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MINIREVIEWS

Recirculating chemohyperthermia as a treatment for non-muscle invasive bladder cancer: Current and future perspectives

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Abstract

About 75% of all bladder cancer diagnosed are non-muscle invasive bladder cancer (NMIBC), recurring over 50% of them after transurethral resection of the bladder tumor. In order to prevent recurrences, adjuvant intravesical chemotherapy with mitomycin C and immunotherapy with bacillus Calmette-Guérin (BCG) is traditionally used. Unfortunately, many patients relapse after receiving these treatments and a significant proportion of them require surgery. After a one-to-three years BCG maintenance, the risk for progression at 5 years was 19.3% for T1G3 tumors. Many new treatment approaches are being investigated to increase the effectiveness of adjuvant intravesical therapy. One of the developing treatments for intermediate and high-risk NMIBC is the combination of intravesical chemotherapy and hyperthermia, called chemohyperthermia. This article provides a review of the mechanism of action, current status and indications, results and future perspectives.

Key words: Bladder cancer; Thermotherapy; Non-muscle invasive; Chemohyperthermia; Recirculating; Intravesical chemotherapy; Treatment; Mechanism of action

Core tip: Chemohyperthermia has demonstrated a selective cytotoxicity on tumoral cells without affecting the remaining healthy cells and it significantly increases the penetration of MMC during intravesical instillations. Moreover, hyperthermia and many chemotherapeutic agents have a synergistic effect, significantly reducing the relative risk of tumoral recurrence in patients non-muscle invasive bladder cancer. Recirculative systems are a novel way to apply endovesical chemohyperthermia, which achieves excellent clinical results with a better side effects profile and a lower price than the one of other chemohyperthermia technologies.

Flores-Carbajal J, Sousa-Escandón A, Sousa-Gonzalez D, Rodriguez Gomez S, Lopez Saavedra M, Fernandez Martinez ME. Recirculating chemohyperthermia as a treatment for non-muscle invasive bladder cancer: Current and future perspectives. *World J Clin Urol* 2017; 6(2): 34-39 Available from: URL: http://www.wjgnet.com/2219-2816/full/6/i2/34.htm DOI: http://dx.doi.org/10.5410/wjcu.v6.i2.34

INTRODUCTION

Bladder cancer is the fourth tumor with the highest incidence in men, after lung, prostate and colorectal cancers. About 75% of all bladder cancer diagnosed are non-muscle invasive bladder cancer (NMIBC), recurring over 50% of them after TURBT[1].

In order to prevent recurrences, adjuvant intravesical chemotherapy with MMC and immunotherapy with bacillus Calmette-Guérin (BCG) is traditionally used. Intravesical chemotherapy, with single postoperative or with maintenance protocols, is the common treatment for patients with low and intermediate NMIBC risk[2]. Immunotherapy with BCG is the gold standard treatment for high-risk patients. However, BCG is associated with important side effects as systemic tuberculosis and bladder retraction[3]. Unfortunately, many patients relapse after receiving these treatments and a significant proportion of patients require surgery, therefore, 19% of those patients with T1G bladder cancer, after adjuvant treatment with BCG (1-3 years), progressed after 5 years[4].

Considering the high relapse and progression after the adjuvant treatment, treatment alternatives have been investigated in order to improve the intravesical treatment outcomes. For those patients with intermediate and high NMIBC risk, the combination of intravesical therapy with hypertemia (CHT) has been developed.

To write this paper, we reviewed all major database available on internet (MEDLINE, EMBASE, Cochrane Library, Web of science and ClinicalTrials.gov) including both clinical trials as general reviews.

HYPERTHERMIA

Also called thermotherapy, is a type of therapy for tumors in which the whole body, or part thereof, is subjected to high temperatures (up to 45 ℃). Numerous studies have shown that high temperatures damage and kill cancer cells by preventing the denaturing of their proteins and the DNA repair. However, hyperthermia causes little damage to normal tissue[5,6]. The first clinical experiences in the use of hyperthermia as a treatment for cancer were performed by Coley[7] more than a century ago. Hyperthermia may be applied in different ways, such as a whole body, regional, intracavitary, local, or interstitial hyperthermia. Similarly, sources of heat vary and include microwaves, ultrasound, radiofrequency and recirculating liquid systems.

