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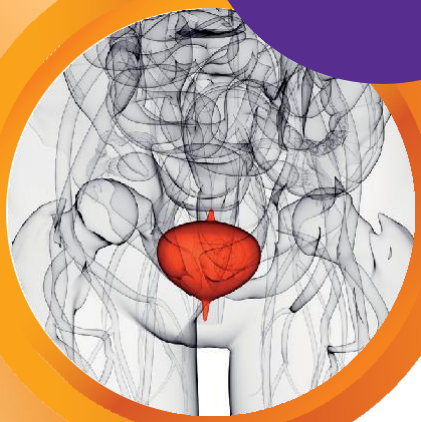

Clinical Evidence
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Results presented at AUA 2020 show that CHT with MMC (HIVEC) is not inferior to BCG in terms of efficacy and patients had milder side effects than those under BCG treatment.

See page 6 for full abstract

COMBAT Medical is committed to investing in research and development, clinical trials and evidence based studies. Demonstrating the effectiveness of COMBATs patented technology and creating a solid foundation for its use.

COMBAT is continously adding to its HIVEC® bibliography of evidence in Non-Muscle Invasive Bladder Cancer (NMIBC).

In use since 2010 the **COMBAT BRS** is a technically advanced, easy to use and affordable system that optimises the intravesical instillation of chemotherapy to achieve real, measurable results.

Clinical Trials

COMBAT has invested in the following trials and is due to announce the start of recruitment for a further series of trials soon. See Appendix for trial protocol flowcharts.

HIVEC®-I HIVEC®-II

Prospective, Randomised International Multicentre Clinical Trials in 598 Intermediate Risk NMIBC Patients. HIVEC I and II have now successfully completed recruitment with data release expected in 2020.

HIVEC®-HR HIVEC®-R HIVEC®-PREMITO

Further trials encompassing 269 patients are currently evaluating the efficacy of HIVEC at various stages of the NMIBC treatment pathway.

Urologists from hospitals throughout Europe continue to evaluate and present their results at worldwide congresses. COMBAT will continue to update its summary of clinical evidence as more data is published and presented.

We partner with a global network of distributors to ensure that the **COMBAT BRS** is available to bladder cancer patients in as many countries as possible. COMBAT is constantly working towards increasing its availability on an international level.

For more information on the clinical programme or clinical evidence please contact us or see www.combatcancer.com

> "Our mission is to optimise the efficacy of the conventional chemotherapy instillation. Reducing recurrence and progression rates in Non-Muscle Invasive Bladder Cancer in a cost effective way that fits alongside current practices."
>
> Edward Bruce-White, Combat Medical, CEO

Targeting NMIBC with HIVEC®

Clinical Evidence Presentation AUA 2020

BCG vs Chemohyperthermia with Mitomycin C for High-Risk Non-Muscle Invasive Bladder Carcinoma: Preliminary Results of HIVEC-HR Randomised Clinical Trial

Presenting Authors: Felix Guerrero-Ramos*, Daniel Antonio Gonzalez-Padilla, Alejandro Gonzalez-Diaz, Felipe Villacampa-Auba, Marta Rodriguez-Izquierdo, Carmen Gomez-Cañizo, Federico de la Rosa-Kehrmann, and Alfredo Rodriguez-Antolin

The Journal of Urology. Vol. 203, No. 4 | May 2020

Introduction and objective: There is an increasing interest in finding a valid alternative for patients with non-muscle invasive bladder cancer (NMIBC). HIVEC-HR is a pilot trial that aims to compare efficacy and safety between BCG and chemohyperthermia (CHT) with mitomycin C (MMC). Here we present our preliminary results once randomization has been completed.

Methods: Open pilot **randomised clinical trial 1:1 including patients with high-risk NMIBC** according to EAU Guidelines (EudraCT 2016-001186-85). Patients with CIS, intolerance or contraindication for receiving BCG or MMC were excluded. Patients were randomly assigned to one of the following groups:

- **BCG** (TICE strain): 50 mg diluted in 50 mL of sterile saline held for 2 hours in the bladder, one weekly instillation for 6 weeks and maintenance according to SWOG protocol.
- **CHT:** 40 mg MMC diluted in 40 mL of distilled water at 43ºC using **COMBAT®** recirculation system for 60 minutes, one weekly instillation for 6 weeks and one monthly instillation for 6 months.

Follow-up was performed with cytology+cystoscopy every 3 months as well as upper urinary tract imaging yearly, as stated by EAU Guidelines. Primary endpoint was recurrence-free survival at 24 months. **Secondary objectives:** safety, progression rate, overall survival and quality of life.

Results: Fifty patients randomised (100% recruitment completed), 48 finally starting treatment. Median age is 73 years, 87.6% males and 83% primary tumours. Baseline characteristics were comparable in both groups. Median **follow-up is 24.8 months** from TURBT. For the **BCG group, 6 recurrences (from which 5 progressions to T2)** were reported, and **only 3 recurrences (from which 2 progressions) happened in the CHT group.** Regarding safety profile, adverse events (AE) appeared in 12 patients from CHT and 10 from BCG group, with no differences in the severity (4 patients in each group for CTCAE grade 3). AE in CHT group were mostly grade 1.

Conclusions: According to our trial preliminary results, CHT in high risk NMIBC patients seems at least not to be inferior to BCG in terms of efficacy. Moreover, patients under CHT have milder side effects than those under BCG treatment.

Chemohyperthermia with Mitomycin C (MMC) and COMBAT System in High Risk Non Muscle Invasive Bladder Cancer (HR NMIBC): A New Alternative?

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AUA 18-21 May 2018 San Francisco, CA, USA | The Journal of Urology, Vol. 199, Issue 4, e1119 | April 2018

Introduction and Objective: The recommended treatment for high risk non-muscle invasive bladder cancer (HR NMIBC) is maintenance intravesical BCG therapy. However, adverse effects and problems with BCG supply and production has led to significant disruption in the treatment of these patients. We present the results of a multicentre European series of HR patients treated with MMC and chemohyperthermia (CHT) with COMBAT HIVEC® treatment.

Material and Methods: A retrospective analysis of 145 patients with HR papillary only NMIBC, treated by 14 centres across Europe between December 2014 to October 2017 was performed. High risk disease was defined according to EAU risk classification. Following transurethral resection of bladder tumour (TURBT), all patients were treated with adjuvant intravesical instillations of 40mg MMC at 43°C, for 60 minutes using COMBAT HIVEC® treatment. All patients received CHT treatment because BCG was unavailable, or they could not tolerate BCG due to adverse events. Approval of local ethics committee was obtained. Treatment protocols were decided by individual institutions although majority received 6 weekly instillations of induction with a variable maintenance regime. Performing ReTURBT prior to instillation was at the discretion of the clinician and local institutional recommendation. Patients had check cystoscopy at 3 monthly intervals.

Results: 145 patients were treated with the COMBAT system with a median follow up of 20.8 months. The mean age of patients was 70.6 years. 65% of NMIBC were primary tumours with 65% pTl and 66% G3. 46% of patients had multiple tumours and 36% were >3cm. 116 patients (80%) received a minimum of 6 weekly instillations as part of induction therapy. 79 patients (55%) received some form of maintenance therapy. In the Intention to Treat analysis (145 patients), mean follow up 21 months, recurrence free rate (RFR) was 82% (27 patients) and progression free rate (PFR) to T2 was 98% (3 patients). In the Per Protocol analysis (at least 6 instillations, 116 patients), mean follow up was 22 months, RFR was 83% (20 patients) and PFR to T2 1 was 93% (2 patients). RFR at one year follow up was 87.3%.

Conclusions: CHT with 6 weekly induction 40mg MMC using the COMBAT system represents an attractive alternative to intravesical BCG therapy. RFR and PRF at 12 months are comparable to EORTC nomograms. Randomised controlled trials are eagerly awaited.

Chemohyperthermia with Mitomycin C and COMBAT System in High Risk Non-Muscle Invasive Bladder Cancer Patients: Initial Experience in a Single Centre

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Global Congress on Bladder Cancer 2nd Edition | Poster Presentation 5-6 October 2017, Edinburgh, UK

Introduction and Objective: The absence of BCG has led to the treatment of patients with High Risk (HR) Non-Muscle Invasive Bladder Cancer (NMIBC) with instillations different than usual. We present the results of our series in patients treated with Mitomycin C (MMC) and chemohyperthermia with the COMBAT device.

Materials and Methods: From November 2014 to May 2017, 74 patients with high-risk NMIBC according to EAU criteria were treated with instillations of 40 mg MMC at 43°C, using the COMBAT recirculation system. The protocol followed uses 6 weekly and 6 monthly maintenance instillations. Patients were selected because of poor tolerance to prior BCG, absence of BCG or participation in clinical trial. Performing ReTURBT prior to instillation was at the discretion of the specialist, depending on the patient's overall condition and tumor size.

