Chemohyperthermia in non-muscle-invasive bladder cancer: An overview of the literature and recommendations

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Chemohyperthermia in non-muscle-invasive bladder cancer: An overview of the literature and recommendations

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Non-muscle-invasive bladder cancer (NMIBC) is characterised by a high risk of recurrence for the present standard treatment of transurethral resection of the bladder (TURB) followed by intravesical instillation of Mitomycin-C (MMC) or bacillus Calmette–Guérin (BCG). To decrease this high recurrence rate, alternative treatments are studied. Intravesical MMC combined with hyperthermia could be an interesting alternative active treatment for intermediate- and high-risk NMIBC, and has been investigated in the past years. Hyperthermia, raising tumour temperatures to 40–44°C, can be achieved with several hyperthermia systems, based on three different techniques: 1) intravesical microwave induced heating, 2) conductive heating, and 3) loco-regional, using external radiofrequency antennas. In this review an overview is given of the available hyperthermia systems and the reported outcomes. Future directions are discussed. Optimal implementation of a combined regimen of MMC and hyperthermia requires further clinical trials to identify patients who will benefit most from this treatment, to optimise treatment schedules and to compare the efficacy of different hyperthermia devices.

Chemohyperthermia principles

Hyperthermia combined with intravesical chemotherapy is used to enhance the effects of the chemotherapy. Temperatures for combined treatment range between 40 and 44°C. Temperatures in this range do not achieve direct tissue ablation. To thermally ablate tumour tissue higher temperatures are necessary.

Previous studies have shown that combined treatment of MMC and hyperthermia is more effective than MMC alone, or hyperthermia alone [6]. Heat causes alteration of the intracellular metabolism. This results in DNA damage of the cell and induces apoptosis of tumour cells. The increased temperature also leads to an enhanced blood perfusion and an increase in cell permeability. This allows an increased MMC uptake. Additionally, MMC is more effective at higher temperatures, resulting in a synergistic effect [7]. Another suggested mechanism is that hyperthermia activates an immune response, by mimicking fever. Heat shock proteins activate dendritic cells, T-cells, and natural killer cells, triggering an anti-tumour response [8].

The most common application for combined CHT is adjuvant treatment (prophylactic) after TURB, to lower the chance for tumour recurrence. Neoadjuvant treatment (ablative) is also applied in the case of residual tumour or if carcinoma in situ (CIS) is present.
Available hyperthermia systems

At the moment several hyperthermia systems are available, based on three different techniques. Heating of the bladder can be achieved by 1) microwave induced heating using an intravesical radiofrequency-emitting antenna incorporated in a catheter, 2) conductive heat, when chemotherapy fluid is externally heated, and 3) loco-regional, using external radio-frequency (RF) energy.

Intravesical microwave-induced heating

Synergy
The Synergy® system (Medical Enterprises, Amsterdam, Netherlands) is the most widely applied form of chemohyperthermia treatment and is the most extensively studied. This system uses RF microwave energy to directly heat the bladder wall. It consists of a RF generator that delivers RF energy at 915 MHz, a drug-circulating unit, and a microprocessor with application-specific software. A disposable sterile triple lumen catheter (20 Ch) is connected to the system and is used to heat the bladder wall to approximately 42 ± 2 °C. A RF antenna generates the heat, and multiple thermocouples integrated with the antenna monitor the temperature. Cooled MMC is administered through the catheter and circulated in a closed system (Figure 1A).

In general, patients are treated prophylactically (adjuvant) with 20 mg MMC diluted in 500 mL distilled water. For ablative treatment (neoadjuvant) patients receive 40 mg MMC. Each treatment session consists of 60 min, after 30 min the intravesical solution is refreshed. This results in a total dosage of 40 mg MMC for adjuvant treatment and 80 mg MMC for neoadjuvant treatment [9–11].

Advantages of this system are that it is FDA approved, and efficacy of this hyperthermia device has been reported most frequently, with the availability of long-term data. Disadvantages of this system are the relatively high costs, partially due to expensive disposable catheters, and a small risk of severe bladder wall necrosis resulting in posterior wall ulceration or burn [12].

Conductive-based heating fluid

COMBAT BRS (HIVEC)
The COMBAT BRS® device (Combat Medical, Wheathampstead, UK) is a system that recirculates MMC through a closed system (Figure 1B). It consists of a recirculating system with a conductive aluminium heat exchanger that heats and controls the temperature of MMC at 43 °C. The MMC, in neoadjuvant setting 80 mg, is recirculated via a 3-way catheter (16 Ch) through the bladder and the system at a constant flow rate [13].

Advantages of this system are that the COMBAT BRS® system is a small device, which can be used at any location. It is easy to use and cost-effective compared to other systems. Disadvantages are a lower depth of heat penetration and the lack of long-term data.

Unithermia
The Unithermia® system (Elmedical, Hod-Hasharon, Israel) is a device that allows instillation of a heated solution of chemotherapy (Figure 1C). It consists of a compact console, a peristaltic pump and a heat exchanger. The heat exchanger heats the MMC up to 42–45 °C, and MMC is continuously pumped with a high flow in a closed circulating unit using a 3-way catheter (18 Ch) in the bladder. For adjuvant treatment patients receive 40 mg MMC. A needle-tip thermometer placed in the catheter monitors the temperature. Based on conductive-heat mechanism, it is claimed that a uniform temperature can be reached throughout the whole bladder, without hot or cold spots. This is important as a heterogeneous heat distribution will cause toxicity as well as potentially undertreating parts of the bladder wall [14].

