Chapter 2

Intravesical Chemohyperthermia for NMIBC: Rationale and Results of This Developing Treatment

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Abstract

Bladder cancer is the fourth most common cancer in men, and the lifetime risk of getting bladder cancer is 2.4%. Approximately 75% of newly diagnosed cases of bladder cancer are non-muscle-invasive bladder cancer (NMIBC), and half of them will show recurrence and/or progression after transurethral resection. Therefore, after transurethral resection, in high-risk patients, intravesical therapy is mandatory. However, bacillus Calmette-Guérin (BCG) is associated with important side effects such as systemic tuberculosis and bladder retraction. Chemohyperthermia (CHT) has shown a 60% lower recurrence rate than standard mitomycin C (MMC). However, its effectiveness in high-risk patients, especially CIS and BCG refractory patients, is even more important. CHT will probably be an option for patients unsuitable for radical cystectomy or those on whom BCG can't be used. Two main technologies are currently available for intravesical CHT: microwaves and recirculating heated fluids. Both of them have pros and cons that should be known and evaluated by a urologist. In this chapter, we will speak about rationale, technical options, clinical results, ongoing studies, and future perspective for this interesting treatment option for intermediate and high-risk patients with NMIBC.

Keywords: NMIBC, MMC, BCG, chemohyperthermia, radio frequency, recirculant systems, adjuvant, neoadjuvant

1. Background

In 2002, the world-adjusted incidence rate of bladder cancer was 33 new cases/100,000 inhabitants/year. That makes it the fourth tumor with the highest incidence in men, after lung, prostate, and colorectal cancers [1].

Each body tumor has unique characteristics in terms of its presentation, histological types, surgical approaches, and sensitivity to different types of treatment (surgery, chemotherapy, radiotherapy).

Approximately, 95% of bladder neoplasms are urothelial carcinomas, and 75% of them will be diagnosed as non-muscle-invasive tumors. However, they have a high tendency to recur, and one-third of them will reappear during the first 5 years after transurethral resection. Incidence of recurrence and progression is directly related to the tumoral grade and stage, being higher in carcinoma in situ and T1G3 tumors.

Most recidives have similar grade and stage to the original tumor. However, a significant number of bladder cancers progress to invasive tumors whose prognosis and treatment are completely different. Therefore, intravesical postoperative therapy is mandatory, especially in those with medium and high-risk tumors.

The urethra allows ease of access from the outside, which generally allows a resection of the tumor and the application of chemo- and/or immunotherapy locally with minimal systemic toxicity.

Intravesical chemotherapy, *with single postoperative or with maintenance protocols*, is the usual treatment for patients with low and intermediate risk of non-muscle-invasive bladder cancers (NMIBCs). Their side effects are well tolerated, but there is general consensus that chemotherapy is effective in reducing short-term risk for recurrence, but its efficacy is only marginal in the long term [2].

On the other hand, immunotherapy with bacillus Calmette-Guérin (BCG) is the gold standard treatment for high-risk patients. However, BCG is associated with important side effects such as systemic tuberculosis and bladder retraction [3]. Moreover, in the recent past, there has been a limited availability of BCG, which has made us change our old protocols for new ones using a lower dose or reducing the number of instillations. Clearly, there is a scope to optimize and improve current intravesical chemotherapy.

Many new treatment approaches are being researched to increase the effectiveness of adjuvant intravesical therapy. One of the developing treatments for high-risk NMIBC is the combination of intravesical chemotherapy and hyperthermia, called chemohyperthermia (CHT).

Chemotherapy combined with thermal energy has proven higher anticancer activity than chemotherapeutic instillation alone at diminishing recurrence rates. It also appears to improve the bladder preservation rate. Moreover, in the future, CHT may become a standard therapy for high-risk patients with recurrent tumors, for patients who are unsuitable for radical cystectomy, and in cases for which BCG is contraindicated [4].

In this chapter, we will speak about rationale, technical options, clinical results, ongoing studies, and future perspective for this interesting option of treatment for intermediate and high-risk patients with NMIBC.

2. Intravesical therapies for the treatment of NMIBC

2.1. Historical review

The first intravesical treatments can probably be traced to the eleventh century. In the third book of his treatise *Canon of Medicine*, Avicenna described how to inject a list of drugs into the bladder through a hollow cylindrical instrument [5].

The first description of specific intravesical treatment for bladder cancer was carried out in the 1950s by Walton and Sinclair [6]. In the following years, radioactive solutions of sodium bromide and colloidal gold were used with relative success but also important complications.

Jones and Swinney [7] described in 1961 the use of intravesical thiotepa which was later the first intravesical drug FDA approved for NMIBC; however, its side effect rates were high, so it was not commonly used.

Mitomycin C (MMC) is a cross-linking agent that inhibits DNA synthesis, which was discovered by Wataki et al. [8] in 1962. Seven years later, Ogawa [9] instillated MMC simultaneously with radioactive phosphorus, but its toxicity was high. In the following year, Shida et al. [10] published the first results by using intravesical MMC. Almost a decade went by before Kaufman et al. [11] began using it in the USA who was followed a few years later by German urologists. Due to its high molecular weight (329 kDa), there is reduced risk of transurothelial absorption, and side effects are minimal [2].

In 1976, Morales et al. [12] demonstrated the power of immunotherapy to treat bladder cancer by showing BCG effectiveness in patients with carcinoma in situ. Both treatments, chemotherapy with MMC and immunotherapy with BCG, became the gold standard of intravesical therapy for low-medium and high-risk patients, respectively.