Results: With a median follow-up of 14.7 months and a median age of 75 years, 74 patients were analyzed, 57 with primary tumours and 17 have had previous tumours. The TNM was Ta (44 pac); T1 (29 pac); Tis (1 pac). The WHO grade was HG (68 pac), LG (6 pac). Divided by the simplified EAU risk scale, 70 patients and 4 patients were in the high-risk and intermediate-risk groups, respectively. The overall recurrence rate was 24% (16% relapses and 8% progressions). The mean time to relapse was 9.8 months. Of the 6 progressions, 3 were M1 in elderly patients with high surgical risk and with large tumours, suggesting initial underestimation. Stratified by EAU recurrence risk groups, recurrences were 50%, 29% and 17% in the high, intermediate-high and intermediate-low risk groups respectively. Stratified by EAU progression risk groups, progressions were 0%, 10%, 3% and 0% in the high, intermediate high, intermediate-low and low risk groups respectively. Of the total, 46 patients completed treatment, 11 were still on treatment and 17 dropped out (4-5% - due to allergy to mitomycin, 4-5% - due to intolerance, and 9-12% - due to other causes). The median number of instillations until dropout was 5. Of those who completed the treatment, 29% relapsed compared to 28% of those who dropped out.

Conclusions: Chemohyperthermia with MMC and the COMBAT system, used according to the previous protocol, is effective in the treatment of HR-NMIBC. The high rate of progression to M1 in our series corresponds to elderly patients with high surgical risk and probable initial under-staging. Chemohyperthermia is well tolerated, with 10% of withdrawals due to side effects, with no influence on relapse rate.

Clinical Evidence Presented EAU 2020

Intravesical Chemohyperthermia (HIVEC) in BCG Unresponsive Non-Muscle Invasive Bladder Cancer Patients: Oncological Outcomes of a Multi-Centre European Registry

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EAU20 Virtual 17-26 July

Introduction: The recommended treatment option for BCG unresponsive non-muscle invasive bladder cancer (NMIBC) is radical cystectomy. However, radical cystectomy may not be suitable for all patients and therefore alternative treatments are an unmet clinical need. Here, we report oncological outcomes of patients with BCG unresponsive NMIBC who were treated with adjuvant conductive chemohyperthermia (CHT).

Material and Methods: Patients with BCG unresponsive NMIBC treated with CHT between 2011-2019 recruited to a multicentre European registry were included for analysis. CHT was delivered using the Combat BRS system. All patients had complete resection of all papillary tumours prior to intravesical treatment. Each treatment instillation comprised of 40mg mitomycin C with hyperthermia delivered at 41-43^{o}C over 60 minutes. BCG-unresponsive NMIBC was defined as papillary disease ± carcinoma in situ (CIS) within 12 months of last instillation of adequate BCG, or recurrent high grade papillary disease within 6 months of last instillation of adequate BCG therapy, or stage T1 disease at first 3 month cystoscopy following induction BCG. Primary endpoint was the 24-month recurrence-free survival (RFS) and the progression-free survival (PFS). For patients with CIS the end point was complete response rate at 6 months. RFS was defined as patients alive and without evidence of any disease recurrence while PFS was define as patients alive who did not develop ≥pT2.

Results: A total of 135 patients from 15 European institutions met the criteria for BCG unresponsive disease. Median age was 70.1 years (62.1-78.0) with male patients comprising of 111 patients (82.2%). A total of 34 patients (25.2%) had CIS only disease, 84 patients (62.2%) with papillary only disease and 17 patients (12.6%) with concurrent CIS and papillary disease. A total of 52 patients (38.5%) had pT1 and 49 patients (36.3%) had pTa disease.

With a median follow-up of 14 (IQR: 8-23) months, 56 patients (41.5%) developed disease recurrence. RFS at 24 months was 53.9% and 24 month PFS was 92.1%. In patients with concomitant CIS, 6-month complete response rate was 70.6%.

Conclusions: BCG-unresponsive NMIBC patients who are treated with CHT had a 24-month DFS of 53.9% and PFS of 92.1%. CHT seems a valid treatment option for BCG unresponsive NMIBC patients who are unsuitable for radical cystectomy.

Hyperthermic Intravesical Chemotherapy for BCG-Unresponsive Non-Muscle Invasive Bladder Cancer Patients

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AUA 18-21 May 2018 San Francisco, CA, USA | The Journal of Urology, Vol. 199, Issue 4, e1234–e1235 | April 2018

Introduction and Objective: Adjuvant intravesical instillations with Bacillus Calmette-Guerin (BCG) is the recommended treatment option for patients with intermediate and high-risk non-muscle invasive bladder cancer (NMIBC). Despite adequate BCG treatment, a large proportion of patients experiences a recurrence. Although radical cystectomy is the Gold Standard for BCG-unresponsive NMIBC, a number of patients are unfit for or unwilling to consider this option. The optimal therapy in such cases is unknown. The objective of the present study was to assess the efficacy of hyperthermic intravesical chemotherapy (HIVEC®) in BCG-unresponsive intermediate and high risk NMIBC patients.

Methods: From October 2014 to July 2017 NMIBC patients who were defined BCG-unresponsive (recurrence of high-grade disease after having had a minimum of 5/6 induction and 2/3 maintenance BCG instillations) were prospectively included at three academic institutions. All patients were planned to receive HIVEC™ treatment, consisting of an induction phase followed by maintenance therapy. Only patients who had a minimum of 5 HIVEC™ instillations were included in the present analysis. Patients were followed by cystoscopy and cytology every three months and a CT-scan yearly. The primary outcome was the recurrence free survival (RFS). The Common Terminology Criteria for Adverse Events (CTCAE) was used to assess side-effects.

Results: The study population consisted of 59 BCG-unresponsive NMIBC patients (8% intermediate and 92% high risk) of whom 55 underwent ≥ 5 HIVEC™ treatments. Histology was urothelial carcinoma in all patients and T-stage was pTis in 31, pTa in 10, pT1 in 9, pT1+CIS in 3 and pTa+CIS in two patients. The median age and follow-up was 72 years and 9.0 months (IQR 7.1 - 19.5). The overall recurrence rate was 58% and the mean RFS was 16.6 months [SE 2.1]. In patients having carcinoma in situ (n= 36), the recurrence rate was also 58% and the mean RFS was 16.2 months [SE 2.8]. Progression occurred in 3 patients and two patients experienced severe side-effects (CTCAE >2).

Conclusions: HIVEC® seems a valid treatment option for BCG-unresponsive intermediate - or high-risk NMIBC patients. We report a mean RFS of > 1 year, potentially avoiding or postponing the need for radical surgery in these patients.

Heat Targeted Drug Delivery (COMBAT) in Superficial TCC: First Midterm Results in a Cohort of High-Risk Patients Scheduled for Cystectomy

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2018 Genitourinary Cancers Symposium | J Clin Oncol 36, 2018 (Suppl. 6S; Abstr. 442) Presented February 9 | 2018

Background: Due to the suboptimal outcomes in recurrent superficial TCC over the last 30 years the search for new treatments continues. We report the first mid term results of a high risk cohort of heavily pretreated patients by a circulating device for intravesical thermochemotherapy. It is known that the effect of mitomycin increases at a temperature over 40°C.

Methods: 58 patients with different failed methods of former intravesical therapy and recurrent TCC (21 intermediate risk and 37 high risk patients) were treated with the COMBAT device which facilitates irrigation of the bladder with mitomycin 40 mg at exactly 43 degrees Celsius for 1 hour/6 courses weekly. Side effects were monitored prospectively, and success of the treatment was controlled by ReTUR whenever possible and afterwards by 3 monthly cystoscopy and cytology.

Results: 22 patients had dysuria during treatment and 9/58 suffered from hematuria but without intervention. In 6 cases urinary tract infection occured and 3 patients had allergic reaction. In one patient thermochemotherapy must be terminated due to pain and discomfort, no long term morbidity was recorded over the whole period. The FU was 14 months (3-29) for the entire cohort, 17 patients had a FU of over 2 years. One patient had recurrent pTaGIII Tumor managed successfully by TUR. 2 patients underwent cystectomy because of invasive recurrence early after intravesical therapy, one patient developed bone metastasis 2 years after therapy without intravesical tumor.

Conclusions: Thermochemotherapy with heated mitomycin is a well tolerated new option for patients with superficial TCC who are at high risk of recurrence or progression. The toxicity is acceptable and no long term morbidity was observed. The rate of cystectomies in this heavily pretreated group of patients including 18 BCG failures was very low with N = 2 respective 1,9%. Intravesical thermochemotherapy seems to be a new therapeutic bladder preserving option in high risk patients with superficial TCC. It is of note that thermochemotherapy has now been included in the European Guidelines.

Clinical Evidence Presented AUA 2020

Chemo-Resection with Hyperthermic Intravesical Instillation (HIVEC-R) Vs Standard Treatment in Patients With Intermediate-High Risk NMIBC: Comparative, Prospective, Randomized, Controled Study of Efficacy and Tolerability: Preliminary Results

Alejandro Sousa* , Ignacio Gonzalez-Valcárcel , Juan Leon Mata , Jose Manuel de la Morena , and Luis Martínez-Piñeiro
Volume 203 | Issue Supplement 4 | April 2020

Introduction and Objective: The rationale about neoadjuvant chemo-hyperthermia (NCHT) in NMIBC is based on the concept of "immunogenic cell death (ICD)". Some kinds of antineoplasic treatments, including CHT, may destroy tumoral cells by ICD. We hypothesized that NCHT may stimulate patient´s immune response acting as a vaccine against cancer.