Advantages of the Unithermia® system are low costs in comparison to other systems, and disposable catheters. Disadvantages are the uncertainty of reaching a well-defined temperature at the bladder wall and the lack of long-term data.

Loco-regional hyperthermia

BSD-2000
The BSD-2000® hyperthermia system (BSD Medical, Salt Lake City, UT) induces heat by delivering a focused power deposition pattern using electromagnetic waves (Figure 1D). This system consists of a control console, an applicator with four twin dipole antennas including a flexible coupling bolus, and temperature probes. Prior to the first hyperthermia treatment combined with MMC, a CT-scan is made for treatment positioning, temperature probe localisation, and planning. Via the software on the control console, settings for the applicator can be set, and manually adjusted during treatment. Using an external phased array of four antenna pairs, mounted around the torso of the patient, RF waves within a range of 75–120 MHz are delivered in a focal region within the pelvis. A coupled water bolus is filled with distilled water at approximately 25 °C for impedance matching for RF waves and thermal cooling of the skin. Temperature probes, placed intravesically via a Foley catheter (18 Ch) and in the rectum, are used for temperature monitoring and mapping, aiming for a bladder temperature of 42 ± 2 °C. The bladder, including MMC, is heated using the four antenna pairs to a temperature of 40 °C for at least 40 minutes, but with a maximum total duration of 60 minutes. For adjuvant treatment 40 mg MMC is administered to patients [15–17].

Advantages of the BSD-2000® system are the possibility to target deep tissue, including lymph nodes alongside the bladder, the possibility to manually adjust treatment settings, and that the FDA sanctioned device exemption for the BSD-2000®. Disadvantages of this system are the high start-up costs and large size of the device, which is accompanied by the need for a large, shielded room. Its use is more complex and requires the expertise of an experienced physicist. Furthermore, treatment with this system requires a planning CT to set up applicator settings. Very obese patients (BMI > 40 kg/m²) are difficult to treat, and patients with metal implants, pacemakers or sacral nerve stimulators are excluded for treatment, because these metal parts can create hot spots.
The AMC 70 MHz phased array system allows for regional hyperthermia (Figure 1E). It consists of a phase- and amplitude-controlled RF generator (SSB Electronic, Lippstadt, Germany), 1 or 2 rings with four wave-guided antennas, and thermocouple probes. Phase settings of the RF generator are optimised using an E-field probe, and are validated before treatment. During treatment, manual adjustments in phase and amplitude can be made. The RF generator is connected to the 4 antennas, which are positioned around the pelvis of the patient. In between the patient and the antennas are water pillows filled with cooled water (13 °C) to connect the

Figure 1. Available hyperthermia systems. (A) A schematic overview of the Synergo® system. A triple lumen catheter with integrated RF antenna and multiple thermocouples connected to the device. (B) COMBAT BRS® system. (C) Unithermia® system and schematic overview. MMC is heated via heat exchanger and pumped around via a 3-way catheter. (D) BSD-2000® system. (E) AMC 70 MHz system.

AMC 70 MHz system
The AMC 70 MHz phased array system allows for regional hyperthermia (Figure 1E). It consists of a phase- and amplitude-controlled RF generator (SSB Electronic, Lippstadt, Germany), 1 or 2 rings with four wave-guided antennas, and thermocouple probes. Phase settings of the RF generator are optimised using an E-field probe, and are validated before treatment. During treatment, manual adjustments in phase and amplitude can be made. The RF generator is connected to the 4 antennas, which are positioned around the pelvis of the patient. In between the patient and the antennas are water pillows filled with cooled water (13 °C) to connect the
antenna power to the patient and to cool the skin. First the
MMC 40 mg solution (adjuvant treatment) is instilled into the
bladder through an open-end catheter (18 Ch), followed by
a temperature probe holding 14 thermocouple sensors.
Subsequently temperature probes are placed into the rectum
and in women also into the vagina, to monitor temperature.
When the bladder temperature has reached 41 °C, treatment is
continued for 60 minutes, with a maximum total time of
90 minutes. Temperature measurements in the rectum and
vagina are used to optimise phase settings for optimal blad-
er temperatures [18].
Advantages of the AMC 70 MHz system are the possibility
to deliver deep hyperthermia and target tissue close to the
bladder, including lymph nodes, and homogeneity of bladder
temperature, because of external heating. During treat-
ment it is possible to manually adjust treatment settings.
Disadvantages of this system: it is a large system, and
requires a large shielded room. It can be time-consuming
before adequate temperatures are reached. Patients with
metal implants, pacemakers, or sacral nerve stimulators
cannot be treated with this system. This system has recently
become commercially available (Alba Hyperthermia System,
Rome, Italy).

Capacitive hyperthermia systems

Besides the hyperthermia systems described above, other
hyperthermia devices are available. The HY-deep 600WM®
(Verde Andromedic, Italy), Celsius TC5® (Celsius 42+., Cologne,
Germany), Synchrotherm RF 1200® (Sychrotherm, Vigevano,
Italy), and Thermotron RF-8® (Thermotron, MPR and Yamato,
Japan) are capacitive hyperthermia systems which use elec-
trodes to excite hyperthermia. In the past, the Thermotron
RF-8® device has been used for treatment of invasive bladder
carcinoma [19,20]. We do not discuss these systems further in
this paper, since no recent clinical trials have been published
regarding these hyperthermia systems in the treatment of
bladder cancer.

