–47 mo)	82.7	66.0	48.6
Sousa et al, ³² 2016	Observational	16	40 mg MMC dissolved in 50 mL of distilled water for 60 min	Combat (43 ± 0.5°C)	Once weekly ×4	No	High risk (71) Intermediate risk (29)	81.3	24 mo	100	88.1	—

Dose in the maintenance group is similar to treatment unless stated otherwise.

Abbreviations: BCG, Bacillus Calmette-Guerin; CR, complete response; HT, hyperthermia therapy; Hx, history; IQR, interquartile range; RFS, recurrence free survival.

this study, 34 patients with recurrent, intermediate risk NMIBC underwent a 6-week course of HIVEC (MMC 40 mg) for 45 minutes. The 1-, 2-, and 5-year RFS were 85%, 74%, and 55%, respectively. The other 2 trials used the Synergo system in high- and intermediate-risk NMIBC. Patients in both studies received 2 30-minute sessions of HIVEC (MMC 20 mg) for 6 to 8 cycles. The 1- and 2-year RFS ranged from 67% to 87% and 61% to 75%.^{34,42}

Phase III Trials

To date, there are no phase III trials using neoadjuvant HIVEC for NMIBC, but there are 3 adjuvant HIVEC trials. In 2003, Colombo and colleagues⁴³ randomized 83 patients (>50% with high risk NMIBC) to HIVEC versus standard MMC. In both arms, patients received 20 mg/50 mL of MMC for two 30-minute sessions for 6 weeks. The 2-year RFS and 5-year RFS were 83% versus 38% and 62% versus 21% for HIVEC and standard MMC, respectively. The hazard ratio for HIVEC was 0.21.

Arends and colleagues⁴⁴ subsequently reported a phase III randomized, controlled trial where 190 patients with intermediate and high risk NMIBC were randomized to HIVEC or BCG. Patients in the BCG arm received induction OncotICE BCG

+ maintenance at 3, 6, and 12 months. HIVEC patients received MMC (20 mg/50 mL) for 2 30-minute sessions for 6 weeks, and maintenance course (3 cycles) at 3, 6, and 12 months. The 2-year RFS was better for HIVEC (82%) than BCG (65%).

More recently, in the HYMN trial 104 patients with BCG unresponsive NMIBC were randomized to HIVEC (MMC 20 mg/50 mL) versus standard MMC. Patients received induction followed by 3 once-weekly maintenance instillations at 3, 6, 12, 18, and 24 months. There was no statistical difference in RFS between the arms at 2 years (hazard ratio, 1.33; 95% confidence interval, 0.84–2.10; $P = .23$).⁴⁵ At a median follow-up of 35 months, the rate of disease progression was 8%.

In addition to the trials noted, there are 6 observational studies of neoadjuvant HIVEC and 10 of adjuvant HIVEC and these are summarized in **Tables 1** and **2**.^{28,31,35,46–57} Recurrence-free survival curves from the various studies using the Synergo, Combat BRS and Unithermia devices are pooled and shown in **Fig. 1**.

CLINICAL EXPERIENCE WITH ELECTROMOTIVE DRUG ADMINISTRATION

The combination of MMC and EMDA has been used both in the neoadjuvant (before TURBT)