Methods: A Phase III comparative, prospective, randomized, controlled clinical trial with Mitomycin C (MMC) was designed to compare the efficacy and tolerability of NCHT with 8 neoadjuvant weekly doses of 80 mg MMC recirculating at 43°C with the BRS system, Combat Medical (Hertfordshire. UK) vs 15 passive, normothermic, standard, adjuvant doses (4 weekly + 11 monthly) of 40 mg MMC after TURBT or BCG if high risk category. The primary endpoint of the study was 24-months recurrence free survival (RFS) of NCHT compared with standard treatment. Secondary endpoints were efficacy of NCHT in terms of complete and partial response (CR, PR) after 4 and 8 doses. Tolerability, Quality of life and cost-effectiveness of NCHT compared with standard instillation. Inclusion criteria: Histological confirmed previous urothelial cell carcinoma (UCC), NMIBC following recurrence of G1-3 pTa or G1-2 pT1, ≤6 number of tumours, Aged ≥18 years. Exclusion criteria: Patients with solid tumour, muscle infiltrating aspect or CIS suspicious, positive citology and recurrence of previous T1G3 or CIS tumours in the last 12 months Between March 2015 and June 2019, 68 patients from 2 hospitals in Spain were randomized to neoajuvant CHT or standard TURBT. We present the preliminary results with a mean follow up of 38 months (4-54 months).

Results: Initial pathological response (NCHT arm): 21 patients showed CR (pT0) 61.8%, 10 patients showed PR 29.4%, 3 patients showed NR 8.8%. After 38 months, in the NCHT arm 7/34 (20.5%) patients showed recurrences and 1/34 (2.9%) progression to T1G3/Cis. In the standard MMC arm, 13/34 (38.2%) patients showed recurrences, 3/34 (8.8%) local progression and 1/34 (2.9%) muscular invasion (T2G3). Differences were statistically significative for recurrence ($p<0.02$), superficial ($p<0.05$) and muscular progression ($p<0.01$). Tolerance and adverse events were similar in both groups ($p<0.3$). In the NCHT arm, 18/34 pts (52.9%) showed grade 1-2 AE (irritative symptoms, bladder spasms, pain, hematuria, urinary infection and MMC alergy) and 3/34 (8.8%) grade 3 (bladder retraction, bladder calcification and urethral stenosis). Among the St MMC arm 15/34 pts (44.1%) showed grade 1-2 AE (irritative symptoms, bladder spasms, pain, hematuria, urinary infection and MMC alergy) and 2/34 (5.8%) grade 3 (bladder retraction and urethral stenosis)

Conclusions: In the preliminary analysis, 60% of patients showed complete response after NCHT and the recurrence and progression rates after a mean follow up of 3 years were significantly better in the NCHT arm vs. standard TURBT and adjuvant therapy. Further studies are needed to confirm a protective effect of NCHT against tumoral recurrence and progression.

Source of Funding: IIS clinical trial sponsored by Dr. Alejandro Sousa BRS system and sets were supplied with no cost by Combat Medical ltd.Insurance policy cost was financed by Combat Medical Ltd.

The Reduction of the Neutrophil / Lymphocyte Ratio (NLR) is Associated with a Complete Response and Disease-Free Survival in Patients with Non-Muscle Invasive Bladder Cancer Treated with Intravesical Neoadjuvant Chemohyperthermia

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XXXIV Reunión Nacional del Grupo de Urología Oncológica. Madrid | 4th- 5th April 2019

Introduction and Objective: Different articles have shown that the neutrophil / lymphocyte ratio can predict survival in different cancers including muscle invasive bladder cancer.

Objective: To determine if NLR can predict pathological response and recurrence-free survival in non-muscle invasive bladder cancer treated with neoadjuvant intravesical chemohyperthermia (HIVEC).

Patients and Methods: We conducted an observational, analytical and retrospective cohort study of 43 patients with High and Intermediate risk NMIBC treated with neoadjuvant HIVEC between January 2009 and June 2017 in a single institution. The neoadjuvant treatment comprised 8 weekly instillations of HIVEC using the Combat BRS device (London, United Kingdom) with 80mg of Mitomycin-C (MMC) in 50ml of water for 1 hour. All patients had transurethral bladder resection (TURB) 2 weeks after treatment with HIVEC. The primary objective was to determine the complete response rate (CR) obtained in post-treatment TURB and disease-free survival (DFS) at 12 months. NLR was determined before and after treatment with neoadjuvant HIVEC.

Results: After neoadjuvant treatment with HIVEC, 27 (63%) patients had CR and 13 (30%) patients had a partial response (PR) at TURB. The median follow-up after TURB was 51 months (Interquartile Range (IR)): 12.9-108.0 months with a DFS of 81.4% without the patients developing progression. Post-HIVEC reduction in NLR (before and after treatment) was predictive of CR. A lower NLR post-HIVEC and a reduction after neoadjuvant treatment were associated with a higher DFS.

Discussion: Some chemotherapeutic drugs (such as anthracyclines and oxyplatin) induce immunogenic cell death (ICD), resulting in increased immunity. However, many chemotherapeutic agents, including MMC, Etopoxide and Cisplatin, do not cause ICD. It is possible that neoadjuvant HIVEC induces ICD or activates the immune system through heat shock proteins or other factors.

Given that neoadjuvant HIVEC is performed before TURB, it could generate a tumor ICD that would improve immunological activation and clinical response to treatment. Functioning, at least theoretically as a self-vaccine that would explain the reduction of tumoral recurrences.

Conclusions: Treatment with neoadjuvant HIVEC resulted in a CR of 62.8% and was associated with a durable DFS in 89% of patients. The mechanisms by which HIVEC affects local and systemic immune function are not known with certainty, but the reduction in NLR was associated with an improvement in the response to treatment in both the CR and DFS index.

Clinical Evidence Presented AUA 2020

Prospective Randomised Clinical Trial of Chemo-hyperthermia with Mitomycin-C Prior to Transurethral Resection of the Bladder and its Relationship with the Rate of Early Recurrence in Non-Muscle Invasive Bladder Cancer: Intermediate Analysis

Ana Plata Bello , Carlos Garcia Alvarez, Julio Plata Bello, Marco Antonio Tamayo Jover and Tomas Concepcion Masip
The Journal of Urology | Volume 203 | Issue Supplement 4 | May 2020

Introduction and Objective: Immediate postoperative instillation (IPOP) of mitomycin-C (MMC) having been shown to be effective in preventing recurrence. 30% of patients are not suitable candidates for IPOP. In these circumstances theuse of chemohyperthermia (CH) immediately prior to TURBT is a safe and effective alternative with improved penetration of MMC through the urothelium. OBJECTIVE: to evaluate the early recurrence rate of low to intermediate risk NMIBC with the CH instillation of MMC prior to TURBT (compared to single immediate IPOP MMC) at 12, 18 and 24 months. Safety and tolerability will also be evaluated.

Methods: Single center prospective randomized control clinical trial. Primary analysis: non-inferiority study, safety and tolerability of pre-operative instillation of MMC-CH in 152 patients: 76 in the control arm (CA: postoperative MMC normothermic), 76 in the experimental arm (EA: Hyperthermic pre-operative MMC). Inclusion Criteria: Low to intermediate risk NMIBC, single tumor <30mm or multiple <8 lesions and <30mm. Follow up with cystoscopy, cytology and ultrasound. Assessment tools for tolerability of the instillation (pain scale analogue–visual) and global satisfaction.

Results: 152 recruitment patients: 76 CA, 76 EA. 125 were male (82.2%) and 132 were smoker/ex-smoker (86.8%). Pathological Anatomy analysis: - Comply with the PA criteria for low to intermidiate risk NMIBC 86 patients (56.6%)-> pTaG1-3. - Do not comply with PA criteria 66 patients (43.4%)-> 34 No tumor (22.4%) and 32 high risk tumor: 22 pT1 (14.1%), 8 pT2 (5.3%), 2 pTis (1.3%). Received instillations (pre/post operative) 127 patients (80.9%). a) EA: 76 (100%). b) CA: 51 (67.1%) = 25 (32.9%) did not receive: 22 macroscopic hematuria and 3 deep resections. Good global tolerability to MMC-CH: only 1 patient received <1h instillation. Side effects: 6 bladder spasm, 4 irritation, 3 allergic reaction (cutaneous eruption). Median pain scale analogue: 2 points. Mean follow up: 12 months. Recurrence-> 3 patients (3.5%) with PA valid criteria: 1 CA, 2 EA.

Conclusions: Chemohyperthemia treatment (HIVEC) with Mitomycin-C pre-TURBT seems to be a safe and well tolerated alternative. After a follow-up period of 12 months the recurrence rate in both arms seems to be equivalent.

Source of Funding: None.

Two-Year Follow-Up Results After Sequential Intravesical Bacillus Calmette-Guérin (BCG) and Device-Assisted Chemo-Hyperthermia (Combat BRS) for High-Risk (HR) Non-Muscle Invasive BladderCancer (NMIBC) Patients... a BCG-Sparing Strategy

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Introduction & Objectives: Until October 2014, our standard bladder sparing treatment for HR-NMIBC was a full-dose intravesical BCG 6-week induction course and maintenance BCG for 1-3 years. In response to the BCG shortage, we modified our regimen to sequential full-dose BCG and device-assisted chemo-hyperthermia (Mitomycin C [MMC] delivered by the Combat BRS system). Here we present our 2-year results after start of treatment.

Material & Methods: The 6-week induction regimen became BCG (weeks 1,2), Combat BRS (weeks 3,4,5) and BCG (week 6). Nine further Combat BRS maintenance treatments were given by 1 year comprising 3 sets of weekly instillations for 3 weeks. Sixty-one patients commenced treatment for HR-NMIBC (high grade [grade 3] and/or carcinoma in situ [CIS]) between October 2014 and September 2015. T1 tumours were routinely re-resected. We excluded 11 patients because of concurrent upper urinary tract or prostatic urothelial tumours, previous radiotherapy or BCG or a course of MMC. During this time-period, only 5 patients with HR-NMIBC underwent primary cystectomy.