Outcomes

For this overview of clinical outcomes we conducted a
PubMed MEDLINE search using a combination of the follow-
ing keywords: bladder neoplasms, bladder tumour, bladder
cancer, MMC, hyperthermia, thermotherapy, and thermoche-
motherapy. The outcomes of clinical trials regarding CHT of
NMIBC of the past 12 years are stated below. Notable is the
great heterogeneity of the patient populations, the treatment
delivery and modality, and the reported outcomes. In Table 1
the outcomes of the clinical trials are summarised.

Synergo system

Intermediate–high-risk NMIBC
In a multicentre, prospective, randomised trial, Colombo et al.
evaluated the efficacy of adjuvant CHT in 83 patients with pri-
mary or recurrent NMIBC [21]. Patients were randomised fol-
lowing TURB complete transurethral resection of bladder
tumour to chemotherapy alone (MMC, 41 patients) or chem-
otherapy combined with hyperthermia (MMC + HT, 42
patients). All patients received an induction cycle of eight
treatment sessions once a week, followed by a maintenance
regimen of four sessions once a month. Eight patients did
not complete the treatment schedule. The treatment schedule
of MMC + HT was more effective than MMC alone, with recur-
rence rates of 17.1% and 57.5%, respectively. In 2011 updated
long-term results were published [22]. The authors reported a
10-year disease-free survival rate for MMC alone of 15% and
MMC + HT of 53% (p < 0.001). In five patients tumour pro-
gression occurred at the time of recurrence (three in the
MMC group, two in the MMC + HT group), requiring radical
cystectomy. Four patients underwent radical cystectomy for
recurrent high grade NMIBC. Bladder preservation rate after
10 years was 78.9% for the MMC alone group, and 86.1% for
the MMC + HT group.
Van der Heijden et al. conducted a prospective study and
included 90 patients with intermediate- or high-risk NMIBC.
Following TURB, patients received adjuvant therapy with
MMC and hyperthermia using Synergo° [23]. The treatment
schedule consisted of six to eight sessions once a week fol-
lowed by four to six sessions once a month. The authors
reported a risk of recurrence after 1 and 2 years of 14.3% and
24.6%, respectively. No progression of stage and grade was
seen during 24 months of follow-up.
The efficacy of the Synergo° system in patients with recur-
rent intermediate- or high-risk NMIBC was prospectively
studied by Moskovitz et al. [10]. Patients were treated prophyl-
actically after complete TURB or in an ablative way after
incomplete TURB. Seven out of 39 patients were unable to
complete the treatment schedule with CHT. Prophylactic
treatment (22 patients) consisted of six to eight sessions once
a week, of 20 mg MMC (total 40 mg MMC), followed by four
to six sessions once a month, with a total of 12 instillations.
Ablative treatment (10 patients) consisted of eight courses of
40 mg of MMC once a week (total 80 mg MMC), followed by
during each of the 40 mg treatment sessions by a fresh solution
(total 40 mg MMC). Additionally, this was followed by six mainte-
nance sessions, every 6 weeks. In the ablative protocol (26 patients), patients
received eight once-weekly treatment sessions (induction) of 20 mg MMC, which after 30 minutes of
heating was replaced by a fresh solution (total 80 mg MMC). Following four treatments with 20 mg MMC once a month, with a total of 12 treatment sessions. After a mean follow-up of 9.6
months 91% of patients treated prophylactically were recur-
rence-free. In the ablative group 80% achieved complete
response after 3.5 months.
Moskovitz et al. reported long-term outcomes of patients
treated in an adjuvant (prophylactic) or neoadjuvant (ablative)
setting using CHT [24]. In total 92 patients were treated with
CHT. In the prophylactic protocol (66 patients), following com-
plete TURB, patients received six once-weekly treatment ses-
sions (induction) of 20 mg MMC, which after 30 minutes of
heating was replaced by a fresh solution (total 40 mg MMC).
Additionally, this was followed by six maintenance sessions,
every 6 weeks. In the ablative protocol (26 patients), patients
received eight once-weekly treatment sessions (induction) of
40 mg MMC, which after 30 minutes of heating was replaced
by a fresh solution (total 80 mg MMC), followed by six add-
tional maintenance sessions, every 6 weeks. Two patients
could not complete the prophylactic induction treatment.
Recurrence rate in this group at 2 years was 32.8%. In three