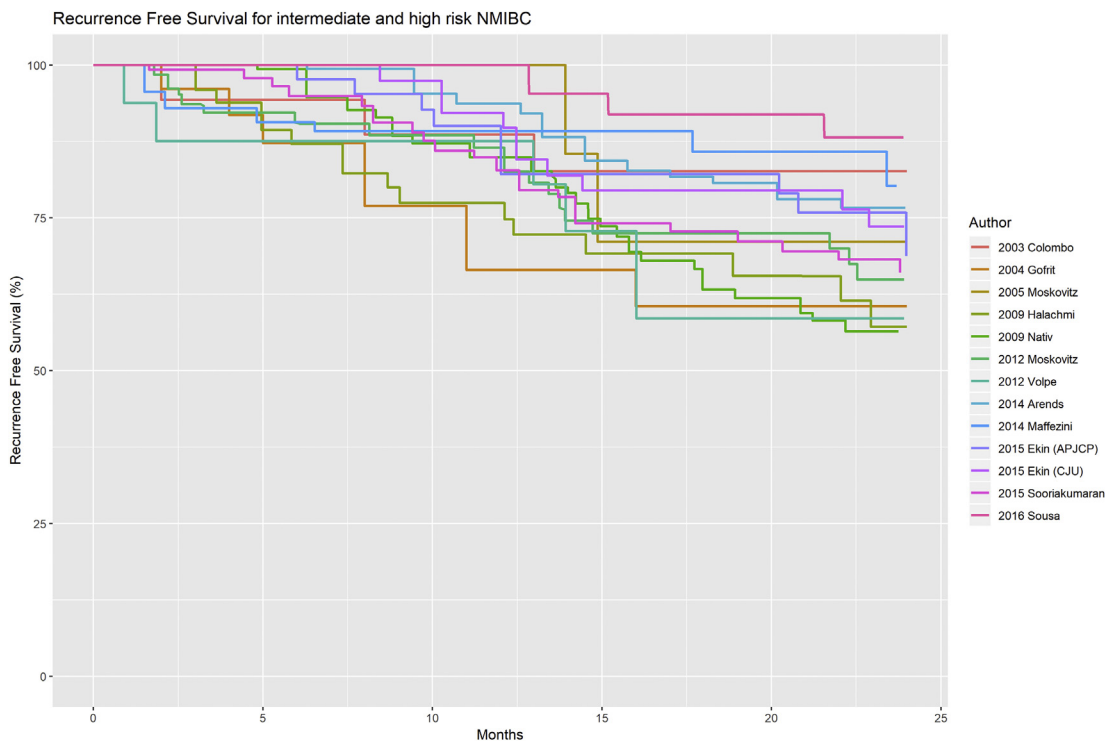


Fig. 1. Combined Kaplan-Meier graph of recurrence free survival (RFS) for all studies on chemothermia therapy for intermediate and high risk non-muscle invasive bladder cancer.

Table 3
Adverse events from Phase I, II, and III trials and observational studies on intravesical chemothermia

Author, Year	Study Type	N	Energy	Complete Treatment (%)	Grade ≥ 3 Adverse Events (%)	Hematuria (%)	UTI or Sepsis (%)	Stricture (%)	Allergic Reaction (%)
Colombo et al, ³⁹ 1995	Phase I	44	RITE	—	—	—	—	2	2
Gofrit et al, ³⁴ 2004	Phase I	52	RITE	96	—	2	10	2	10
Sousa et al, ³⁸ 2014	Phase I	15	Conduction	—	0	20	13	0	7
Soria et al, ³² 2016	Phase I/II	34	Conduction	88	12	—	4	—	—
Colombo et al, ⁴⁰ 1996	Phase II	29	RITE	93	—	—	—	0	—
Colombo et al, ⁴¹ 2001	Phase II	29	RITE	100	0	—	—	—	—
van der Heijden et al, ⁴² 2004	Phase II	90	RITE	100	—	9	0	4	9
Colombo et al, ⁴³ 2003	Phase III	42	RITE	69	—	7	0	7	12
Arends et al, ⁴⁴ 2016	Phase III	184	RITE	—	—	—	—	—	—
Tan and Kelly, ⁶⁵ 2018	Phase III	48	RITE	90	10	48	23	6	15
Moskovitz et al, ⁴⁸ 2005	Observational	47	RITE	—	4	17	0	6	4
Nativ et al, ⁵² 2009	Observational	111	RITE	95	8	19	2	5	8