Results: We report on 50 patients with HR-NMIBC (CIS detected in 40% and T1 in 62%) who now have 2-year follow-up. Of these, 47 (94%) are progression-free, 46 (92%) are cystectomy-free, 38 (76%) are disease free. In the 4 patients with refractory HG-NMIBC who underwent cystectomy, we report no pathological upstaging to MIBC. Forty-seven patients are alive (2 deaths due to metastatic BC and 1 non BC-related death). Forty-two patients (84%) tolerated Combat BRS treatment; 3 stopped because of rashes during maintenance and 5 discontinued following bladder-related tolerability issues.

Conclusions: In an era of BCG shortage, we are pleased with the 2-year follow-up results of this regimen where 12 of 15 instillations utilized heated MMC using the Combat BRS device. In this non-selected HR NMIBC series, the low progression rates and good tolerability are reassuring.

One-year Follow-up Results after Sequential Intravesical Bacillus Calmette-Guérin and Device-Assisted Chemo-Hyperthermia (Mitomycin C Delivered by the COMBAT BRS System) for High Risk Non-Muscle Invasive Bladder Cancer Patients... A Bacillus Calmette-Guérin Sparing Strategy

TR Leyshon Griffiths*, William JF Green, Peter T Grice, Jonathan C Goddard, Roger C Kockelbergh,
Leicester, United Kingdom

The Journal of Urology, Vol. 197, Issue 4, e367 | April 2017 | AUA Boston

Introduction and Objective: Until October 2014, our standard bladder-sparing treatment for HR-NMIBC was a full-dose intravesical BCG 6-week induction course and maintenance BCG for 1-3 years. In response to the BCG shortage, we modified our regimen to sequential full-dose BCG and device-assisted chemo-hyperthermia (Mitomycin C [MMC] delivered by the COMBAT BRS system). Here we present our 1-year results after start of treatment.

Material & Methods: The 6-week induction regimen became BCG (weeks 1,2), COMBAT BRS (weeks 3,4,5) and BCG (week 6). Nine further COMBAT BRS maintenance treatments were given by 1 year comprising 3 sets of weekly instillations for 3 weeks. We reviewed the 1-year follow-up results of 50 HR-NMIBC (high grade [grade 3] and/or carcinoma in situ [CIS]) patients who commenced treatment between October 2014 and September 2015. T1 tumours represented 62% of cases and were routinely re-resected. CIS was detected in 40% of cases. We excluded 11 patients from this series who had concurrent upper urinary tract or prostatic urothelial tumours, previous radiotherapy or BCG or a course of MMC.

Results: Of 50 patients, 44 (88%) were disease-free by 1 year; 3 (6%) had refractory HR-NMIBC at 6 months, 2 (4%) progressed to MIBC by 6 months and 1 (2%) presented with metastatic disease at 1 year. All 6 had CIS and/or T1 at diagnosis. Forty-three patients (86%) tolerated COMBAT BRS treatment; 2 reacted with rashes during maintenance and 5 had bladder-related tolerability issues.

Conclusions: Our oncological results with sequential BCG/COMBAT BRS at 1 year are at least comparative at this time-point with those expected for HR-NMIBC patients on maintenance BCG. Tolerability and compliance shows great promise.

HIVEC in Intermediate – High Risk Non-Muscle Invasive Bladder Cancer

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International Journal of Hyperthermia, 2016 Vol. 32, No. 4, 374–380

Purpose: To examine the effectiveness of hyperthermic intravesical chemotherapy (HIVEC) with Mitomycin-C (MMC) for patients with intermediate–high-risk non-muscle invasive bladder cancer.

Materials and Methods: From November 2010 to April 2015, 40 patients with intermediate–high-risk NMIBC received HIVECtreatment with a COMBAT BRS system. Of these patients, 24 received neoadjuvant HIVECtreatment (eight weekly instillations) before a transurethral resection of the bladder (TURBT) and 16 received adjuvant HIVEC treatment post-TURBT (four instillations weekly + six monthly). The pathological response of each tumour was evaluated after the neoadjuvant treatment. Recurrence rates and adverse effects were evaluated in both groups.

Results: A total of 40 patients completed the induction therapy: 24 patients received the Neoadjuvant HIVEC treatment. Of these patients, 15 (62.5%) showed a complete response. Eight patients (33.3%) showed a partial response, and one patient (4.1%) showed no response at all. The 4-year cumulative incidence of recurrence was 20.8%. The adjuvant HIVEC treatment was given to 16 patients. The 2-year cumulative incidence of recurrence was 12.5% for this group. The incidence and severity of side effects were slightly lower in the adjuvant group than in the neoadjuvant group. However, the difference was not statistically significant ($p< 0.3$). Most of the side effects were low grade and had virtually no effect on the treatment plan, and 97% of patients completed all of the HIVEC instillations scheduled.

Conclusions: The recirculation of hyperthermic MMC using COMBAT's HIVEC treatment is safe and effective and is capable of achieving good success rates in both neoadjuvant and adjuvant settings. This treatment seems to be appropriate for NMIBC intermediate – high-risk patients who cannot tolerate or have contraindications for standard BCG therapy or in cases in which there are supply issues or shortages of BCG.

Safety and Tolerability Analysis of Hyperthermic Intravesical Mitomycin to Mitomycin Alone in HIVEC I and HIVEC II: An Interim Analysis of 307 Patients

Tan W.S.[1], Palou J.[2], Kelly J.[1]
Institutes: [1] University College Hospitals London, Dept. of Surgery and Interventional Sciences, London, United Kingdom, [2] Universitat Autònoma De Barcelona – Fundació Puigvert, Dept. of Urology, Barcelona, Spain
European Urology Supplements | Vol. 16, Issue 3 | e1150–e1151 | March 2017

Introduction: There is increasing evidence that hyperthermic MMC (HM) is an effective treatment for non-muscle invasive bladder cancer (NMIBC). The COMBAT BRS system is a novel hyperthermia delivering device which allows temperature controlled delivery and recirculation of HM via a urethral catheter using an external heat source. HIVEC I and II are two randomised control trials to determine if HM is superior to MMC alone in intermediate risk NMIBC. We report safety and tolerability outcomes comparing the two treatment arms.

Methods: HIVEC I and II are multicentre, open-labelled phase II randomised controlled trials recruiting patients from 25 Spanish and UK centres. The HIVEC I randomises patients to either MMC, HM for 30 mins and HM for 60 mins (HM 60). Patients receive 4 once weekly treatments followed by 3 one monthly treatments. HIVEC II randomises patients to MMC or HM 60 where both treatment arms receive 6 weekly treatments. Both trials use 40 mg MMC in all arms diluted in either 50 ml (HIVEC I) or 40 ml (HIVEC II) of sterile water. We compared all HIVEC I and II patients who were randomised to MMC (n=154) or HM 60 (n=153). Main inclusion criteria included complete resection of visible tumour prior to enrolment into the trial. Patients with urothelial cell carcinoma of the prostatic urethra or upper urinary tracts were excluded. HM was delivered by heating MMC to 43°C and delivered using a 16 Fr catheter. Adverse events (AE) were reviewed by the independent data monitoring committee.
HIVEC I was registered with the EudraCT (2013-002628-18) while HIVEC II was registered with ISRCTN (23639415).

Results: 307 patients were included for analysis. 88.9% and 94.8% of HM and MMC patients completed adjuvant inductive therapy respectively. Reasons for stopping therapy in 17 HM patients include: MMC allergy (n= 11), urinary symptoms (n=2), pain (n=1), haematuria (n=1), pneumonia (n=1) and in 8 MMC patients include: MMC allergy (n=7) and angina (n=1). AE which led to early termination of treatment were Grade II. 218 and 137 related AE were reported in HM and MMC arms respectively. There was no significant difference in AE between HM (n=78, 51%) and MMC (n=66, 42.9%) (p=0.154). There were 118 unrelated AE in the HM arm and 140 unrelated AE in the MMC arm. Most AE were Grade ≤II (HM: 97.7%, MMC: 98.5%). Grade III AE included: pain (N=1) and MMC allergy (n=2) in the HM arm and pyrexia (n=1) and MMC allergy (n=1) in the MMC arm. There was no Grade >III related AE. There was no difference in pain (HM: 13.1% vs MMC: 8.4, p=0.190), dysuria (HM: 5.2% vs MMC: 6.5%, p=0.617), urgency (HM: 11.8% vs MMC: 3.9%, p=0.067), incontinence (HM: 3.3% vs MMC: 0.6%, p=0.097), nocturia (HM: 3.9% vs MMC: 3.9%, p=0.991), urinary tract infection (HM: 3.3% vs MMC: 2.6%, p=0.728) and rash/ allergic reaction (HM: 7.8% vs MMC: 5.2%, p=0.327). HM treated patients were significantly more likely to develop urinary frequency (HM: 15.0% vs MMC: 5.8%, p=0.008), haematuria (HM: 11.8% vs MMC: 3.9%, p=0.010) and bladder spasm (HM: 6.5% vs MMC: 0.6%, p=0.006). No urethral strictures were reported in either treatment arm.

