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# An Update on Chemohyperthermia for Non-Muscle Invasive Bladder Cancer

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## Introduction

Urothelial Carcinoma (UC), the most common type of bladder cancer, is the 4th most common cancer worldwide [1]. In the United States, an estimated 75,000 patients will be newly diagnosed with UC, and 15,000 will die from the disease in 2017 [2]. About 20% of newly diagnosed UC cases are muscle invasive, which are treated with neo adjuvant chemotherapy followed by radical cystectomy [3]. The other 80% of patients have Non-Muscle Invasive Bladder Cancer (NMIBC) and are more complex to manage [4]. Despite adequate risk stratification, primary tumor eradication, intravesical therapy administration, and surveillance, it is expected that 15% to 30% of patients with de novo NMIBC will progress to muscle invasion and ultimately require cystectomy [5]. Chemohyperthermia (CHT-also known as thermochemotherapy) is a promising variation of intravesical chemotherapy that appears to safely reduce or delay tumor recurrence and progression in NMIBC by heating the treatment during instillation.

### Hyperthermia: historical perspectives

Oncologists have used hyperthermia for decades as an adjuvant therapy to radiation or systemic chemotherapy [6]. Tissue studies have shown that hyperthermia to >40°C increases the effectiveness of chemotherapy through several mechanisms including vasodilation, direct cytotoxicity, and induction of immunomodulation [6]. At temperatures >43°C, unchecked vasodilatory effects of hyperthermia results in increased vascular permeability of tissues surrounding tumors resulting in local perfusion steal and hypoxia [7]. Irreversible cell cycle growth arrest secondary to DNA and RNA synthesis inhibition as well as impaired DNA repair mechanisms exemplify the direct cytotoxic effects of hyperthermia [8]. Finally, heat causes alterations to the loco-regional adaptive immune system via increased production of heat shock proteins and modulation of lymphocytic and NK cell responses resulting in synergistic enhancement of anti-tumor immunity [9].

In the context of NMIBC, the application of hyperthermia to intravesical Mitomycin C (MMC) solutions has been a focus of ongoing biomedical development. Indeed, heated MMC regimens have been shown in vitro to increase tumor cell membrane permeability to the drug [10]. In the next section, contemporary delivery systems which can safely heat intravesical MMC solutions will be discussed.

### Contemporary CHT Delivery Systems for NMIBC

Three techniques can be used to heat an intravesical aqueous solution of MMC. The Dutch system Synergoincorporatesa microwave-emitting antenna to a Foley catheter which is inserted transurethrally into the bladder. Thermocouple sensors continuously monitor the temperature at the bladder wall while the MMC solution is cycled in a closed circuit with heat exchangers for cooling. The British COMBAT system utilizes an external warming console and a three-way Foley catheter to rapidly cycle fluid through the bladder thereby maintaining controlled hyperthermia. Lastly, two commercially available systems, the BDS-2000 and AMC 70 MHz, achieve loco-regional hyperthermia by radiofrequency wave generation via paired external antennae [11].

### Synergo

The Synergo system is the most widely-studied device for CHT in NMIBC and the only method

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currently mentioned in EUA guidelines [12]. A 2011 systematic review evaluated 22 studies which used the Synergo system to investigate the effects of CHT in patients with NMIBC [13]. The combined data showed a 59% reduction in the risk of cancer recurrence in patients receiving heated MMC compared to patients receiving conventional MMC (RR: 0.410, 95%CI: 0.290-0.579). The risk of adverse events increased slightly with CHT, but most were low grade, transient effects such as exacerbation of lower urinary tract symptoms (frequency, dysuria, urgency and nocturia) and nonspecific rashes. These data should be interpreted with caution, however, as the systematic review was limited by inclusion of primarily retrospective studies with a lack of design uniformity and inconsistent follow-up periods. A multicenter randomized, controlled trial published in 2016 compared the Synergo system with MMC to standard Bacillus Calmette-Guerin (BCG) therapy in 190 patients with intermediate or high risk NMIBC [14]. Participants were randomly assigned to receive either a 6-week induction course of CHT with MMC followed by six maintenance courses, or a similar regimen of BCG. The primary outcome studied was recurrence-free survival at 24 months. In the intention-to-treat analysis, no significant difference was observed in 24-month recurrence free survival between the two groups (CHT: 78.1% *vs.* BCG: 64.8%, p=0.08). Analysis per-protocol, however, demonstrated 82% of CHT-treated patients were recurrence-free at 24-months versus 65% of BCG-treated patients (p=0.02). There was no significant difference in rates of disease progression between the two treatments (CHT: 0% *vs.* BCG: 1.4%, p=1.0). In terms of adverse events, the authors reported significantly more frequent lower urinary tract symptoms in the CHT group than the BCG group; however no novel safety concerns were reported with Synergo [14]. Unfortunately, the applicability of these results is severely limited as the trial was subject to numerous biases secondary to under powering (premature closure due to slow accrual) and lack of blinding.