Many other drugs and immunotherapeutic agents have been tried against NMIBC in the last half century, but intravesical chemotherapy with MMC remains the most widely used worldwide. However, the reduction of tumoral recurrences is not very high, and even this small difference is lost after 2 years of follow-up, and tumoral progression is not reduced [2].

2.2. What limits the effectiveness of intravesical chemotherapy?

From the evolutionary point of view, the urinary bladder appeared in amphibians as a reservoir to store urine with intention of using it for osmotic regulation of the body by reabsorbing water and sodium in the case of dehydration. However, mammals have an impermeable bladder used as a simple urine reservoir which allows them to eliminate it only a few times a day. Thus, the animal would seek a convenient time to expel it, rather than eliminate it continuously, thereby avoiding the creation of an odorous trail that could be traced by possible predators [13].

Urine contains urea and other toxic substances which have been removed from the bloodstream by the kidney. If they were newly reabsorbed by the bladder, it would be a serious

problem to the body. For this reason, the bladder of higher animals has evolved as an almost completely waterproof bag which is also resistant to toxic chemicals present in it.

This is achieved through four fundamental mechanisms [14, 15]. First, the turnover of the urothelium is the slowest of all epithelia in the body. After the division of basal cells, the urothelial cells need 200 days to progress before flaking into the bladder. Due to this slowness in cell division, urothelial cells rarely enter mitosis, and therefore its DNA is less exposed to intravesical toxins. Second, there are some specialized cells called "umbrella" on the endoluminal surface, which have lateral interdigitations and proteins called "uroplakins." Both structures keep umbrella cells intimately connected to their neighbors in an almost completely waterproof way. Third, urothelial cells possess surface structures called "asymmetric unit membrane" (AUM) in both lumen and intraepithelial cells. AUM works as membrane-binding sites for cytoplasmic microfilaments. Its intraepithelial location and association with microfilaments support the hypothesis that AUM has a mechanical function and modulates the surface area of the cell during the relaxation-contraction cycle of the urinary bladder maintaining tightness even at the time of maximum dilatation [16]. And fourth, to help strengthen the sealing, the endoluminal surface of the bladder is covered by a thick layer of negatively charged glycosaminoglycans. This charge is responsible for the electrical rejection of many compounds present in urine and whose resorption would be toxic to the body.

Low absorption of the MMC is not due solely to the waterproof properties of the bladder wall but also to the characteristics of the drug. The MMC is a high molecular weight molecule (*334* Dalton), with a weak negative charge and a relatively hydrophobic behavior. These features make absorption through the urothelium less than 3% of the amount instilled which severely limits its effectiveness [2].

Pharmacokinetic studies [17–19] have shown that systemic absorption of the MMC does not reach significant plasma levels. Average of MMC plasma concentration on patients treated after urothelium recovery was 5.24 ng/mL. Conversely, absorption of MMC instilled immediately after TUR reaches an average of 50 ng/mL, which varies significantly with the resected surface of the bladder mucosa ($p < 0.026$). However, even given immediately after TUR, the MMC fails to achieve the minimum accepted as myelotoxic dose of around 400 ng/mL.

2.3. Why does NMIBC recur so often?

Urothelial bladder carcinoma appears in the form of two main phenotypic variants. The most frequent (80%) is papillary tumors of medium or low grade. Of these, 33–70% will reappear in the first 5 years and 4–9% progress to invasive disease. By contrast, 20% of urothelial carcinomas are high grade (T1-GIII or carcinoma in situ). Of these, one 68–80% will relapse in the first 3 years and, 13–23% will progress to invasive disease [20].

It is important to know what are the mechanisms of recurrence are to try to reduce them. It is thought that there are a total of four mechanisms potentially involved.

The first and clearest is incomplete tumor resection (*evidence level 1*). Its incidence is clearly related to the quality of TURB performed. According to the guidelines of the European Association of Urology, when performing a re-TUR in patients with T1 tumors, 33–53% have residual tumor, and 10% presented infiltrative tumors (T2) after the second TUR-B [20].

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In some publications, the numbers of residual tumor reach a high of 78%, and 25–40% of cases will be restaged to more advanced tumors [21]; the surgical methodology of these centers must be reviewed.

In 2006, Divrik et al. [22] compared the efficacy of TUR-B + 8 weeks of MMC (Group 1:68 pts) vs the second TUR-B + 8 weeks of MMC (Group 2:74 pts) in patients with T1 bladder carcinoma achieving significant differences. Disease-free survival at 1 and 3 years was 47 and 37% for Group 1 vs 86 and 68% for Group 2. Recurrences of GII and GIII were 64 and 90% for Group 1 vs 25 and 60% for Group 2. Finally, they observed progression in 11.7% of Group 1 vs 4% in Group 2.

Based on recurrence-free survival as well as the grade and stage of the tumors relapsed, they concluded that recurrences are due to residual tumor and that intravesical chemotherapy post-TUR-B does not compensate inadequate tumor resection.

The second mechanism is the reimplantation of circulating tumor cells that are released during the TUR-B. This process was demonstrated by Soloway et al. [23] by introducing transplantable tumor cells (1×10^6) in the bladder of 50 mice of which half had part of the urothelium electrocoagulated, while the other half did not. Tumoral implants occurred in 54% of mice with burned bladder mucosa, while it appeared in only 12% of those with an intact bladder ($p < 0.005$). They further showed that immediate intravesical MMC, thiotepa, and cisplatin significantly reduced the occurrence of tumoral implants.

The first clinical use of this principle was made by Solsona et al. [24, 25] who administered a dose of MMC within the first 24 hours post-TUR-B and found a decrease in the number of relapses at 2 years in patients with low-risk tumors.