Conclusions: HM delivered using the COMBAT BRS system is safe and well tolerated. The majority of AE observed in the HM arm were low grade with urinary frequency and haematuria more common in HM in comparison to MMC treated patients. HM represents a safe and well tolerated intravesical treatment for NMIBC.

Quality of Life (QoL), Non Muscle Invasive Bladder Cancer (NMIBC) and Endovesical Treatments: Instillation Matters

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Global Congress on Bladder Cancer 2nd Edition | Poster presentation 5-6 October 2017 | Edinburgh, UK

Introduction and Objective: The spectrum of instillations available for the treatment of bladder cancer is increasing. Apart from effectiveness, quality of life may be a factor when choosing an instillation or another. The aim of this study is to evaluate and compare the quality of life of patients treated, during the induction phase, with three types of instillations: passive Mitomycin C (MMC), BCG and chemohyperthermia (CHT) with MMC using the COMBAT system.

Material and Methods: In 56 consecutive NMIBC patients with indication for endovesical treatment, QoL has been prospectively measured, as well as the side effects during the induction phase. The MMC protocol was 40 mg weekly for 4 weeks, the BCG protocol used a weekly TICE strain vial for 6 weeks, and the one on CHT used 40 mg of MMC at 43°C using the COMBAT recirculation system, a weekly application for 6 weeks. Spanish validated questionnaires IPSS, FACT, FACT BL, and CTCAE were used for QoL and side effects. QoL was measured before the first instillation, at the fourth, and at the end of the induction phase. Side effects were measured after each instillation.

Results: A total of 293 instillations (158 BCG, 75 CHT and 60 MMC) were performed. BCG instillations had more side effects (20.88%) than CHT (5.33%) and MMC (5%) according to CTCAE, being non-infectious Grade I cystitis the most frequent . Concerning QoL, most of the patients start from a similar baseline, finding significant differences in the 4th instillation, in which QHT gives a better quality of life compared to BCG. With regard to changes of QoL over induction period, both FACTBL and FACT are significantly better when comparing CHT versus BCG. All groups improve their quality of life at the end of instillations. Regarding IPSS, there are no significant differences between the three treatments.

Conclusions: QoL is altered during treatment with intravesical instillations, although without major differences among the groups. QoL of all treatments improve upon discontinuation of instillations. Patients on instillations with CHT have a better quality of life halfway through treatment than those with BCG. The IPSS does not present significant differences among the three types of instillations. Regarding side effects, CHT is better tolerated than BCG, with fewer side effects and less severe.

Clinical Evidence Presented AUA 2019

The Effect of Conductive Hyperthermia on Mitomycin C Absorption During Intravesical Chemotherapy

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AUA 3-6 May 2019, Chicago, USA | The Journal of Urology, Vol. 201, Issue 4S , May, 2019

Introduction: Hyperthermia (heating to 43°C) activates the innate immune system and improves bladder cancer (BC) chemosensitivity. In this study, we evaluated the impact of convective hyperthermia on intravesical mitomycin C (MMC) pharmacokinetics in live porcine bladder models.

Methods: Forty 60 kg female swine were anesthetized and catheterized with a 3-way, 16-F catheter. The Combat BRS device was used to heat the porcine bladders to a target temperature of 43°C with recirculating intravesical MMC (2 mg/mL) at doses of 40mg, 80mg and 120mg. Dwell-heat time ranged from 30 to 120 minutes, after which rapid necropsy with immediate flash freezing of tissues (bladder, lymph nodes, liver, kidney, spleen, heart and lung) occurred. Blood and urine were collected longitudinally. Serum and tissue MMC concentrations were measured by liquid chromatography tandem-mass spectrometry (Agilent 1200, Applied Biosciences/SCIEX API 5500 QTrap). Data acquisition and quantification was performed by Analyst 1.6.2 software.

Results: As shown in the Table, 3 factors increased MMC absorption into the bladder: dwell time, drug concentration, and the presence of heat. Bladder MMC concentrations were, in general, significantly higher in pigs that underwent convective hyperthermia than in those that did not (it is uncertain why this relationship was not present at the 120 mg dose with 1-hour dwell time). The relationship between bladder penetration of drug and heating showed a weak linear relationship with dose (Kendall's tau = 0.35). In the hyperthermia arm, drug penetration saturated at 80 mg dose, suggesting that with heating, drug absorption may saturate and not require higher doses to achieve the maximal biological effect. Importantly, convective hyperthermia did not increase the MMC concentration in the liver, heart, kidney, spleen, lung, lymph node tissue and plasma and is therefore not expected to result in excess toxicity in humans, even at the 120 mg dose.

Conclusions: Convective bladder hyperthermia using **the Combat BRS device increases MMC penetration into the bladder wall but does not result in an increase of MMC levels in the liver, heart, kidney, spleen, lung, lymph node tissue and plasma.** The use of hyperthermia may saturated drug delivery and allow lower doses. These data support the use of the Combat BRS device to improve MMC penetration into the bladder wall.

MMC dose & dwell time	Bladder wall Mitomycin C concentration (ng/ml)			
	Room Temperature		Hyperthermia	
	Median	IQR	Median	IQR
40mg (1 hour)	329	91 - 422	470	260 - 1029
80mg (1 hour)	617	311 - 785	7135	3604 - 9107
120mg (30 mins)	3970	2401 - 13040	6822	91 - 7048
120mg (1 hour)	6636	5860 - 13490	2286	91 - 5794

Heat-Targeted Drug Delivery using the COMBAT BRS Device for Treating Bladder Cancer

Presentation Authors: Steven C. Brousell*, Thomas A. Longo, Joseph J. Fantony, Wiguins Etienne, David Needham, Mark W. Dewhirst, Paolo F. Maccarini, Ivan Spasojevic, Brant A. Inman, Durham, NC

The Journal of Urology, Vol. 197, Issue 4, e855, April 2017

Introduction and Objective: Mild bladder hyperthermia (~43°C) can be used to improve intravesical drug delivery, to trigger payload release from systemically-administered thermally-sensitive liposomes, and to elicit immune responses. In this study we assess a novel conductive bladder heater, the COMBAT BRS device, in a live porcine bladder model to assess its ability to function as a heat-targeted drug delivery platform for use in bladder cancer.

Methods: Eleven 60 kg female swine were anesthestized and catheterized with a 3-way 16 French catheter. A multidimensional and multiparametric thermal monitoring system (fiberoptic microprobes, semiconductor germanium thermistors, custom designed/fabricated thermistor strips, and infrared cameras) was surgically implanted for high resolution 3D bladder temperature mapping. The COMBAT BRS device was used to heat the bladders to ~43°C for 2 hours. Pigs received intravesical mitomycin C (MMC, 2 mg/mL), systemic thermally-sensitive liposomes containing doxorubicin (Dox), or both. Pharmacokinetic testing was done by measuring MMC and Dox levels in blood and tissues (bladder, lymph nodes, liver, kidney, spleen, heart, and lung) by liquid chromatography tandem-mass spectrometry (Agilent 1200 - Applied Biosciences/SCIEX API 5500 QTrap). Data acquisition and quantification was performed by Analyst 1.6.2 software.

Results: Heat mapping showed consistent intravesical temperatures of 42.9°C (±0.14) and a transmural gradient of 1.5°C across the detrusor, resulting in full thickness bladder heating >41°C. Adjacent organ and core body temperature increased only minimally, well below safety thresholds. Mean bladder tissue MMC level was 0.9 µM. Mean tissue Dox level was 117.2 µM in the bladder and 6.7 µM in the heart, a 17-fold difference. Liver, kidney, spleen, lung, and LN tissue all contained significantly lower Dox levels than the bladder.

Conclusions: The COMBAT BRS device effectively heated the entire bladder wall to acceptable target temperatures and with excellent temperature safety parameters. COMBAT BRS was able to effectively trigger the release of Dox from systemically-administered thermally-sensitive liposomes, resulting in bladder Dox levels far exceeding levels required for anti-neoplastic effects, while concurrently minimizing unwanted drug delivery to other organ sites. Heat-targeted drug delivery has the potential to make systemic chemotherapy much more effective while also dramatically improving safety.

Thermal Dosimetry for Bladder Hyperthermia Treatment: An Overview

Schooneveldt Ga, Bakker Aa, Balidemaj Ea, Chopra Rb, Crezee Ja, Geijsen EDa, Hartmann Jc, Hulshof MCa, Kok HPa, Paulides MMd, Sousa-Escandon Ae, Stauffer PRf, Maccarini PFg. a Department of Radiotherapy, Academisch Medisch Centrum, Amsterdam, the Netherlands; b Department of Radiology, University of Texas Southwestern Medical Center, Dallas, Texas, USA; c Department of Radiation Oncology, Universitätsklinikum Erlangen, Friedrich-Alexander-Universität Erlangen-Nürnberg , Erlangen , Germany; d Department of Radiation Oncology, Erasmus Medical Centre, Rotterdam, the Netherlands; e Department of Urology , Hospital Comarcal de Monforte, Lugo, Spain; f Department of Radiation Oncology, Thomas Jefferson University, Philadelphia, Pennsylvania, USA; g Department of Biomedical Engineering, Duke University, Durham, North Carolina, USA.

International Journal of Hyperthermia. 2016 June, 32(4):417-33.

"A recent porcine trial using the COMBAT system measured the temperature on both the internal and external surfaces of the bladder wall, employing thermistors. The results demonstrate that spatial distribution of the temperature on the bladder surface is relatively uniform (<0.4 C)."