patients disease progressed to muscle-invasive bladder can-
cer. In the ablative treated group two patients withdrew from
<table>
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<th>Treatment</th>
<th>Reference</th>
<th>Study type</th>
<th>No. of patients</th>
<th>Study description</th>
<th>Patient population</th>
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<th>Follow-up, median (months)</th>
<th>Outcome: recurrence</th>
<th>Outcome: progression</th>
<th>Treatment not completed</th>
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<td><strong>Synergy®</strong></td>
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<td>Prophylaxis: 8× weekly, 40-60 min 2×20 mg MMC</td>
<td>Colombo et al., 2003 [21]</td>
<td>Prospective</td>
<td>83</td>
<td>Multicentre, comparing CHT (n = 42) vs MMC (n = 41)</td>
<td>Intermediate or high risk</td>
<td>42 ± 2</td>
<td>&gt;24</td>
<td>Recurrence: CHT 17.1%, MMC 37.5%</td>
<td>CHT: none</td>
<td>8 of 83 (9.6%)</td>
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<td>Prospective</td>
<td>52</td>
<td>Multicentre, prophylaxis (n = 24), ablative (n = 28)</td>
<td>High risk (Ta-T1, G3)</td>
<td>42 ± 2</td>
<td>15.2 (6-90)</td>
<td>Overall: recurrence-free survival rate 71%</td>
<td>Prophylaxis: 62% recurrence-free Ablative: 75% complete response, 80.9% recurrence-free</td>
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<td>Van der Heijden et al., 2004 [23]</td>
<td>NA</td>
<td>90</td>
<td>Multicentre, adjuvant</td>
<td>Intermediate or high risk</td>
<td>41-44</td>
<td>18 (4-24)</td>
<td>1-year risk of recurrence 14.3%</td>
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<td>Moskovitz et al., 2005 [10]</td>
<td>Prospective</td>
<td>47</td>
<td>Single centre, prophylaxis (n = 22), ablative (n = 10)</td>
<td>Intermediate or high risk</td>
<td>42 ± 2</td>
<td>10</td>
<td>Prophylaxis: 91% recurrence-free Ablative: 80% complete response</td>
<td>None</td>
<td>7 of 39 (17.9%)</td>
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<td>56</td>
<td>Multicentre, adjuvant</td>
<td>High risk (T1G3)</td>
<td>42 ± 2</td>
<td>18 (2-49)</td>
<td>2-year recurrence rate 42.9%</td>
<td>4 muscle-invasive (7.8%)</td>
<td>5 of 56 (8.9%)</td>
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<td>Retrospective</td>
<td>51</td>
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<td>High risk (CIS)</td>
<td>41-44</td>
<td>22 (3-77)</td>
<td>Overall: Complete response 92% Recurrence 49%</td>
<td>NA</td>
<td>2 of 51 (3.9%)</td>
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<td>Nativ et al., 2009 [30]</td>
<td>Retrospective</td>
<td>111</td>
<td>Multicentre, adjuvant</td>
<td>Recurrence after BCG</td>
<td>42 ± 2</td>
<td>16 (2-74)</td>
<td>1-year recurrence-free probability 83% 2-year recurrence-free probability 56%</td>
<td>3 muscle-invasive (2.9%)</td>
<td>6 of 111 (5.4%)</td>
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<td>Prophylaxis: 8× weekly, 40-60 min 2×20 mg MMC</td>
<td>Colombo et al., 2010 [22]</td>
<td>Prospective</td>
<td>83</td>
<td>Multicentre, comparing CHT (n = 42) vs MMC (n = 41)</td>
<td>Intermediate or high risk</td>
<td>42 ± 2</td>
<td>90 (6-154)</td>
<td>Recurrence: CHT 14 of 35 (40%), MMC 32 of 40 (80%) 10-year disease-free survival rate: CHT 53%, MMC 15%</td>
<td>Prophylaxis: 43.8% recurrence-free Ablative: 42.9% complete response</td>
<td>5 patients (6.7%)</td>
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<td>Volpe et al., 2012 [28]</td>
<td>Prospective</td>
<td>30</td>
<td>Single centre, prophylaxis (n = 18), ablative (n = 14)</td>
<td>High risk, not responding to previous chemotherapy</td>
<td>42 ± 2</td>
<td>14</td>
<td>Overall:</td>
<td>3 muscle-invasive (10%)</td>
<td>NA</td>
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<th>Study description</th>
<th>Patient population</th>
<th>Temp. (°C)</th>
<th>Follow-up, median (months)</th>
<th>Outcome: recurrence</th>
<th>Outcome: progression</th>
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<td>Moskovitz et al., 2012 [27]</td>
<td>Retrospective</td>
<td>92</td>
<td>Single centre, prophylaxis (n = 66), ablative</td>
<td>Intermediate or high risk</td>
<td>42.2</td>
<td>23 (3-84)</td>
<td>1-year disease-free survival 77%</td>
<td>2-year disease-free survival 55%</td>
<td>Prophylaxis: 2-year recurrence-rate 32.8% Ablative: complete response 79%, Recurrence 16%</td>