Numerous studies to date have demonstrated its usefulness in significantly reducing tumor recurrence in the first year, regardless of maintenance treatment during this time whether preformed [26] or not [27] ($p < 0.02$). One-year recurrences with immediate instillation ranged from 3.2 to 11.3%, while in the control group ranged between 18.7 and 29%. Although differences persist within 2–3 years, they are not significant statistically [25–27]. A recent meta-analysis quantified the effect on a 1.35 absolute reduction of relapses and the need to treat 7.2 patients to prevent recurrence [28]. However, the main problem with the immediate postoperative instillation is the severe side effects, which may appear if MMC reaches the bladder fat and surrounding organs, which would have devastating consequences [29].

The third cause of relapse is the possible growth of small preexisting microscopic lesions (*which cannot be considered insufficient resections*) originating around the initial tumor and which share genetic characteristics with the original tumor; this area is called *preneoplastic urothelial plate* (*PUP*). The first recurrence seen on patients treated with immediate MMC post-TUR-B appears at 40 months and does so four times more frequently in the area of the previous tumor, in other words, arising from the same PUP [30].

Finally, recurrences may appear years later, by gradual malignization of other dysplastic areas. In fact, first tumoral recidives are four times more frequent in a neighboring area of the original tumor, while only 13% are multifocal. However, from the sixth recurrence, 100% of tumors are multifocal [30]. Once this point is achieved, there are significant clinical implications, which have to be taken into account when choosing patient treatment [31].

PUP theory is based on studies of different vesical urothelial clones by inactivation of chromosome X. This investigation showed that the bladder is lined with a mosaic made up of numerous clones, which are derived from a single stem cell. Each bladder contains about 200–300 patches of 1–2 cm^2. There are usually preexisting genetic alterations in most urothelial tumors, usually located in chromosome 9. Some toxins act by inducing additional genetic changes in the carcinogenesis step process until you get to a point where abnormal cell proliferation is initiated then a hyperplastic epithelium that can develop into cancer in one or more PUP [32].

MMC instillation with extended maintenance has been shown to reduce the number of tumor recurrence in intermediate-risk patients. However, this treatment has no effect on tumoral progression and global survival [33, 34]. Moreover, comparative studies between MMC and BCG have shown that BCG is clearly superior in intermediate and high-risk tumors [33, 34]. To explain this data, we must understand the pathophysiology and pharmacokinetics of MMC applied within the bladder.

3. What is antineoplastic hyperthermia?

Also called thermotherapy, it is a type of therapy for tumors in which the whole body, or part thereof, is subjected to high temperatures (up to 45°C). Numerous studies have shown that high temperatures damage and kill cancer cells by denaturation of their proteins and by preventing DNA repair. However, hyperthermia causes little damage to normal tissue [35, 36].

The first clinical experiences in the use of hyperthermia as a treatment for cancer were performed by Coley [37] more than a century ago. He injected bacterial toxins of *Streptococcus erysipelas* and *Bacillus prodigiosus* with the intention of producing fever. He supposed that fever would activate the immune system and heal a patient with an inoperable sarcoma.

Hyperthermia is almost always used with other forms of treatment for cancer [35, 38]. Numerous studies have shown that hyperthermia makes cancer cells more sensitive to radiation and chemotherapy. These studies have been conducted on different cancers such as sarcoma, melanoma, and cancers of the bladder, brain, breast, cervix, esophagus, lung, rectum, and peritoneal metastases [35, 38–43].

Hyperthermia may be applied in different ways such as to the entire body (*whole body*), regional, intracavitary, local, and interstitial. Similarly, sources of heat are varied and include microwaves, ultrasound, radio frequency, and recirculating liquid systems.

In the case of bladder tumors, there are two types. The first, used in infiltrating cancers, involves the application of external heat on the entire pelvis associating radio- or chemotherapy [42].

The second, used in NMIBC, consists of the intravesical application of heat through microwaves or recirculation of heated liquids. In this type of treatment, a chemotherapeutic agent is associated to the heat in order to achieve a synergistic effect by using both treatments together, which is known as CHT [40, 42].

3.1. Mechanism of action of antineoplastic hyperthermia

The human body has several independent mechanisms to regulate its temperature within appropriate ranges for an adequate function of all its organs. They include vasodilation plus sweating against heat and by body tremors plus vasoconstriction against cold [44]. The body's metabolic processes serve as the main sources of internal heat generation.

The normal thermoregulatory response begins when sensory receptors on the surface of the skin or organs of the core body are activated depending on their temperature thresholds. The information is integrated along their way to the hypothalamus, the main thermoregulatory center. The efferent thermoregulatory answer of the hypothalamus is sent to effector organs of the body to trigger a response able to recover thermic homeostasis [44, 45]. Clinical effects produced by antitumoral hyperthermia are summarized in **Table 1**.

Temperature range	Direct cytotoxic effects	Immune effects	Vascular effects	Others
39–41°C	Slight growth arrest	Initial increase intracellular HSP followed by increase of extracellular HSP - Signals to immune cells - Cross priming of CD8+ T cells - Dendritic cell activation - Natural killer activation - Increase cytocine release (IL-6, IL-10)	Vasodilatation which means: Improved tumor blood flow - Improved tissular O2 - Reduced acidosis - Improved drug absorption	Increased drug delivery Increased drug solubility Increased efficacy of many chemotherapeutic drugs - MMC - Gemcitabine - Cisplatin - Cyclophosphamide - Doxorubicin
41–43°C	Reversible growth arrest - Mainly in phases M and S - Brief RNA synthesis impaired - Prolonged DNA synthesis impaired			
43–45°C	Irreversible growth arrest - Permanent protein denaturalization - DNA repair impaired - Activation of both apoptotic routes	Altered cytocine production Inactivation of immune cells Reduced expression of extracellular HSP	Reduced tumor blood flow due to vascular collapse - Microthrombosis - Endothelial cell damage - Vessel permeation - Increased acidosis and reduced tissular O2	

Table 1. Action mechanism of chemohyperthermia in NMIBC.