Refer to results on P.21 - Heat targeted drug delivery using the COMBAT BRS device for treating bladder cancer.

Abstract

The urinary bladder is a fluid-filled organ. This makes, on the one hand, the internal surface of the bladder wall relatively easy to heat and ensures in most cases a relatively homogeneous temperature distribution; on the other hand, the variable volume, organ motion, and moving fluid cause artefacts for most non-invasive thermometry methods and require additional efforts in planning accurate thermal treatment of bladder cancer. We give an overview of the thermometry methods currently used and investigated for hyperthermia treatments of bladder cancer and discuss their advantages and disadvantages within the context of the specific disease (muscle-invasive or non-muscle-invasive bladder cancer) and the heating technique used. The role of treatment simulation to determine the thermal dose delivered is also discussed. Generally speaking, invasive measurement methods are more accurate than non-invasive methods, but provide more limited spatial information; therefore, a combination of both is desirable, preferably supplemented by simulations. Current efforts at research and clinical centres continue to improve non-invasive thermometry methods and the reliability of treatment planning and control software. Due to the challenges in measuring temperature across the non-stationary bladder wall and surrounding tissues, more research is needed to increase our knowledge about the penetration depth and typical heating pattern of the various hyperthermia devices, in order to further improve treatments. The ability to better determine the delivered thermal dose will enable clinicians to investigate the optimal treatment parameters, and consequentially, to give better controlled, thus even more reliable and effective, thermal treatments.

Hyperthermia as Adjunct to Intravesical Chemotherapy for Bladder Cancer

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BioMed Research International | Volume 2013 Article ID:262313 | 2013

Abstract

Non muscle invasive bladder cancer remains a very costly cancer to manage because of high recurrence rates requiring long-term surveillance and treatment. Emerging evidence suggests that adjunct and concurrent use of hyperthermia with intravesical chemotherapy after transurethral resection of bladder tumor further reduces recurrence risk and progression to advanced disease. **Hyperthermia has both direct and immune-mediated cytotoxic effect on tumor cells including tumor growth arrest and activation of antitumor immune system cells and pathways. Concurrent heat application also acts as a sensitizer to intravesical chemotherapy agents. As such the ability to deliver hyperthermia to the focus of tumor while minimizing damage to surrounding benign tissue is of utmost importance to optimize the benefit of hyperthermia treatment.** Existing chemohyperthermia devices that allow for more localized heat delivery continue to pave the way in this effort. Current investigational methods involving heat-activated drug delivery selectively to tumor cells using temperature-sensitive liposomes also offer promising ways to improve chemohyperthermia efficacy in bladder cancer while minimizing toxicity to benign tissue. This will hopefully allow more widespread use of chemohyperthermia to all bladder cancer patients, including metastatic bladder cancer.

Ex Vivo Assays to Predict Enhanced Chemosensitization by Hyperthermia in Urothelial Cancer of the Bladder

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PLoS ONE 13(12): e0209101. https://doi.org/10.1371/journal.pone.0209101 eCollection 2018.

Introduction: Bladder cancer (urothelial carcinoma) is a common malignancy characterized by high recurrence rates and intense clinical follow-up, indicating the necessity for more effective therapies. Current treatment regimens include intra-vesical administration of mitomycin C (MMC) for non-muscle invasive disease and systemic cisplatin for muscle-invasive or metastatic disease. Hyperthermia, heating a tumor to 40-44°C, enhances the efficacy of these chemotherapeutics by various modes of action, one of which is inhibition of DNA repair via homologous recombination. Here, we explore whether ex vivo assays on freshly obtained bladder tumors can be applied to predict the response towards hyperthermia.

Material And Methods: The cytochrome C release assay (apoptosis) and the RAD51 focus formation assay (DNA repair) were first established in the bladder cancer cell lines RT112 and T24 as measurements for hyperthermia efficiency, and subsequently tested in freshly obtained bladder tumors (n = 59).

Results: Hyperthermia significantly increased the fraction of apoptotic cells after cisplatin or MMC treatment in both RT112 and T24 cells and in most of the bladder tumors (8/10). The RAD51 focus formation assay detected both morphological and numerical changes of RAD51 foci upon hyperthermia in the RT112 and T24 cell lines. In 64% of 37 analyzed primary bladder tumor samples, hyperthermia induced similar morphological changes in RAD51 foci.

Conclusion: The cytochrome C assay and the RAD51 focus formation assay are both feasible on freshly obtained bladder tumors, and could serve to predict the efficacy of hyperthermia together with cytotoxic agents, such as MMC or cisplatin.

COMBAT BRS

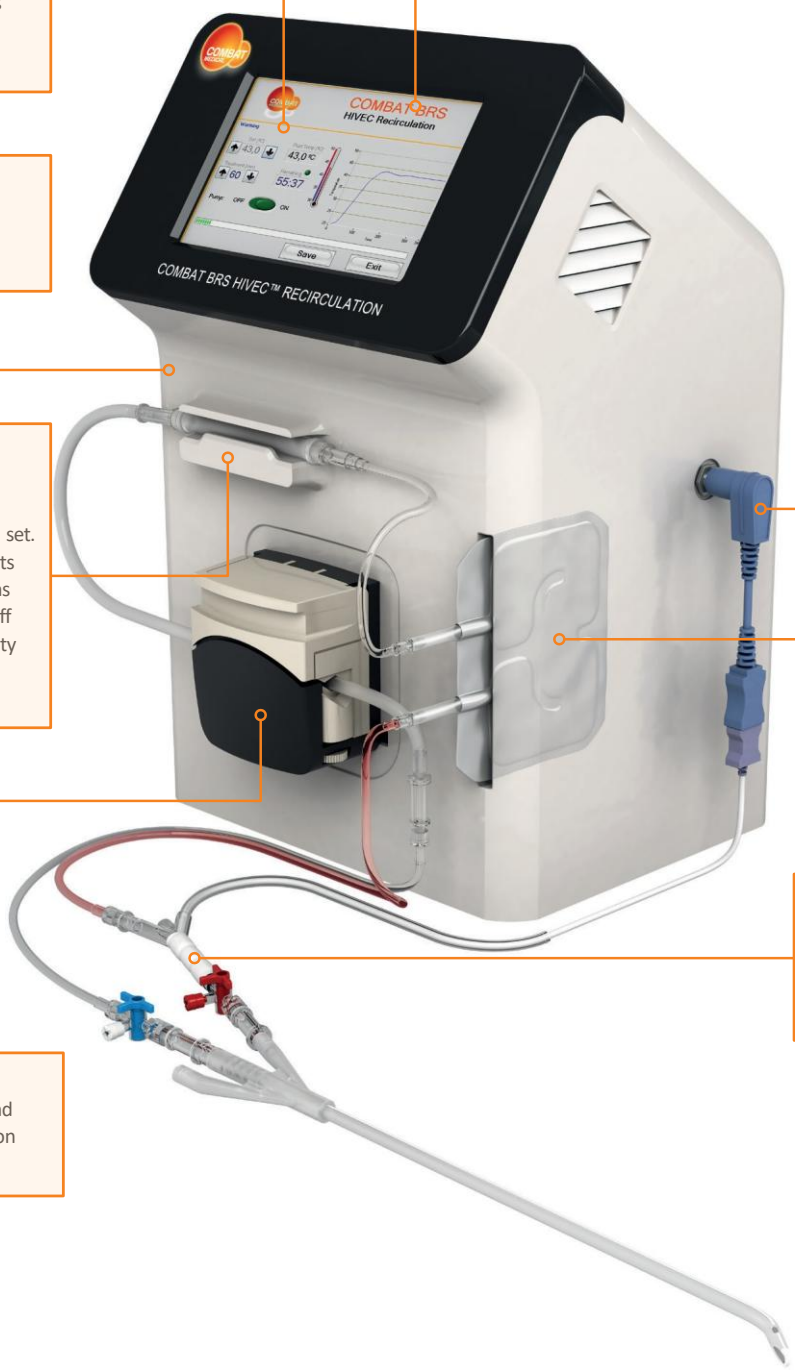
Touch Screen
Simple user interface. Automated setup checking procedure. Continuous monitoring and graphical temperature readings.

Safety Alarms
Audible and visible alarms for high and low temperature and overpressure.

USB Port
Data can be stored to USB drive in csv or txt format.