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<td>Ablative: 8× weekly, 60 min 2 × 40 mg MMC</td>
<td>Maffezzini et al., 2014 [27]</td>
<td>Propective</td>
<td>42</td>
<td>Single centre, adjuvant</td>
<td>High risk</td>
<td>42.5 ± 1.5</td>
<td>38 (4-73)</td>
<td>Recurrence: 30.9%</td>
<td>7 muscle-invasive and/or CIS (16.7%)</td>
<td>10 of 42 (23.8%)</td>
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<td>Maintenance: 6× every 6 weeks, 2 × 20 mg MMC</td>
<td>Ablative: 8× weekly, 60 min 40 mg MMC</td>
<td>Retrospective</td>
<td>8</td>
<td>Single centre, prophylaxis (n = 26)</td>
<td>1-year recurrence-rate 77%</td>
<td>2-year disease-free survival 55%</td>
<td>Prophylaxis: 2-year recurrence-rate 32.8% Ablative: complete response 79%, Recurrence 16%</td>
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<td>Phase 1: 4× weekly, 60 min 40 mg MMC</td>
<td>Ablative: 8× weekly, 60 min 40 mg MMC</td>
<td>Retrospective</td>
<td>60</td>
<td>Single centre, prophylaxis (n = 42)</td>
<td>Intermediate or high risk</td>
<td>43 ± 1</td>
<td>29</td>
<td>Complete response 53% 3-year cumulative incidence of recurrence 19%</td>
<td>NA</td>
<td>None</td>
</tr>
<tr>
<td>Phase 2: 6× every 2 weeks, 60 min 40 mg MMC</td>
<td>Maintenance: 6× every 6 weeks, 2 × 20 mg MMC</td>
<td>Retrospective</td>
<td>60</td>
<td>Single centre, prophylaxis (n = 42)</td>
<td>Intermediate or high risk</td>
<td>43 ± 1</td>
<td>29</td>
<td>Complete response 53% 3-year cumulative incidence of recurrence 19%</td>
<td>NA</td>
<td>None</td>
</tr>
<tr>
<td>Phase 3: 4× monthly, 60 min 40 mg MMC</td>
<td>Ablative: 12× weekly, 60 min 40 mg MMC</td>
<td>Retrospective</td>
<td>42</td>
<td>Single centre, prophylaxis (n = 10), ablative</td>
<td>Refractory to regular intravesical treatment</td>
<td>42 ± 2</td>
<td>76</td>
<td>Overall: 1-year recurrence-free survival 60% 2-year recurrence-free survival 47% Ablative: 77.5% complete response</td>
<td>7 muscle-invasive (4.3%)</td>
<td>10 of 160 (6.3%)</td>
</tr>
<tr>
<td>Prophylaxis: 6× weekly, 60 min 2 × 20 mg MMC</td>
<td>Kiss et al., 2015 [29]</td>
<td>Retrospective</td>
<td>160</td>
<td>Single centre, prophylaxis (n = 10), ablative</td>
<td>Recurrent NMIBC</td>
<td>42 ± 2</td>
<td>50 (1-120)</td>
<td>Recurrence-free 29%</td>
<td>6 radical cystectomy (multifocal recurrence, or muscle-invasive) (29%)</td>
<td>8 of 21 (38.1%)</td>
</tr>
<tr>
<td>Ablative: 6× weekly, 60 min 2 × 20 mg MMC or 2 × 25 mg EPI</td>
<td>Ablative: 6× weekly, 60 min 2 × 40 mg MMC or 2 × 50 mg EPI</td>
<td>Retrospective</td>
<td>15</td>
<td>Pilot, neoadjuvant</td>
<td>Intermediate or high risk</td>
<td>43 ± 1</td>
<td>29</td>
<td>Complete response 53% 3-year cumulative incidence of recurrence 19%</td>
<td>NA</td>
<td>None</td>
</tr>
<tr>
<td>Maintenance: every 6 weeks for 1 year, 2 × 20 mg MMC or 2 × 25 mg EPI</td>
<td>COMBAT-BRS(3)</td>
<td>Retrospective</td>
<td>15</td>
<td>Pilot, neoadjuvant</td>
<td>Intermediate or high risk</td>
<td>43 ± 1</td>
<td>29</td>
<td>Complete response 53% 3-year cumulative incidence of recurrence 19%</td>
<td>NA</td>
<td>None</td>
</tr>
<tr>
<td>Prophylaxis: 6× weekly, 60 min 2 × 20 mg MMC</td>
<td>Sousa et al., 2014 [13]</td>
<td>Retrospective</td>
<td>15</td>
<td>Pilot, neoadjuvant</td>
<td>Intermediate or high risk</td>
<td>43 ± 1</td>
<td>29</td>
<td>Complete response 53% 3-year cumulative incidence of recurrence 19%</td>
<td>NA</td>
<td>None</td>
</tr>
<tr>
<td>Ablative: 8× weekly, 60 min 40 mg MMC</td>
<td>Ekin et al., 2015 [31]</td>
<td>Retrospective</td>
<td>43</td>
<td>Single centre, phase I-II, adjuvant</td>
<td>Non-G3 recurrence after BCG</td>
<td>42.5 ± 1</td>
<td>41 (18-78)</td>
<td>Recurrence: 35.3% 6 - G3 (17.6%) 2 - ≥ T2 (5.9%)</td>
<td>4 of 34 (11.8%)</td>
<td>10 of 160 (6.3%)</td>
</tr>
<tr>
<td>Maintenance: 3× weekly at 3 and 6 months, 60 min 40 mg MMC</td>
<td>Unithermia(4)</td>
<td>Retrospective</td>
<td>34</td>
<td>Single centre, phase I-II, adjuvant Multicentre, adjuvant</td>
<td>Non-G3 recurrence after BCG</td>
<td>42.5-45</td>
<td>30 (9-39)</td>
<td>Recurrence: 32.9% 1-year recurrence-free rate 82% 2-year recurrence-free rate 61%</td>
<td>7 muscle-invasive (4.3%)</td>
<td>10 of 160 (6.3%)</td>
</tr>
<tr>
<td>BSD-2000(5)</td>
<td>Prophylaxis: 6× weekly, 40-60 min 40 mg MMC</td>
<td>Prospective</td>
<td>368</td>
<td>Pilot, adjuvant</td>
<td>BCG refractory</td>
<td>42 ± 2</td>
<td>38</td>
<td>Recurrence: 66.7%</td>
<td>None</td>
<td>1 of 15 (6.7%)</td>
</tr>
</tbody>
</table>