In bladder tumors, there are two types. One is used in infiltrating cancers and involves the application of external heat on the entire pelvis associating radio or chemotherapy[8] while the other is used in NMIBC, consisting in 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 are known as CHT[9].

MECHANISM OF ACTION OF HYPERTHERMIA

The human body has several autonomic mechanisms of regulating body temperature to ranges suitable for normal functioning[10].

Cellular necrosis and apoptosis occurs at a temperature above 40.5 ℃ and cell, molecular and metabolic disorders, also known as HT effect, contribute to this fact[11].

The effect of heat on both normal body cell function and on cancerous cells varies based on the degree of hyperthermia with different cytotoxic, vascular and immune effects (Table 1).

MMC AND HEAT

MMC absorption increases with high temperatures. 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%[12].

In 2001, Paroni *et al*[13] showed that microwave-induced hyperthermia increased considerably the MMC absorption, after 30, 45 and 60 min ($P < 0.008$). It is important to understand that the MMC absorption increase is not only due to increased permeability of the bladder urothelium, but also to a noteworthy increase in solubility. Therefore, while at 25 ℃, the maximum concentration that can get by dissolving 1 g of MMC is 0.8 mg/mL, this value is doubled at 40 ℃ since concentrations are up to 1.7 mg/mL (Data from Kyowa Hakko Kirin Co Ltd.).

It stems from the above that the chemohyperthermia (CHT) is the combination of intravesical chemotherapy and hyperthermia in order to increase efficiency. In summary, the increased cell permeability, the changes in the blood perfusion, and the direct cytotoxic effect, are the reasons why the MMC efficacy increases when it is combined with heat[13,14].

CHEMOHYPERTHERMIA

There are two types of treatment: Adjuvant (intermediate and high-risk NMIBC) and neoadjuvant. To improve the effectivity of intravesical chemotherapy are

Table 1 Mechanisms of action of hyperthermia

	39-41	41-43	43-45
Direct Cytotoxic Effects	Slight growth arrest	Reversible growth arrest Mainly in phase M and S Brief RNA synthesis impaired Prolonged DNA synthesis impaired	Irreversible growth arrest Permanent protein denaturalization DNA repair impaired Activation of both ways of apoptosis
Immune effects	Initial increase of 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 cytosine release (IL-6, IL-10)	As above	Altered cytosine production Inactivation of immune cells Reduced expression of extracellular HSP
Vascular effects	Vasodilatation which means: Improved tumor blood flow Improve tissue O_2 Reduce acidosis Improve drug absorption	Improved tumor blood flow: Improve tumor oxygenation Improve drug delivery	Reduced tumor blood flow due to vascular collapse Microthrombosis Endothelial cell damage Vessel permeation Increased acidosis and reduce tissue O_2

Adapted from Rampersaud *et al*[11]. IL: Interleukin.

used "device assisted", these are fundamentally two: Electromotive drug administration (EMDA) that enhance the absorption of MMC by using iontophoresis. On the other hand, it is the chemohyperthermia (CHT) the one that is based on heating the bladder with the instilled chemotherapeutic drug.

EMDA, CHT and device assisted

EMDA uses an electric current to enhance transepithelial drug penetration. EMDA is administered *via* a battery-powered generator delivering an electric current of 0-30 mA DC at 0-55 V, which is passed between two electrodes: An active electrode is placed into the bladder as part of a transurethral catheter and the dispersive ground electrode pads are placed on the skin of the lower abdomen. EMDA takes advantage of three phenomena: Iontophoresis, electro-osmosis and electroporation. Iontophoresis involves propelling a substance into tissues by passing an electrical current through a solution containing the charged active ingredient[15].

The first CHT system approved for human use was the Synergo™ System. This system has been used for 15 years and has conclusive studies in both neoadjuvant and adjuvant settings. It has proved clinical efficacy in high-risk patients (including BCG failures and CIS). It has demonstrated a 60% reduction of tumoral recurrences when comparing to standard MMC. Moreover, its better results were maintained during time periods up to 10 years.