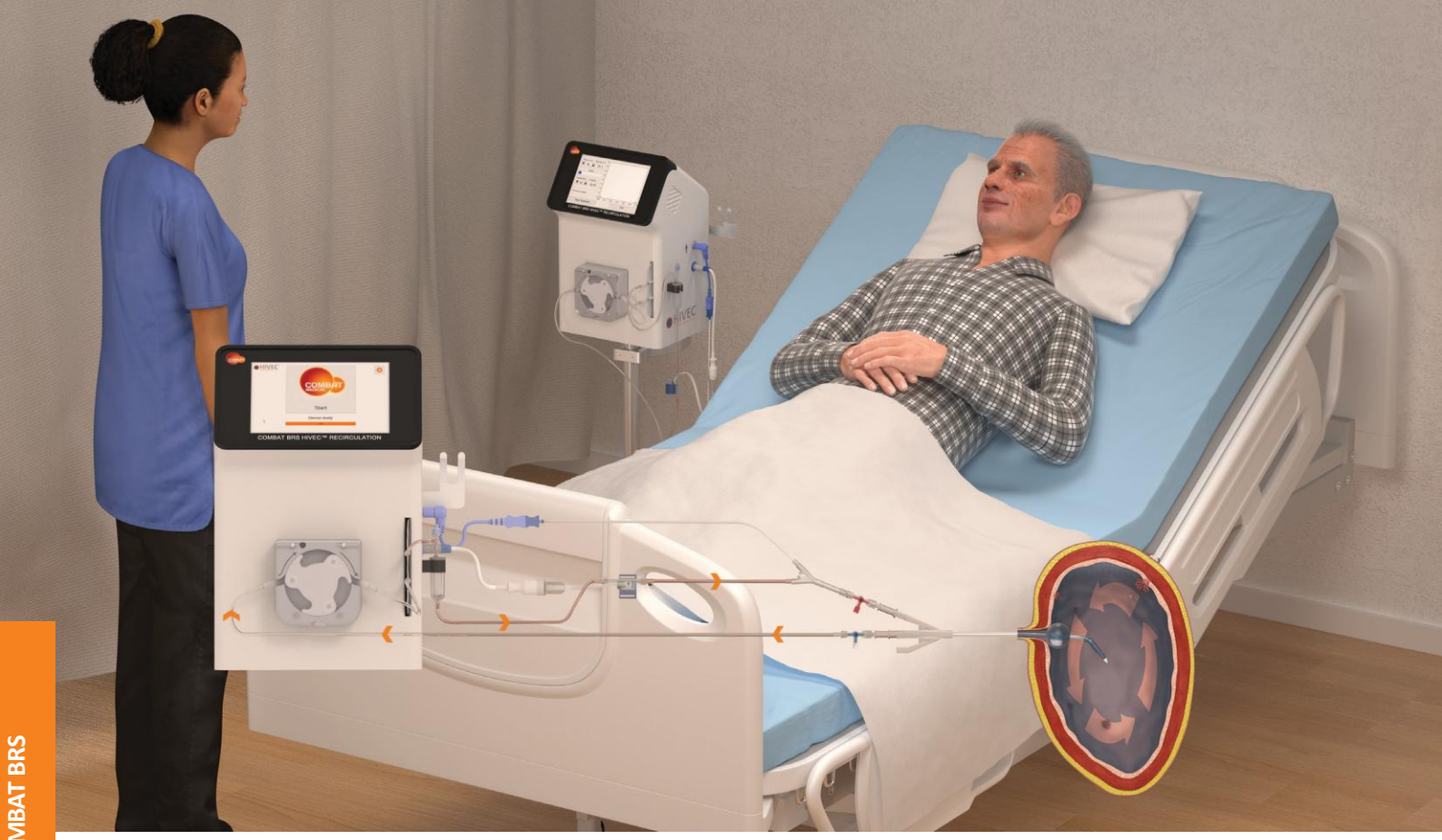
Heat Exchanger
Easy to insert our innovative aluminium foil heat exchanger provides effective and accurate heat control and transfer. Low priming volume, ensuring minimal dilution of chemotherapy agent.

Pressure Sensor and Tube Detection
Ensures correct setup and use of disposable set. Pressure sensor detects overpressure situations with automated cut off to ensure patient safety and comfort.



Temperature Probe Port
In line fluid temperature probe for continuous and accurate monitoring throughout treatment.

Peristaltic Pump
Maintains accurate and continuous recirculation and flow rates.



Combined Effects of Hyperthermia in NMIBC

Clinical hyperthermia is defined as the therapeutic use of temperature between 41°C to 44°Ca. The introduction of thermal energy affects the cancer cells more because of their inability to manage the heat as well as healthy cellsb. MitomycinC (MMC) is stable at temperatures up to 50°Cf, but has shown to be **1.4 times more active at 43°C**c. Hyperthermia **inhibits the formation of new blood vessels** (angiogenesis) by the tumour massd. At 43°C the **cytotoxicity increases by 10 times,** without any increase in the toxicity to the patientc. At elevated temperatures the lipid-protein cellular membrane bilayer will become more permeable, due to the unfolding (denaturing) of the cellular membrane and cytosolic proteins. These resulting in **higher intracellular concentration of the chemotherapy agent.** Direct effects on the DNA include; **strand breaking, impaired transcription**, **reducing replication and cell division**a. **Thermotherapy has profound effects on the immune system** resulting in **increased activation of more natural killer cells** (NKC) that target heat stressed cancer cells as they signal heat shock proteins on the cancer cell surfacee. The consequence is that the cancer cells actively participate in their own demise through the natural process of **apoptosis**.

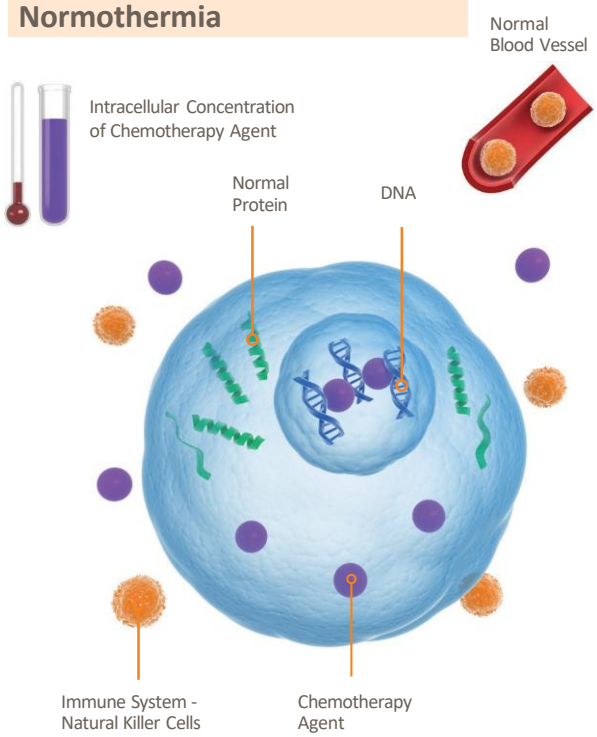
Chemo-hyperthermia multifactorial modes of action create a strong combination effect, ensuring cancer tumours and cells are specifically targeted. **Therefore hyperthermia substantially increases the effectiveness of chemotherapy compared to instillation at room temperature.** The **COMBAT BRS** is the **first system** to allow the delivery of thermotherapy within the tight parameters necessary **to optimise the delivery of chemo-hyperthermia without compromising patient safety, comfort or increasing resources required.**

Based on the body of evidence, and real world experience from urology teams using HIVEC, it is recommended to achieve the best results with the COMBAT BRS, that intermediate risk patients receive a minimum of 6 weekly induction treatments plus an additional 1 year maintenance for high risk patients.

Cell Diagram

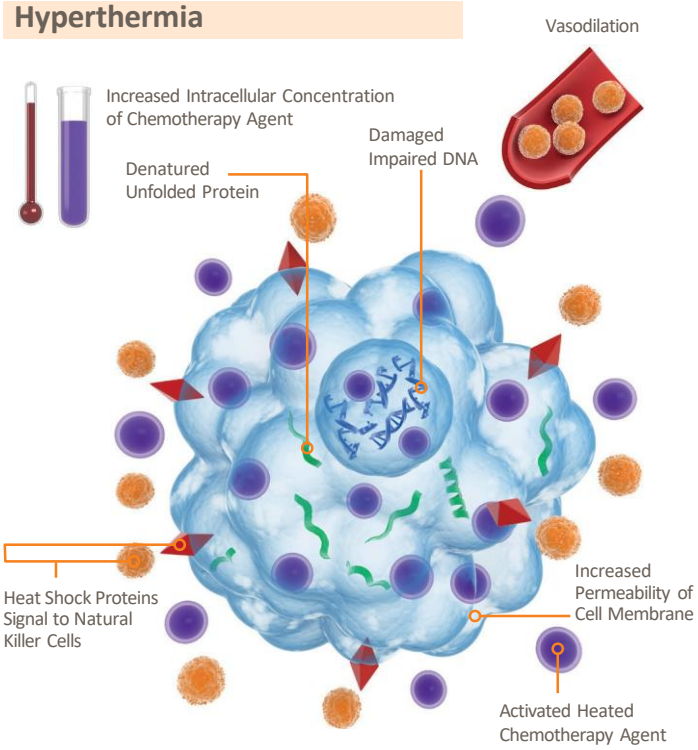
Cancer cell with Mitomycin C
Delivered at room temperature

Normothermia



Cancer cell with Mitomycin C
Delivered at 43°C

Hyperthermia

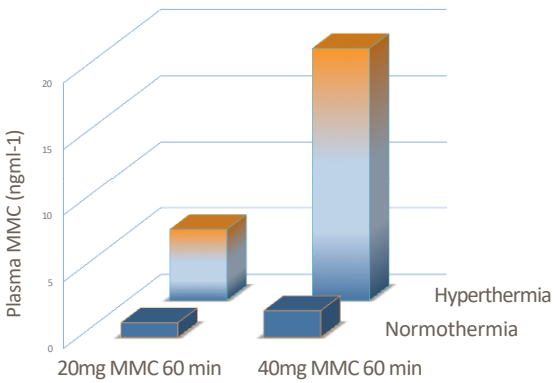


Effect of hyperthermia on alkylating agents
Teicher et al (1981) demonstrated activation rates 1.3 – 1.4 times higher at 41°C, 42°C, and 43°C compared to 37°Cc.