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Table 3
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Author, Year	Study Type	N	Energy	Complete Treatment (%)	Grade ≥ 3 Adverse Events (%)	Hematuria (%)	UTI or Sepsis (%)	Stricture (%)	Allergic Reaction (%)
Alfred Witjes et al, ⁴⁹ 2009	Observational	26	RITE	92	—	3%	—	—	—
Halachmi et al, ⁶⁷ 2011	Observational	56	RITE	91	—	4	0	2	12.5
Moskovitz et al, ⁵⁰ 2012	Observational	92	RITE	96	4	7	1	5	1
Volpe et al, ⁵¹ 2012	Observational	30	RITE	100	—	27	7	0	13
Maffezzini et al, ⁵⁴ 2014	Observational	42	RITE	88	0	62	0	0	0
Ekin et al, ⁵⁵ 2015 (APJCP)	Observational	43	Conductive	93	12	9	0	0	7
Ekin et al, ⁵⁶ 2015 (CJU)	Observational	40	Conductive	95	—	—	—	—	—
Sooriakumaran et al, ⁶⁸ 2016	Observational	97	RITE	93	7	14	23	0	0
Kiss et al, ⁴⁷ 2015	Observational	21	RITE	62	52	24	0	10	10
Sousa et al, ³¹ 2016	Observational	40	Conductive	98	8	23	23	3	3

Abbreviations: RITE, radiofrequency-induced thermo-chemotherapeutic effect; UTI, urinary tract infection.

Table 4
Clinical trials and observational studies on adjuvant intravesical MMC and EMDA

Author and Year Published	Trial	Sample Size	Treatment per Session	EMDA Device/Current	Induction Schedule	Maintenance Schedule for CR Group	Risk Group (% Patients)	Hx of Intravesical Therapy (% Patients)	Follow-up, Median (IQR)	1-y RFS	2-y RFS	5-y RFS
Di Stasi et al, ⁵⁹ 2003	Phase III	36	40 mg MMC in 100 mL of distilled water for 60 min and EMDA	20 mA for 30 min	Once weekly × 6	Nonresponders: second induction course Responders: Once monthly × 10	High grade (100)	—	43 mo	100	66	38
		36	40 mg MMC in 100 mL of distilled water for 60 min	—	Once weekly × 6	Non-responders: second induction course Responders: Once monthly × 10	High grade (100)	—		100	62	34
		36	81 mg BCG in 50 mL saline for 120 min	—	Once weekly × 6	Nonresponders: second induction course Responders: Once monthly × 10	High grade (100)	—		100	39	21
Di Stasi et al, ⁶⁰ 2006	Phase III	105	81 mg BCG for 120 min	—	Once weekly × 6	Once monthly × 10	High grade (100)	41	88 mo (63–110)	73	77	56
		107	(Week 1 and 2: 81 mg BCG for 120 min Week 3: 40 mg MMC in 100 mL of distilled water and EMDA) × 3	20 mA for 30 min	3 cycles (9 wk total)	Month 1, 2, 4, 5, 7, and 8: MMC + EMDA Months 3, 6, and 9: BCG	High grade (100)	42		100	49	40

(continued on next page)

Table 4
(continued)

Author and Year Published	Trial	Sample Size	Treatment per Session	EMDA Device/Current	Induction Schedule	Maintenance Schedule for CR Group	Risk Group (% Patients)	Hx of Intravesical Therapy (% Patients)	Follow-up, Median (IQR)	1-y RFS	2-y RFS	5-y RFS
Di Stasi et al, ⁶³ 2011	Phase III	124	TURBT	—	Once	Low-risk: none	High grade (82)	No previous intravesical treatment	92 mo (61–126)	62	42	37
		126	TURBT + immediate postoperative 40 mg MMC in 50 mL water for 60 min	—	Once	40 mg MMC dissolved in 50 mL of sterile water for 60 min weekly ×6	High grade (81)		82 mo (50–125)	65	47	43
		124	Neoadjuvant 40 mg MMC in 100 mL water for 30 min and EMDA + TURBT	20 mA for 30 min	Once	High risk: 81 mg BCG dissolved in 50 mL of saline for 120 min weekly ×6	High grade (82)		85 mo (57–126)	87	70	62
Riedl et al, ⁶¹ 1998	Observational	22	40 mg MMC in 100 mL saline	15 mA for 20 min	Once weekly ×4	—	High grade (95)	—	7.3 mo (mean)	—	—	—
Gan et al, ⁶² 2016	Observational	22	(Week 1 and 2: BCG Week 3: 40 mg MMC and EMDA) ×3	Physionizer® 30: 20 mA for 30 min	3 cycles (9 wk total)	(Once weekly BCG) ×3 on month 3 and every 6 mo for 3 y	High grade (100)	—	24 mo	86	80	—

Dose in the maintenance group is similar to treatment unless stated otherwise.