(continued)
treatment before completing the induction series. Complete response was seen in 19 patients (79%). A recurrence was reported in three patients (16%) during follow-up (median 9 months, range 2–96 months).

In a prospective study by Kiss et al. the outcome of CHT was evaluated for recurrent NMIBC [25]. In total 21 patients were treated with curative intent (11 patients) or as prophylaxis against recurrence (10 patients). Patients in the prophylaxis group were treated with 20 mg MMC (total 40 mg MMC) in six once-weekly sessions. Patients in the ablative group were treated with 40 mg MMC (total 80 mg MMC) in 12 once-weekly treatment sessions. In eight patients planned treatment cycles had to be abandoned before completion because of side effects. After a median follow-up of 50 months, 29% were recurrence free. An additional 29% underwent a radical cystectomy because of multifocal recurrence or progression to muscle-invasive disease.

High-risk NMIBC

In 2004 Gofrit et al. treated 52 patients using Synergo® with either a prophylactic (40 mg MMC in total) or ablative (80 mg MMC in total) protocol [9]. Treatment course for both groups consisted of eight induction sessions once a week and four maintenance treatment sessions once a month. The authors reported an overall recurrence-free survival rate for the whole group of 71% after a median follow-up of 15.2 months. In the prophylaxis group 62% of patients were recurrence free after a mean follow-up of 35.3 months. In the ablative protocol seven patients could not complete the treatment protocol. Complete response was achieved in 75% of patients in the ablative group. In this group 80.9% were recurrence-free after a mean follow-up of 20 months. No cases of tumour progression to muscle-invasive bladder cancer occurred.

Halachmi et al. evaluated retrospectively the efficacy of MMC combined with hyperthermia in 56 patients with T1G3 NMIBC [26]. Patients underwent combined CHT once a week for 6 weeks consecutively, followed by six maintenance sessions with 4–6-week intervals. Five patients did not complete combined MMC/hyperthermia treatment. Recurrence rates at 2 and 4 years were 42.9% and 51.0%, respectively. In four patients tumour progression to muscle-invasive disease was seen.

A prospective study done by Maffezzini et al. reported outcomes of patients with high-risk NMIBC treated with CHT [27]. Forty-two patients were enrolled in this study and were treated with 4 sessions once a week, followed by six sessions every 2 weeks and finally four treatment sessions once a month. Treatment schedule was not completed as planned in 10 patients, five patients stopped due to side effects and five patients stopped due to recurrence of disease during treatment. After a median follow-up of 38 months, 13 patients developed a recurrence (30.9%). Tumour progression to muscle-invasive disease and presence of CIS occurred in seven patients.

Witjes et al. assessed the efficacy of CHT in patients with CIS [11]. Retrospectively, data were evaluated of 51 patients treated with CHT after TURB with a prophylactic protocol, or when concomitant papillary tumours were not completely
resected or for wide areas of CIS, as an ablative protocol. The prophylactic treatment protocol (18 patients) consisted of 6 instillations once a week with 20 mg MMC, which after 30 min was replaced by a fresh identical solution (total 40 mg MMC). Patients in the ablative schedule (33 patients) received eight sessions once a week with 40 mg MMC (total 80 mg MMC). Both groups received 6 maintenance sessions once a month of twice 20 mg MMC. In two patients induction treatment was not completed. Complete response (biopsy and cytology-proven disappearance of CIS at 3 months) was noted in 45 patients (92%). In 22 patients (49%) a recurrence was reported after a median of 51 months.

**Post previous intravesical treatment**

In a prospective study, Volpe et al. included 30 patients with high-risk NMIBC not responding to previous chemotherapy and/or immunotherapy (MMC, epirubicin or BCG) [28]. Patients were treated with a prophylactic CHT protocol (16 patients) or ablative protocol (14 patients). Prophylactic treatment consisted of six once-a-week sessions with twice 20 mg MMC (total 40 mg MMC) followed by six sessions monthly. Ablative treatment was 8 sessions weekly with twice 40 mg MMC (total 80 mg MMC), followed by six once-a-month sessions. All patients completed the treatment according to protocol. Complete response was achieved in 42.9% of the ablative group. For all patients disease-free survival was 77% and 55% at 12 months and 24 months, respectively. Disease-free survival was not significantly different for the prophylactic and the ablative groups. Progression to muscle-invasive bladder cancer occurred in three patients, all treated within the ablative protocol.

Arends et al. evaluated the efficacy of CHT in 160 patients with NMIBC, refractory to intravesical treatment (MMC, epirubicin, BCG) [29]. Patients were treated with either a prophylactic or an ablative protocol. Patients received 20 mg MMC or 25 mg epirubicin in the prophylactic protocol, and 40 mg MMC or 50 mg epirubicin in the ablative protocol. Each treatment session consisted of two cycles of 30 minutes, after which the intravesical solution was refreshed. In both protocols patients underwent an induction period of six to eight instillations once a week, followed by maintenance sessions every 6 weeks, for 1 year. Treatment was not completed in 10 patients (6.3%). Twenty patients (12.5%) were treated with epirubicin because of MMC allergy. In the ablative group, 77.5% reached a complete response 6 weeks after the induction phase. Recurrence-free survival of 1 and 2 years was 60% and 47%, respectively. In seven patients (4.3%) disease progressed to muscle-invasive disease.