3.1.1. Direct cytotoxic effects of hyperthermia

Hyperthermia has cytotoxic effects on tumor cells by means of several mechanisms, including improved antitumoral immunity by direct cytotoxic effects.

The first phase of direct death is characterized by stopping the linear growth, characterized by decreased synthesis of RNA (*short*) and DNA (*prolonged*) specifically in the S phase but also slowing the M phase of the cellular cycle [36, 45–47]. The G1 and G2 phases are relatively protected due to the temperature-dependent expression of heat shock proteins (HSPs) [48]. Tumoral cells reached a state of rapid division circumventing the apoptotic pathways and avoiding the normal detention mechanisms of the cell cycle. If the cell division speed is turned down, this would allow apoptotic mechanisms to kill tumoral cells. During this phase direct cytotoxicity occurs between 41 and 43°C and is reversible after heat removal.

In addition, heat interferes with the ability of the cell to repair damaged proteins produced as a result of chemotherapy or radiotherapy. It is believed that these proteins play a key role in the activation of apoptotic pathways. Deficiencies in DNA repair mechanisms become evident only at 40°C and continue to worsen when temperatures are higher [49]. Above 43°C, an exponential and irreversible growth arrest occurs, and its intensity is dose and time dependant [50]. This phase is characterized by disruption of the cell membrane and denaturation of cellular and transmembrane proteins, distortion of cellular architecture, and ultimately activation of apoptotic and necrotic pathways.

3.1.2. Antitumoral immune response to hyperthermia

The body's ability to use temperatures within the range of fever (39–41°C) to enhance immune system function against infection is well documented [51]. Activation state of the immune system depends on degree and duration of the applied heat [52]. However, we can only subject the patient to temperatures achievable with fever, those which are achievable in vivo. Dendritic cells, natural killer (NK) cells, and phagocytes that play a key role in antitumoral immune mechanisms are directly activated by hyperthermia. HSPs are chaperone tumor-related antigens that can be released or become apparent on the tumoral surface as a result of chemotherapy, radiation, or heat [53].

These HSPs act as stimulating antigens for dendritic cells [54, 55]. Then, these dendritic cells present tumoral antigens to macrophages and T cytotoxic cells CD8+ leading to the release of pro-inflammatory and proapoptotic cytokines that increase tumoral cell destruction [54–56].

When in the extracellular space, HSPs bind to cancer cells' surface to help identify them for cells of the immune system [52]. Increased expression of intercellular adhesion molecules (ICAM) resulting from hyperthermia also leads to increased lymphocyte trafficking to sites where tumoral antigens are present, helping adaptive response against cancer cells [57]. Furthermore, hyperthermia activates the innate immune system by improving the ability of NK cells to destroy tumoral cells [58].

In vitro temperatures above 43°C may cause paradoxical immune responses to the aforementioned, but these responses are less interesting biologically since such high temperatures are difficult to reach and maintain in vivo [54]. While hyperthermia has been shown to enhance the efficacy of immunotherapy in a murine model of pulmonar metastasis [59], this combination has not yet been studied in bladder cancer.

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3.1.3. Vascular effects of hyperthermia

These effects are variable depending on the intensity of heat and the characteristics of the supplying vascularization. One of the first demonstrations of hyperthermia is vasodilation, which leads to an increase in blood supply to the tumor [60]. This effect enhances the tumor microenvironment for the action of the immune system by improving oxygenation and reducing acidosis [61]. The vasodilation effect is produced with temperature up until about 43°C, above which perfusion will decrease because of vascular collapse; this affects reoxygenation and drug delivery, complicating the empirical formulation of a thermal dose.

In renal tumors, vasodilation has shown an effect of "washing" of the chemotherapeutic and temperature reduction by increasing blood flow at 37°C. However, at the bladder urothelium, the caliber of the blood vessels is small, and its effects by washing the chemotherapeutic or reducing applied heat are very small.

With sustained high temperatures, the opposite effect occurs due to direct endothelial cell damage to the tumoral supplying vessels [62]. These vessels begin to present microvascular thrombosis with consequent decrease in blood flow that leads to the death of tumor cells by hypoxia.

Animal studies performed by Haas et al. [63] showed that hyperthermia alone reduced growth of implanted tumors. However, when administered simultaneously with chemotherapeutic agents its treatment effect increases in a significant way.

Similarly, Van der Heijden et al. [64] showed that chemotherapy and hyperthermia show a synergistic effect increasing the cytotoxicity of epirubicin, EO9, gemcitabine, and MMC. Also, they showed a significant synergy of heat and MMC against four bladder tumoral cell lines [64, 65].

3.1.4. Increased absorption of MMC by heat

Dalton et al. [18] studied that the pharmacokinetics of intravesical MMC observing the absorption thereof is significantly affected by dilution, urinary pH, and exposure time. They observed that, with passive instillations, the absorption of the administered dose is less than 30%.

In 2001, Paroni et al. [66] showed that microwave-induced hyperthermia increased MMC absorption, at 30, 45, and 60 min, significantly ($p < 0.008$). However, even higher plasma concentrations achieved with CHT (67 ng/mL), were six times lower than those needed to be myelosuppressive (approx. 400 ng/mL). Similar results were seen by Milla et al. [67] when causing hyperthermia by using recirculating heat liquids.