### Combat

The commercial device COMBAT, that heats chemotherapy fluid externally, was introduced in 2011 and has been established in the literature through only a handful of preliminary clinical studies. Recent shortages in manufactured BCG availability prompted Griffiths et al., in the United Kingdom, to incorporate COMBAT CHT into their risk-stratified NMIBC protocol [15]. In order to ration BCG doses, MMC was delivered to 50 patients by COMBAT at weeks 3, 4, and 5 of a standard 6-week intravesical therapy induction, with BCG administered only at weeks 1,2, and 6. Three sets of 3-week maintenance courses of MMC were also delivered by COMBAT to complete a full year of therapy. According to unpublished results presented at the 2017 national meeting of the American Urological Association, 88% of participants were disease free after completing 1 year of treatment. 6% were designated treatment-unresponsive and 2 patients (4%) progressed to muscle invasive bladder cancer [15].

Two randomized, controlled trials are currently ongoing in Europe to test the tolerability and safety of hyperthermic MMC delivered by COMBAT in patients with intermediate risk NMIBC [16]. The HIVEC I trial compares heated MMC in 30 min or 60 min instillations against standard solutions of MMC for a 4-cycle induction followed by single, monthly treatments for 3 months. HIVEC II compares heated MMC for 60 min instillations against standard MMC for a 6-cycle induction. Neither trial is designed to demonstrate oncologic efficacy. Interim analysis of 307 patients has shown no significant differences in adverse events between heated MMC and standard MMC [16].

### BDS-2000 and AMC 70 MHz

A final technology that can be used for CHT in NMIBC is loco-regional hyperthermia, a technique that uses external antennae to heat the target tissue with radiofrequency waves. Available devices, including the BDS-2000 and AMC 70 MHz, require detailed planning before treatment. Cross-sectional imaging of the patient is required to predict how various tissue layers will respond to the radio frequency waves. Using this data, a medical physicist determines an optimal steering strategy and radiofrequency intensity for the antenna array17. A 2016 systematic review of the use of regional hyperthermia for bladder cancer was hampered by heterogeneous study designs and non-standard reporting of adverse events 18. Nonetheless, the authors conclude that loco-regional hyperthermia holds promise not only for NMIBC, but also for select muscle invasive bladder cancer patients with acceptable rates of toxicity.

## Conclusion

No studies have yet directly compared CHT systems. Pending such analysis, we summarize the advantages and disadvantages of each system according to Liem, et al. [11] Loco regional hyperthermia systems, such as the BDS-2000, achieve deep heat penetration, can be used to treat a variety of organ systems, and are the only technology currently approved by the FDA for use in the United States. However, these are the most expensive systems to implement because of the upfront purchase costs as well as additional overhead to provide the device with a shielded room and trained personnel to operate it. The Synergo system is less expensive to purchase than the BSD-2000 and has a stronger foothold in the literature, as acknowledged by EAU guidelines. However, treatment with Synergo is still prohibitively expensive for most institutions and practitioners because of its complicated disposable antenna catheter and continuous patient monitoring by nursing personnel. The COMBAT system may achieve uniform bladder heating and is currently the most affordable to operate. While definitive efficacy data has not been formally published, preliminary results are promising.

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