Retrospectively, Nativ et al. reported outcomes of patients with recurrent NMIBC following BCG [30]. In total, 111 patients were treated prophylactically with CHT after complete TURB. Patients were treated with six sessions once a week (twice 20 mg MMC), followed by six maintenance sessions (twice 20 mg MMC) at 4–6-week intervals. In six patients (5.4%) treatment was stopped before completion. Recurrence-free probability at 1 and 2 years was 85% and 56%, respectively. Three patients progressed to muscle-invasive disease during follow-up.

**COMBAT BRS system**

A pilot study regarding the COMBAT BRS® system by Sousa et al. included 15 patients with intermediate- or high-risk NMIBC [13]. Patients were treated with CHT before TURB (ablative protocol). The treatment schedule consisted of eight once-weekly instillations with 80 mg MMC combined with hyperthermia, followed by TURB 7–15 days after completing CHT. Histological complete response (total absence of urothelial carcinoma) was reported in eight patients (53%) and a partial response (>50% reduction of tumour) in seven patients (47%). The 3-year cumulative incidence of recurrence was 15%.

**Unithermia system**

In a phase I–II trial by Soria et al. outcomes were reported for patients with non-G3 NMIBC recurrence after induction BCG [14]. In total 34 patients were adjuvant treated with CHT and received six once-weekly instillations. In four patients (11.8%) CHT-treatment was not completed. Recurrence rate at a median follow-up of 41 months was 35.3%. Two patients progressed to muscle-invasive disease.

Ekin et al. evaluated the efficacy of CHT in patients with high-risk NMIBC [31]. Forty-three patients who underwent CHT were evaluated retrospectively. All patients received chemotherapy within 24 hours after TURB, and a second TURB followed after 2–6 weeks, except in patients with primary CIS. Subsequently, CHT treatment sessions followed, once a week for 6 consecutive weeks, and three once-weekly maintenance sessions at 3 and 6 months. Three patients did not complete induction treatment. The recurrence-free rates at 12 months and 24 months were 82% and 61%, respectively. Tumour progression was reported in two patients.

**BSD-2000 system**

In a pilot clinical trial using the BSD-2000® system, Inman et al. reported outcomes of 15 patients with BCG refractory NMIBC, treated with external deep pelvic CHT [16]. All patients completed a 6-week induction course of BCG prior to their most recent recurrence, or were intolerant to BCG. Following TURB, patients received an induction course of six sessions once-weekly of intravesical MMC (40 mg), and four once-monthly maintenance sessions. Eleven patients completed the full treatment schedule (73%). One patient withdrew from the study before completing the induction phase, and three patients did not complete maintenance treatment because of cancer recurrence. Recurrent bladder cancer occurred in 10 patients (67%), with a median time to recurrence of 15.4 months. No tumour progression was reported.

**AMC 70 MHz system**

Geijsen et al. reported on 18 patients with intermediate- or high-risk NMIBC who were treated with MMC and regional hyperthermia after complete TURB [18]. Treatment consisted of an induction period of six once-weekly courses of MMC
and regional hyperthermia. This was followed by one maintenance session every 3 months for a year. Fifteen patients completed the induction period (83%) and nine patients (50%) completed the full maintenance treatment. The 2-year recurrence-free survival rate was 78%.

Adverse events

Synergo

The reported drop-out rate during CHT treatment with Synergo® varied between 0 and 38%. The adverse events most often described were pain (7.8–38.1%), posterior wall reaction (13–63.5%), bladder spasm (13.1–30.6%), dysuria (6.2–57.7%), and haematuria (3–23.8%), and were mostly grades 1–3. Posterior wall thermal reaction, a phenomenon typically seen on cystoscopy after microwave-induced CHT, is caused by the location of the RF antenna. It appears as a medallion-shaped discoloured scar-like patch, which in general resolves spontaneously and is not associated with symptoms [9–11,21,23–30].

COMBAT BRS

In the only published study of CHT treatment using COMBAT BRS®, five treatment sessions out of a total 119 were abandoned before the intended 60 minutes were reached due to adverse events, but all treatment sessions lasted at least 40 minutes. Most adverse events of hyperthermic intravesical chemotherapy (HIVEC) were mild and self-limiting. No grade 3 or higher toxicity was reported. The most common adverse events were irritative lower urinary tract symptoms (33%), bladder spasms (27%), and genito-urinary pain (27%) [13].

Unithermia

In 7.0–11.9% of patients treated with Unithermia®, the complete induction course of six once-weekly instillations was not possible. The most common side effects reported were non-infectious cystitis (37.2%), bladder spasms (20.9–23.5%), and frequency (14.7–25.2%), mostly grades 1–3. However, one case of a grade 5 adverse event was reported, where the patient died of the consequences of bladder perforation. After the ninth treatment session the patient developed abdominal pain and was diagnosed with a perforation of the posterior wall. It was not reported whether the perforation was caused by the catheter placement or due to the treatment itself [14,31].