It is important to understand that increased MMC absorption is not only due to increased permeability of the bladder urothelium but also due to a significant increase in solubility. At 25°C the maximum concentration that we may get by dissolving 1 gr of MMC is 0.8 mg/mL. However, at 40°C, MMC concentrations up to 1.7 mg/mL can be reached when dissolving the same amount of it. (Data from *Kyowa Hakko Co Ltd*.).

3.2. Adjuvant CHT treatment (after TUR-B)

3.2.1. Clinical outcomes: tumoral recurrences

In 2011, a meta-analysis which was composed of a total of 22 studies showed a 59% reduction in tumor recurrences in the group chemohyperthermia against the MMC [4].

T1G3 and CIS tumors subgroup treated with CHT showed greater differences compared to the MMC at normal temperature were patients with T1G3 and CIS tumors. Witjes et al. [68] observed that 92% of patients treated with CHT showed complete eradication of the tumor and only 50% had recurrence after 30 months of follow-up.

Similar results were seen with conductive heat technology; our group found [69] a recurrence-free disease rate of 87.5% in high-risk patients treated with combat recirculant CHT and followed during 2 years. However, Ekin et al. [70] showed that the recurrence-free rates of high-risk patients treated with BWT recirculant CHT were 82 and 61% at 1 and 2 years of follow-up

The first randomized trial comparing CHT vs BCG was published by Arends et al. [71]. They observed a recurrence-free survival after 2 years of follow-up of 78% in the CHT group vs 64.8% with BCG ($p < 0.0082$). Progression was lower than 2% in both groups (p = ns). On the other hand, Ekin et al. [72] concluded that CHT was not as effective treatment as BCG in high-risk NMIBC patients who are BCG naive. The 2-year recurrence-free interval in CHT and BCG groups was 76.2 and 93.9%, respectively, ($p = 0.02$). However, it was a retrospective propensity score-matched study to compare the efficacy of BCG and chemohyperthermia.

Some studies have shown a long-term effect of treatment with CHT. Colombo et al. [73] published results of 65 NMIBC medium-high risk patients treated with CHT or standard MMC and they found that disease-free survival at 10 years was 53% in the group CHT compared to 15% with standard MMC ($p < 0.001$).

Probably, the most important conclusion of the mentioned meta-analysis [4], *and which seems to be confirmed with all subsequently published studies*, is that in the future, the CHT may become a standard treatment for high-risk patients with recurrent tumors that are unfit for radical cystectomy or when BCG treatment is contraindicated.

3.2.2. Tumoral progression after CHT and bladder preservation rates

Lammers et al. [4] also noted that only 0–8% of patients had tumor progression and although this figure is lower than that observed with standard MMC, follow-up duration was too short and cannot draw definitive conclusions.

The survival of patients who failed intravesical therapy and progress to muscle-invasive disease is worse than that of those with NMIBC from the time of diagnosis. Schrier et al. [74] found a cancer-specific survival at 3 years of 37% for patients who progressed to NMIBC, compared to 67% achieved by patients who originally showed with infiltrative tumors. These results were also confirmed by Guzzo et al. [75].

Several studies have investigated the role of CHT in the rescue NMIBC that has not responded to other intravesical treatments. Ayres et al. [76] prospectively evaluated 38 high-risk patients who had failed after BCG and were treated with CHT and found a 50% survival-free disease at 2 years which is a significant success rate for these kinds of patients.

Some comparative studies between BCG failure patients and non-previously treated patients showed better results in the former group. The interim analysis of the Lombardia project (*unpublished data from R. Colombo, Milan, Italy*) showed that, after two years of follow-up, the recurrence-free rates of patients treated with de novo CHT were significantly better than those who had previously failed intravesical treatment (91 and 62%, respectively, $p < 0.006$). Similarly, Van der Heijden et al. [77] followed 76 patients treated with CHT for 2 years, observing a 42% recurrence in the group with a previous failed BCG treatment compared to a 24% recurrence rate in the de novo treatment group.

However, others like Witjes et al. [78] observed no difference in the response rate among patients who had failed BCG and those without ($p = 0.63$). Similarly, Halachmi et al. [79] did not observe any difference in the rate of recurrence at 4 years among those who had failed BCG and those without (46 vs 44%, respectively, $p = 0.54$).

Overall, although the results of CHT in patients who have failed prior to other intravesical regimens are heterogeneous, the truth is that they managed to rescue a significant number of failures after BCG with CHT which is a major advantage of this treatment regimen.

The overall rate of bladder preservation after CHT was 87.6% compared to 79% for MMC (p = ns). Of the 357 patients in all studies, only 38 patients (10.6%) underwent radical cystectomy. Eleven cases (3.1%) were due to tumor progression, other 25 cases (7.0%) due to a high incidence of recurrences, and other 2 cases ($p < 0.006\%$) because of bladder retraction or miction worsening [4].

Similar data were published by Moskovitz et al. [80], with 72% free of recurrence and only 4.7% progression rate in patients who received adjuvant treatment with CHT.

A sequential treatment study using intravesical BCG and CHT was performed in Leicester, UK, to treat 33 high-risk NMIBC patients (*including 40% with Cis*) who were followed during a median of 16 months [81]. Three of them (9%) did not respond and were proposed for radical cystectomy. Two (6%) showed tumoral progression and were treated with radiotherapy. The other 85% of them were disease-free after follow-up.