Abbreviations: BCG, Bacillus Calmette-Guerin; CR, complete response; Hx, history; IQR, interquartile range; RFS, recurrence free survival; TURBT, transurethral resection of the bladder tumor.

and adjuvant settings (after TURBT). Intravesical EMDA MMC is administered using a controlled electric current of up to 30 mA using a battery-powered generator. A specialized 16 Fr catheter is inserted and urine drained. MMC is then instilled with an operating current of 15 to 20 mA pulsed electrical current for 20 to 30 minutes per session. To date, 2 small clinical trials have used EMDA in the neoadjuvant setting (**Table 3**) and 4 studies have used EMDA in the adjuvant setting (**Table 4**). EMDA was found to have a complete response rate of 40% in the neoadjuvant setting.^{41,58} In the adjuvant setting, EMDA was found to have a 1-, 2-, and 5-year RFS rate of 86% to 100%, 49% to 80%, 38% to 40%, respectively.^{59–62} One study evaluated TURBT, TURBT with immediate postoperative MMC and neoadjuvant MMC with EMDA followed by TURBT. Patients with intermediate-risk and high-risk disease in all 3 groups were then placed on maintenance MMC and BCG, respectively. The group that received neoadjuvant MMC with EMDA followed by TURBT had the highest 5-year RFS of 62% compared with 37% in the TURBT-only arm.⁶³

Safety

The first bladder HT treatment was attempted in 1972 where Thiotepa was used in conjunction with HT up to 44°C for low stage bladder tumors.⁶⁴ Since then, multiple adverse events that include hematuria, urinary tract infection, sepsis, stricture, allergic reaction to chemotherapy agent, dysuria, frequency, urgency and incontinence have been reported (**Table 3**). There were insufficient data to pool for grade 3 or higher adverse events, urinary tract infection, sepsis, and allergic reaction. The rate of grade 3 or higher adverse event rate ranges from 10% to 12% across all sources of energy in patients receiving HT in clinical trials published.^{31,65} Urinary tract infection and sepsis occurred in 0% to 23% of patients, and strictures in 0% to 10%.⁶⁵ Allergic reaction occurred in 0% to 15% of patients.⁶⁵ Pooling data for randomized controlled trials showed that the relative risk of hematuria in the HT arm is 1.28 (95% confidence interval, 0.89–1.83; $I^2 = 0$) when compared to the non-HT arm.

Future Perspectives and Other Novel Agents

For intermediate-risk NMIBC, HIVEC-I (EudraCT 2013–002628–18) and HIVEC-II (ISRCTN 23639415) are multi-institutional randomized controlled trials comparing HIVEC with standard MMC in patients with intermediate-risk NMIBC. Both trials have completed accrual (n = 598 subjects combined). HIVEC-HR (EudraCT 2016–

001186–85) is assessing HIVEC in high-risk NMIBC and HIVEC-R (EudraCT 2014–005001–20) is assessing HIVEC as neoadjuvant chemoablation. All of these trials are using the Combat BRS device. Lastly, the RITE-USA trial (NCT03335059) is assessing HT with the Synergo device for BCG-unresponsive NMIBC.

A novel temperature-sensitive liposome drug delivery system is worth highlighting here. The first drug, called ThermoDox is developed at Duke. It is loaded with doxorubicin and is administered systemically to releases free drug when it arrives in tissues heated to 41°C or greater. When combined with bladder HT, this technology allows for organ-specific targeting of systemic agents. In a swine model, ThermoDox is able to achieve doxorubicin levels far exceeding free doxorubicin while minimizing toxicity in other organs.⁶⁶

SUMMARY

Intravesical chemotherapy and HT therapy is safe and able to augment the efficacy of intravesical chemotherapy for the treatment of BCG refractory NMIBC, especially in a time of BCG shortage. Further prospective randomized controlled trials combining other forms of chemotherapy with HT therapy is warranted to determine if improved efficacy is obtained in those drugs. Other combinations of therapy such as combining HT and intravesical chemotherapy therapies such as programmed death-1/programmed death ligand 1 blockade is also warranted.

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