BSD-2000

In the pilot study by Inman et al. [16] no grade 3 or more serious toxicities were reported. The most common adverse events related to treatment with the BSD-2000 system were; urethral pain due to Foley catheter placement (40%), abdominal discomfort from the hyperthermia system (33%), irritative urinary symptoms from chemical cystitis (27%), and heat-induced induration or swelling of the abdominal skin (27%) [16].

AMC 70 MHz

Treatment with the AMC 70 MHz system did not show grade 3 or 4 toxicity. In 54% of treatments grade 1 (43%) or 2 (14%) toxicity was reported. The most common events were; local pain due to heat treatment (24%), discomfort due to treatment position (20%), and bladder spasms (21.7%) [18].

Consensus

Following the workshop on hyperthermia in genito-urinary cancer during the eighth focal therapy meeting in 2015, in Noordwijk, the Netherlands, we sent a questionnaire to participants working with the different hyperthermia systems. Of the participants approached, 86% responded by completing the questionnaire in full. The questionnaire addressed the following topics: indication for combined chemohyperthermia treatment, exclusion criteria, advantages and disadvantages of different hyperthermia systems, treatment protocol, and what improvements or evidence is needed to implement CHT as routine treatment for NMIBC.

Participants shared the opinion that patients with intermediate- and high-risk NMIBC are eligible for treatment with combined MMC and hyperthermia. One can understand of course that the participants are interested in this technique. For patients with recurrence after BCG (including failure, refractory, intolerance), or not fit for radical cystectomy, CHT is considered an alternative treatment.

Exclusion criteria for this therapy are a small bladder capacity (<150 mL), non-controlled bladder overactivity, urethral strictures, active urinary tract infection, and hypersensitivity to MMC. For patients hypersensitive to MMC, treatment with intravesical epirubicin combined with hyperthermia can be considered. Patients with metal implants, pacemakers or sacral nerve stimulators are at risk for creating hot spots and should not be treated with loco-regional hyperthermia systems.

CHT can be given prophylactically (adjuvant) or in an ablative (neoadjuvant) setting, mainly in CIS. Most commonly, the prophylactic treatment schedule consists of an induction phase of six once-weekly sessions. In each session patients receive 40 mg MMC (Synergo® uses 2 × 20 mg), and treatment takes approximately 1 h. The induction phase of ablative protocol consists in general of eight once-weekly sessions, with 80 mg MMC. Both protocols can be followed by a maintenance phase for which the proper schedule is not defined. During maintenance therapy, patients receive 40 mg MMC. The treatment schedule for maintenance ranges from monthly sessions to once every 3 months, for a duration of 4–12 months using 40 mg MMC.

Future perspectives

Results reported of MMC combined with hyperthermia are promising; however, well-powered randomised studies are still lacking. CHT therapy has been shown to be a safe and well-tolerated treatment, and more efficient than MMC alone.
However, the patients in published studies have very heterogeneous characteristics (primary/recurrent tumours, intermediate-, high-risk, prior instillations, for example), making interpretation of results difficult. To implement combined therapy of MMC and hyperthermia in the treatment of NMIBC, it is necessary to identify categories of patients who would benefit most from this treatment. Also, treatment protocols (induction, maintenance, temperatures) should be defined. Prospective, randomised clinical trials should be initiated in primary treatment of intermediate- and high-risk NMIBC and BCG-refractory patients. Furthermore, clinical trials that compare the efficacy of different hyperthermia systems and cost-effectiveness are necessary. The majority of studies have used the Synergo® system; it should be investigated whether these results also apply to other systems. To our knowledge, no studies have been done that compare different hyperthermia systems.

Currently no optimal treatment protocol for CHT is known, most of the existing schedules are based on existing chemotherapy instillation protocols. Ideally, standardisation of the treatment protocol should be obtained, including targeted temperature, MMC dosage, number of instillations, interval and maintenance schedule.

Quality of life is an aspect that so far has not been assessed for CHT treatment using validated questionnaires. If this treatment is to be introduced as an alternative bladder sparing treatment for patients unfit or unwilling to undergo radical cystectomy, it is necessary to determine also the effect on quality of life. Acute toxicity, tolerability and drop-out rates of CHT have not been evaluated yet, and it is unknown whether treatment with different hyperthermia systems leads to a different variety of adverse events.

At present, intravesical CHT has only been studied in NMIBC. Loco-regional hyperthermia systems such as the BSD-2000® and the AMC 70 MHz have the ability to target the whole pelvic area including the perivesical area and lymph nodes. Potentially, this treatment modality could be used for patients with muscle-invasive bladder carcinoma, unfit for radical cystectomy. In the past, hyperthermia combined with systemic chemotherapy has been studied for locally advanced bladder cancer or muscle-invasive bladder cancer [32,33]. For muscle-invasive bladder carcinoma, loco-regional hyperthermia has also been combined with radiotherapy. This treatment combination has a better local response rate than radiotherapy alone. However, overall survival did not improve [34]. A quadrimal treatment, consisting of a TURB, followed by radiochemotherapy combined with regional deep hyperthermia for the treatment of high-risk T1 and T2 bladder cancer has been proposed and seems well tolerated [35].

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Disclosure statement

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References