An alternative way to apply heat to the bladder are those systems based on recirculation of a solution of chemoterapeutic drugs heated externally and reintroduced to the bladder through a triple lumen catheter. Two different devices using this technology are currently available: Combat BRS™ and BWT™ systems, which are based on simple technology, and use cheap disposables that make it attractive for performing CHT in a sustainable public medicine. They both use a triple lumen modified Foley catheter, which are soft and flexible, avoiding most problems related to the urethral catheterization, which appear with other technologies. They both enable the removal of the MMC from the patient in safe disposals without contact to the sanitary staff. They both try to maintain the chemotherapeutic solution at a fixed temperature but there are some differences between them. Main differences about all three devices may be seen in Table 2.

Adjuvant CHT treatment

As described above, most patients with high-risk bladder cancer recur one year after the TURBT[16]. This justifies the study of adjuvant treatment strategies. Colombo *et al*[17] performed a multicenter, prospective and randomized study comparing CHT with MMC and MMC alone, in 42 and 41 patients respectively, as adjuvant treatment after the TURBT. The recurrence rate in the CHT and MMC group was 17.1% *vs* 57% in the other group. The meta-analysis performed by Lammers *et al*[18] found a 59% decrease in recurrences after combined therapy (CHT with MMC) and only 10.6% of patients ended up on radical cystectomy.

In our center[19], there was a recurrence free disease rate of 87.5% in high-risk patients treated with Combat recirculant CHT and to whom a 2-year follow-up was performed. However, Ekin *et al*[20] showed that the recurrence rates of high-risk patients treated with BWT recirculant CHT were 82% and 61% after 1 and 2 years of follow-up.

The first randomized trial comparing CHT *vs* BCG was published by Arends *et al*[16]. They observed a recurrence-free survival after 2 years of follow-up of 78% in the CHT group *vs* 64.8% with BCG ($P < 0.0082$). Progressions were lower than 2% in both groups (P = NS). In another study, the therapy has not been shown to be as effective as the BCG, although this is a

Table 2 Characteristic of devices for intravesical chemohyperthermia treatment

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)
Temperature and fluctuation	40 ℃-44 ℃ ± 3 ℃	45 ℃	43.5 ℃ ± 1 ℃
Priming volume	± 100 mL	± 50 mL	± 30 mL
Catheter characteristics	20 Fr. Rigid (Radiofrequency emitter + cooling system inside)	18 Fr Flexible	16 Fr Flexible
Advantages	Strong supporting evidence (*neoadjuvant and adjuvant*) Long term follow up Proved superior to BCG Proved effectiveness against CIS	Simple and Cheap	Lower dilution of MMC Proved effectiveness in sequential schedules Proved neoadjuvant effectiveness Medium term follow up Simple and Cheap
Disadvantages	Higher side effects Lower patient tolerance Intravesical Hot and cold spots Expensive device and disposables Continuous machine control required while working	Limited evidence Quick and Turbulent flow + higher temperature (increase hematuria and reduce patient tolerance)	Limited evidence (multicentric studies ongoing)

BCG: Bacillus Calmette-Guérin.

retrospective study[21,22].

Some comparative studies between patients who have not responded to treatment with BCG *vs* non-previously-treated patients showed better results in the former group. The interim analysis of 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 previous failed intravesical treatment (91% and 62%, respectively $P < 0.006$). In the same vein, van der Heijden *et al*[23] followed 76 patients treated with CHT during 2 years, observing a 42% recurrence in the group with a previous failed BCG treatment compared to a 24% of recurrences in *de novo* treatment group.

A sequential treatment study by using intravesical BCG and CHT was performed in Leicester United Kingdom to treat 33 high-risk NMIBC patients (including a 40% with Cis) which were followed during a median of 16 mo[24]. 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.