3.3. Neoadjuvant CHT treatment (before TUR-B)

The rationale about neoadjuvant CHT is based on three main ideas. First, all published data seems to support the idea that apoptotic tumoral cells destroyed by the neoadjuvant CHT treatment stimulate the immune response against them acting as a vaccine against cancer. Second, in patients with tumors unable to be resected with only one TUR-B, Neoadjuvant CHT could diminish number and/or size of tumoral implants avoiding need of a second surgery, this treatment could offer both a more effective treatment and better value for the health-care provider, as they might not need a second TUR-B. Third, many early recurrences are

based on growth of minimal tumoral implants which were not seen during surgery and that neoadjuvant CHT is able to eliminate.

Colombo et al. [82] evaluated for the first time the clinical efficacy of neoadjuvant CHT in bladder cancer in 1998. In that study, a total of 19 patients who had tumors that were unresectable in one surgical time or a radical cystectomy was indicated due to its extension. After 8 weekly doses of CHT, the TUR-B was possible in just one surgical time in 16 patients (84%). The histological examination of the sample showed a 47% complete response (CR) and 37% partial response (PR). A radical cystectomy was performed in the remaining three patients because of the extent of the residual tumor. After an average of 33 months of follow-up, eight superficial recurrences were seen, and TUR-B was easily performed without having to remove the bladder.

In 2012, Moskovitz et al. [80] documented a 79% CR rate in a group of patients undergoing neoadjuvant CHT. But what is even more interesting is that 84% of those patients with complete response remained free of recurrence during the follow-up period and the 24% who recurred had TaG1 tumors.

It is important to mention that we do not know that CHT regime is more effective and less toxic. A phase 2 study of Colombo et al. [83] evaluated two CHT protocols including 27 patients each with 40 mg of MMC. Group A received a single weekly dose of MMC (40 mgrs) × 6 weeks, and Group B received 3 weekly doses of MMC (40 mgrs) × 2 months. A 7.4% of patients from Group B did not complete the treatment because of severe urinary local irritative symptoms; other side effects were similar in both groups. However, success rates of both groups were significantly different; histopathological examination of the TUR-B samples showed that only 44.4% of patients from Group A had CR, while 70.4% of Group B patients were free of tumor ($p = 0.04$)

Another study compared the recurrence rate at 5 years among patients who had received more or less than eight doses of CHT in a neoadjuvant setting. While the group receiving more than eight doses ($n = 170$) showed 40% of patients free of disease, the group receiving 8 or fewer doses ($n = 78$) showed only 15% of cases of disease-free ($p < 0.0002$) [68].

In 2014, our group published the results of a small series of 15 patients treated with eight weekly doses of recirculating neoadjuvant MMC achieving a 66.6% CR and 33% PR. As in the previous case, the beneficial effect of CHT remained in time and, after 3 years of follow-up, disease-free survival was 85%, and only two recurrent patients were treated with TUR-B and intravesical adjuvant MMC [84].

The most comprehensive and recent neoadjuvant study was published by Lüdecke et al. [85]; the study group consisted of 271 patients treated with 8 weekly doses of neoadjuvant CHT with MMC (40 + 40 mg). After TUR-B they observed that 76.1% had CR and another 7.6% showed PR.

Unlike our study, all patients with CR were given consolidation adjuvant CHT (six doses every 6 weeks of MMC (20 + 20 mg) for a total of 9 months of treatment [73]. With this treatment, they observed that 80.6% of patients were free of recurrence at 2 years.

It is important to mention that this group included 59.8% of patients who had failed after BCG, but even there, the percentage of patients free of recurrence in this group was 41.7 and 66.7%, respectively, among those who were already resistant to BCG and those who had relapsed early after such treatment.

A comparative study of the recurrence rate after neoadjuvant CHT vs a meta-analysis with BCG shows that after 5 years of follow the CHT group showed 64% of patients free of disease compared to 22% expected in the BCG group ($p < 0.0001$) [86].

3.4. CHT adverse events

Most published works show that the side effects were higher with CHT than with standard MMC, but this difference was not statistically significant; furthermore, these effects were usually mild and reversible. CHT has less systemic effects and bladder retraction than BCG but has more local effects such as spasm, hematuria, and dysuria [71]. In some cases there were severe or permanent side effects such as urethral perforation or bladder retraction [4, 69, 70].

With the microwave technology, the most common adverse events during treatment were spasms of the bladder (21.6%) and bladder pain (17.5%). Bladder spasms tend to occur more frequently with neoadjuvant treatment (17.8 vs 10.7%; $p = 0.398$) [1]. Similar results were seen with BWT™ [70, 73] and Combat™ [69, 84] recirculant systems. Side effects are frequent, but almost all cases were grades 1 and 2.

In our experience, with almost 800 recirculant instillations, only 3.1% of doses were delayed, and less than 1% were not performed. The main reasons for delating were infection, hematuria, and irritative chemical cystitis. The only reasons for anticipated end of the treatment were allergy and intolerance to catheterization.

Approximately 6% of doses were interrupted before 60 min usually because of bladder spasms or pelvic discomfort [69, 84]. Those patients who didn't tolerate the first dose well were orally premedicated with 600 mgs of ibuprofen or antispasmodic treatment depending on if they had complained of pain or spasms. In selected cases, spasmolytic IV was administered during treatment. Both oral medications such as IV proved effective to achieve a good tolerance in subsequent doses of CHT.

3.5. Comparison of treatments assisted by devices

Those forms of intravesical chemotherapy in which any device is used to improve the efficacy of intravesical chemotherapy are called "device assisted." There are fundamentally two: Electromotive drug administration (EMDA) enhances the absorption of MMC by using iontophoresis. On the other hand, there is CHT which is based on heating the bladder with the instilled chemotherapeutic drug.