Neodjuvant CHT treatment

Colombo *et al*[25] evaluated the ablative efficacy of neoadjuvant hyperthermia in bladder cancer for the first time in 1998. In that study, 19 patients with NMIBC tumors which were unresectable in a one-stage TURBT in which a cystectomy was indicated, were instead treated with neoadjuvant CHT. After eight doses of hyperthermic MMC per week, a complete TURBT was possible in 16 patients (84%). A histological examination of the specimen showed a tumor absence in 47% (complete response) of the patients and > 50% tumor reduction (partial response) in the other 37%. A cystectomy was performed on the remaining three patients. After an average follow-up of 33 mo, eight superficial recurrences were resected without having to remove the bladder.

Our group published in 2014 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, only two patients showed recurrences (15%) which were treated with TUR-B and intravesical adjuvant MMC[26]. Lüdecke *et al*[27] reported after TUR-B, 76.1% complete response and 7.6% partial response.

Safety

The CHT Side effects may occur during and after treatment. Arends *et al*[16] analysed the side effects; during the treatment, the most frequent side effects were bladder spasm in 14%, and bladder pain in 11.4%. After the treatment, the most frequent were the dysuria (11.7%) and the increase of the voiding frequency (9.9%).

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%, $P = 0.398$)[18]. Similar results were seen with BWT™[20,21] and Combat™[26,28] recirculant systems. Side effects are frequent but almost all cases were stages 1 and 2.

In our experience, with almost 800 recirculant instillations, only 3.1% of doses were delayed and less than 1% were definitely not performed. The main reasons for delaying were infection, hematuria and irritative chemical cystitis. The only reasons for the anticipated end of the treatment were allergy or intolerance to catheterization. Approximately 6% of the doses were interrupted before the 60 min, usually by bladder spasms or pelvic

discomfort[26,28]. Those patients who did not tolerate well the first dose, were orally premedicated with 600 mg of Ibuprofen or antispasmodic treatment depending on whether they had complained of pain or spasms. In selected cases spasmolytic IV were administered during treatment. Both oral medications and IV proved to be effective to achieve a good tolerance in subsequent doses of CHT.

FUTURE PERSPECTIVES

The growing interest in magnetic nanoparticles for biomedical applications stems, in part, from their ability to respond to applied magnetic fields through translation, physical particle rotation or internal dipole rotation. As a result, there is local conversion of magnetic field energy into either mechanical forces and/or thermal energy. Then, if magnetic nanoparticles are placed in contact with the desired tumoral tissue, either by intravesical instillation or systemically, and an alternating magnetic field is applied, the heat dissipation due to the nanoparticles will apply a high thermal dose, which will cause the tumoral cell death.

Magnetic fluid hyperthermia is attractive because of the possibility of developing particles whose physicochemical properties are able to attach selectively tumoral tissues through a combination of the enhanced permeation and retention effect[29-33] and, even better, through the activation through surface ligands[34]. This could result in the localization of nanoparticles in the extracellular matrix surrounding cancer cells, or in the cellular uptake and accumulation in intracellular structures, such as vesicles, endosomes and lysosomes. But these nanoparticles are not only able to deliver heat near the tumor but also chemoterapics which will develop a synergic effect over tumoral cells[35,36].

Moreover, nanoparticles joined to chemotherapics are not the only way to increase synergistic effect of CHT. Experimental work performed by Dr. Inman at Duke University, showed that by delivering intravenous novel heat-activated drugs and heating up the bladder, the activated form of the drug could allow the administration of a dose that is 10 to 30 times higher and free-floating drug, while reducing toxicity from other parts of the body (not published data).

Also of growing interest is the use of hyperthermia in combination with immunotherapy treatments. Heating the body activates the immune system, increasing interactions between immune cells designed to alert the body when it is under attack and mobilizing immune cells such as T and B cells to tissues where they are needed[37,38].

CHT is a concept and a developing technology, which comes to remain, and many of the future strategies against cancer will include this promising therapy.

CONCLUSION

CHT published results in neoadjuvant and adjuvant therapy are encouraging. It is likely that in the future the CHT is an alternative to BCG and MMC therapy.

Current CHT is an option in BCG refractory tumors. Those who are intolerant to BCG are unsuitable for radical cystectomy or in the context of the international BCG shortage. Their uses instead of MMC, both in adjuvant or neoadjuvant protocols, are promising options pending further evaluation.

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