EMDA is based on creating an electric current through three physicochemical principles (*iontophoresis, electroosmosis, and electroporation*) able to increase the migration of an electrically charged molecule through the bladder wall molecule. In this chapter, we are not going to

evaluate EMDA, but we recommend further investigation reading about it because it is a very interesting way to improve the effectiveness of intravesical chemotherapy.

EMDA has demonstrated reduction on tumoral recurrences compared to standard MMC. Some readers may want to know which delivery system is better, CHT or EMDA. Until now, there is no answer to this question; Colombo et al. [87] published in 2001 a pilot study with marker lesion which resulted in favorable results for CHT.

3.5.1. Microwave technology

The first CHT system approved for humans use was the Synergo™ system. It is a computer-embedded intravesical irrigation system combined with an energy-delivering unit. The system includes an RF generator that delivers radio-frequency energy at 915 MHz, a drug circulating unit, and a microprocessor with application-specific software. A triple lumen transurethral Foley catheter is used for drug intravesical instillation. It has thermocouples for bladder wall temperature monitoring and an RF antenna that radiates the bladder walls, causing phenotypical changes specifically in cancerous cells, creates membrane "micro-poring" and metabolic changes in these cells to increase the uptake of the drug, and enhances drug mobility (*becomes an active diffusion*). To avoid damaging temperatures being reached in the bladder, the Synergo™ system has a cooling circuit that keeps the intravesical temperature at acceptable levels.

Synergo™ system has been used for 15 years and has conclusive studies in both neoadjuvant and adjuvant settings. Clinical efficacy in high-risk patients (including BCG failures and CIS) has been proven. In fact, a 60% reduction of tumoral recurrences were observed when comparing to standard MMC has been demonstrated. Moreover, its superior results were maintained over periods of time as long as 10 years.

Both basic and clinical studies have shown a range of 4°C between different areas of the bladder when treated with Synergo™ [88]. This irregular distribution of the heat may be a significant inconvenience because it produces undertreated areas (40°C) or "cold spots," and others which were clearly cytotoxic temperatures are reached or "hot spots." In fact, the tip of the emitter rests at the posterior bladder wall producing burns in up to 60% of the patients which is not a serious problem that usually heals without complications

Another drawback, associated with its urethral catheter, which is 20fr, is that the microwave emitter is inside the probe which makes it very rigid, which makes it difficult to place for the clinician and uncomfortable for the patient. It may even cause urethral lesions in any of the repeated catheterizations required in a complete treatment. Kiss et al. [89], described that in a group of 21 patients treated with this device, 38% of them had to abandon the therapy because of the severity of the side effects including a case of urethral perforation.

The final drawback of the Synergo™ system is economical. As it is based on microwave technology, each disposable transurethral probe contains an expensive emisor—inside making the cost per patient quite high.

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3.5.2. Heated recirculating fluid technology

An alternative way to apply heat to the bladder is those systems based on recirculation of a solution of chemotherapeutic drugs heated externally and reintroduced to the bladder through a three-lumen catheter. Two different devices using this technology are currently available, Combat HIVEC™ BRS and BWT™ systems which are based on simple technology and use inexpensive disposables that make it attractive for performing CHT in a sustainable public healthcare system.

Both use a three-lumen-modified Foley catheter (HIVEC™ 16fr and BWT™ 18fr) which is soft and flexible, avoiding most problems related to urethral catheterization compared to other technologies.

Both try to maintain the chemotherapeutic solution at a fixed temperature, but there are some differences between them.

The Combat HIVEC™ BRS system uses an external aluminum heat exchanger ensuring efficient heat transfer and accurate temperature control of 43°C within ±0.5°C should this be 0.5 of the set temperature in the inner urothelium while providing homogeneous drug distribution throughout the bladder. Because of the efficiency of its aluminum heat exchanger, it only needs 30 mL to prime the disposable set minimizing dilution and means that the chemotherapy only needs to circulate around the closed circuit at 200 mL/min to maintain the temperature accurately, and this minimizes the pressure exerted on the bladder. It has a range of safety controls, over temperature and high pressure, and auto cutoff function.

BWT™ uses external heating plates with plastic heat exchanger which delivers an exit temperature of 46.5°C to achieve an inlet temperature of 44.5°C of the chemotherapy fluid in order to maintain a temperature within ±2°C.

BWT™ disposable set has a priming volume greater than 50 mL, which increases dilution of the chemotherapy. It recirculates the chemotherapy at 300 mL/min in order to maintain temperature within 2°C, which creates more pressure in the bladder compared to Combat HIVEC™ BRS system.

Patient safety and comfort are paramount to Combat HIVEC™ BRS. To achieve it, some special characteristics have been added. Whenever is desired, progressive increase of heat up to the final temperature (5 min) can be employed, which increases tolerance in sensitive patients. Moreover, if the tip of the catheter is blocked by bladder mucosa or for any other reason, the system can reverse the direction of circulation resolving the problem, which in some cases could cause pain or device malfunction.

Some doubts have been raised whether recirculating systems can achieve effective transfer of heat into the bladder and if they are able to stable temperatures throughout the bladder wall. This question has been answered by Longo from Duke University (USA) [90]. Measuring temperature with 16 surgically placed submillimeter fiber-optic microprobes and silicone germanium thermistors in swines' pelvic organs and at different depths of the bladder wall as well

as high-powered infrared cameras, they found a temperature gradient across the bladder wall (from urothelium to serosa) that was between 1.5 and 2°C, achieving a temperature across the inner urothelium of 42.9°C ±0.4.

Due to both devices being in use for very few years, the greatest drawback of recirculative systems is their limited number of studies and treated patients to confirm their effectiveness. To achieve it, Combat Medical Ltd. is performing multicentric studies in the UK and Spain, *across 20 hospitals*, called HIVEC™-I (303 patients), HIVEC™-II (259 patients), HIVEC™-R (68 patients), HIVEC™-PREMITO (151 patients), and HIVEC™-HR (50 patients), which are all recruiting and progressing well and should complete in 2017 with a complete population over 830 patients. Unfortunately, we have no information about ongoing studies performed with the BWT™ device. The main differences between all three devices may be seen in **Table 2**.

Device	**Synergo™**	**BWT™ system**	**Combat™**
Heat source	Intravesical 915 MHz microwave antenna *(Recirculating cooling system)*	External heating plates *(Recirculating heating system)*	External flat, low-volume heat exchanger *(Recirculating heating system)*
Target temperature and fluctuation	42.5 ± 3°C	44.5 ± 2°C	43 ± 0.5°C
Priming volume	±25 mL	±50 mL	±30 mL
Catheter characteristics	20fr Rigid (Radio-frequency emitter + cooling system inside)	18fr Flexible	16fr Flexible
Advantages	Strong supporting evidence *(neoadjuvant and adjuvant)* Long-term follow-up Proven superior to BCG Proven effectiveness against CIS Minimal dilution of MMC	Simple and cheap	Accurate temperature control and delivery Minimal dilution of MMC Good safety controls Proven effectiveness in sequential and neoadjuvant with medium-term follow-up Simple and easy to use Cheap
Disadvantages	Higher side effects Lower patient tolerance Intravesical hot and cold spots Expensive device and disposables Continuous operator control required throughout treatment	Limited clinical evidence Higher flow rates and operating pressure *(increase hematuria and reduce patient tolerance)* No pressure control or safety alarms	Limited evidence (*multicentric studies ongoing*)

Table 2. Characteristic of devices for intravesical CHT treatment.

3.6. Pharmacoeconomic evaluation

Bladder cancer is the most expensive tumor for public health services from the time of diagnosis to the patient's death [91].

We have studied the relationship between cost-effectiveness and budget impact of a neoadjuvant CHT in NMIBC patients and compared the results with standard treatment of BCG applying recurrence and progression values based on internationally accepted risk charts [92, 93].

For this reason, a model was designed from the perspective of a public health system after a follow-up of 3 years to compare the costs of implementing neoadjuvant CHT (*eight weekly instillations of 80 mg mitomycin C recirculating 43°C for 1 hour prior to TUR-B*) to costs of treating 15 patients with the same risk profile with standard adjuvant BCG treatment (*control group*). The actual costs related to available drugs, disposables, TUR-B, cold biopsy, and risk of tumor recurrence were included. Discarded model costs and follow-up diagnostic tests don't vary between the groups [94].

The model was built using information from actual study data, and estimated costs establish a favorable environment for neoadjuvant CHT in terms of cost to 3 years with a global minimum savings of 10.300 and 687 € per patient difference, all with improved effectiveness in the treatment. In fact, of the 15 patients pretreated with chemohyperthermia (*11 high risk and 4 medium risk*), the expected number of recurrences was reduced from 8 to 2 and progressions from 3 to 0. The conclusion of this study of 3 years is that neoadjuvant CHT is a cost-effective therapeutic strategy [94].

4. Take-home messages

4.1. Oncological results

Randomized studies have shown that CHT get the same or even better results than BCG in high-risk patients (T1GIII) regarding the free disease time, although its effectiveness in CIS has to be confirmed as well as tumoral progression

CHT reduced tumor recurrence by 60% compared to standard MMC in patients with intermediate-high-risk MMC and that these differences are maintained even years after treatment. Lower rates of progression vs standard MMC were also achieved but without significant differences.

Neoadjuvant CHT achieves tumoral eradication in two-third of intermediate-high-risk patients, and four-fifth are disease-free after 3 years of follow-up.

4.2. Tolerance

CHT has a nonsignificant higher side effects rate than standard MMC, but these are always low grade and transient. CHT has less systemic effects and bladder retraction than BCG but has more local effects such as spasm, hematuria, and dysuria.

4.3. Economics

Neoadjuvant CHT is a cost-effective therapeutic strategy against BCG treatment.

4.4. Indications

CHT is an undeniable option in BCG refractory tumors; those who are intolerant to BCG are unsuitable for radical cystectomy or in the context of an international BCG shortage.

Its use instead of MMC, both in adjuvant or neoadjuvant protocols, is promising options pending further evaluation.

Finally, the main pros and cons of CHT are condensed in **Table 3**.

Favorable arguments about its use	Contrary arguments about its use
- Improves results of standard MMC by 60% ($p < 0.001$) - Improvements in disease-free survival persist after 10 years vs standard MMC ($p < 0.002$) and 2 years vs BCG ($p < 0.008$) - Less systemic effects and bladder retraction than BCG - Bladder preservation rate to 10 years of 86 vs 79% CHT MMC cold (p = ns) - Useful in CIS and high-grade tumors - Excellent alternative to current or future shortage of BCG - Effective in BCG failures (41–66%) - As effective as BCG in CIS and T1G3 (89.5 vs 85.7%) - Lower rates of progression vs BCG (1.7 vs 2.8%, p = ns) - Reduces the overall cost of bladder cancer treatment (p = ns)	- The need for greater scientific evidence - Increased side effects vs normothermic MMC - Increases initial cost of adjuvant treatment - Operational problems by having a patient on a gurney for 60 min while medication is instilled instead of sending the patient home

Table 3. Pros and cons about chemohyperthermia.

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