Mitomycin C remains stable at higher temperaturesf.						
Temp.	Solvent	Parameter	Storage Period			
			0 hr*	1 hr	3 hr	6 hr
37°C	5 ml water	Content %	100.0	94.9	92.8	91.6
	5 ml of saline	Content %	100.0	94.2	90.6	90.4
50°C	5 ml water	Content %	100.0	91.0	88.0	87.3
	5 ml of saline	Content %	100.0	91.3	90.2	89.7

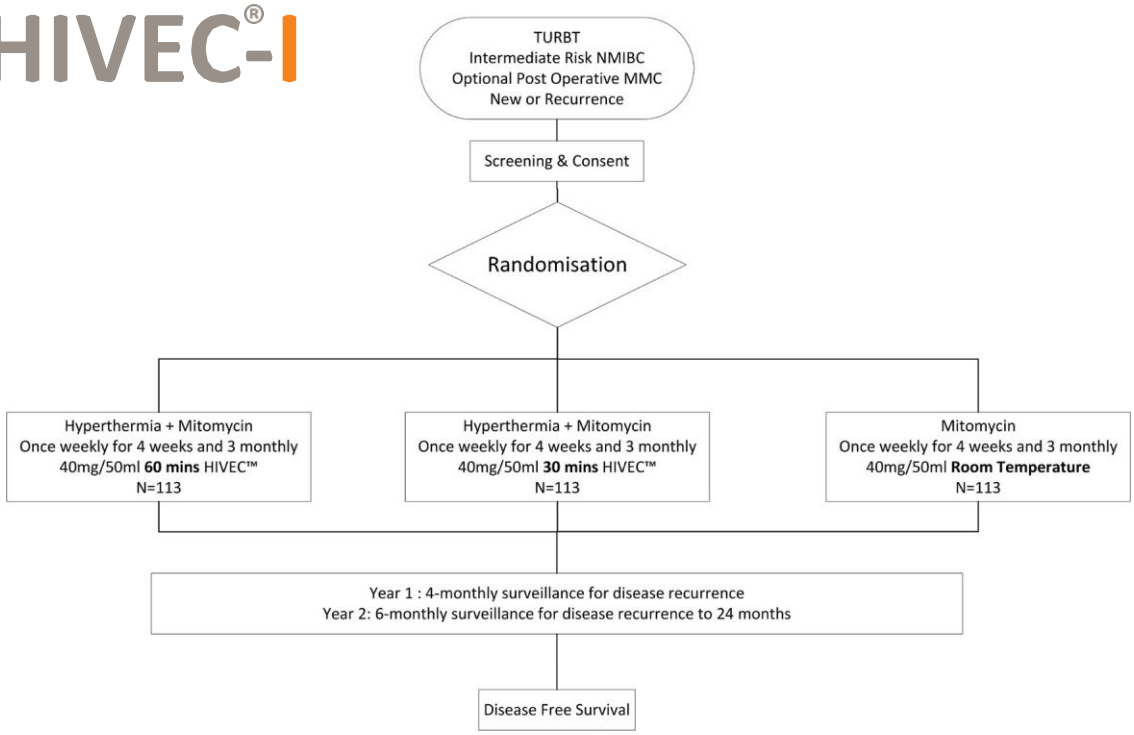
*0 hr : immediately after reconstitution.

Mitomycin C (MMC) plus hyperthermia achieves greater plasma concentration than MMC alone g, but is well below 400ng/ml associated with systemic side effects like myelosuppressionh.

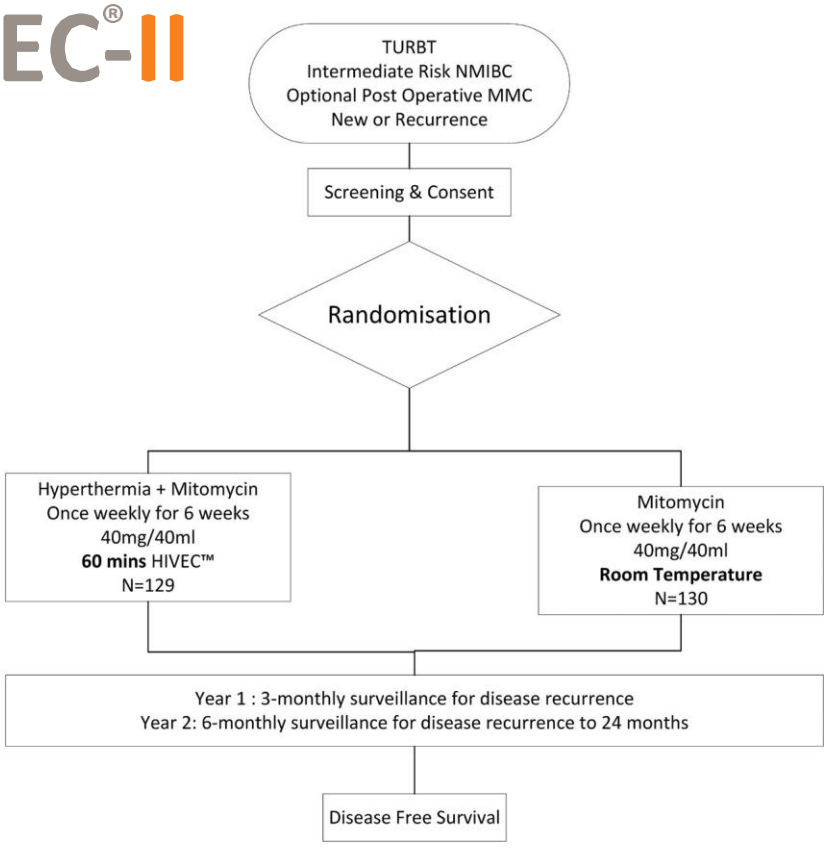


Appendix: Clinical Trial Protocol Flow Charts

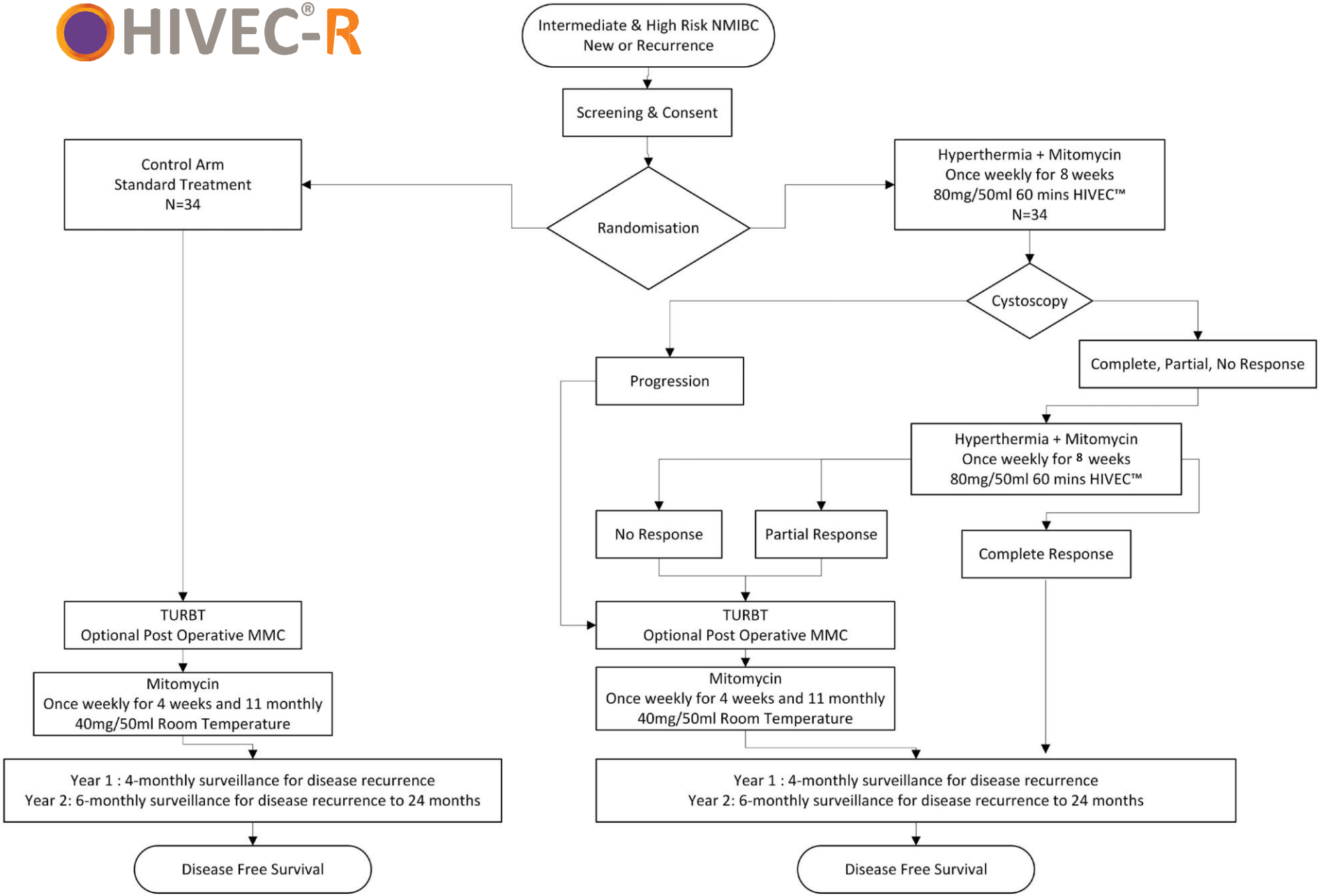
HIVEC®-I



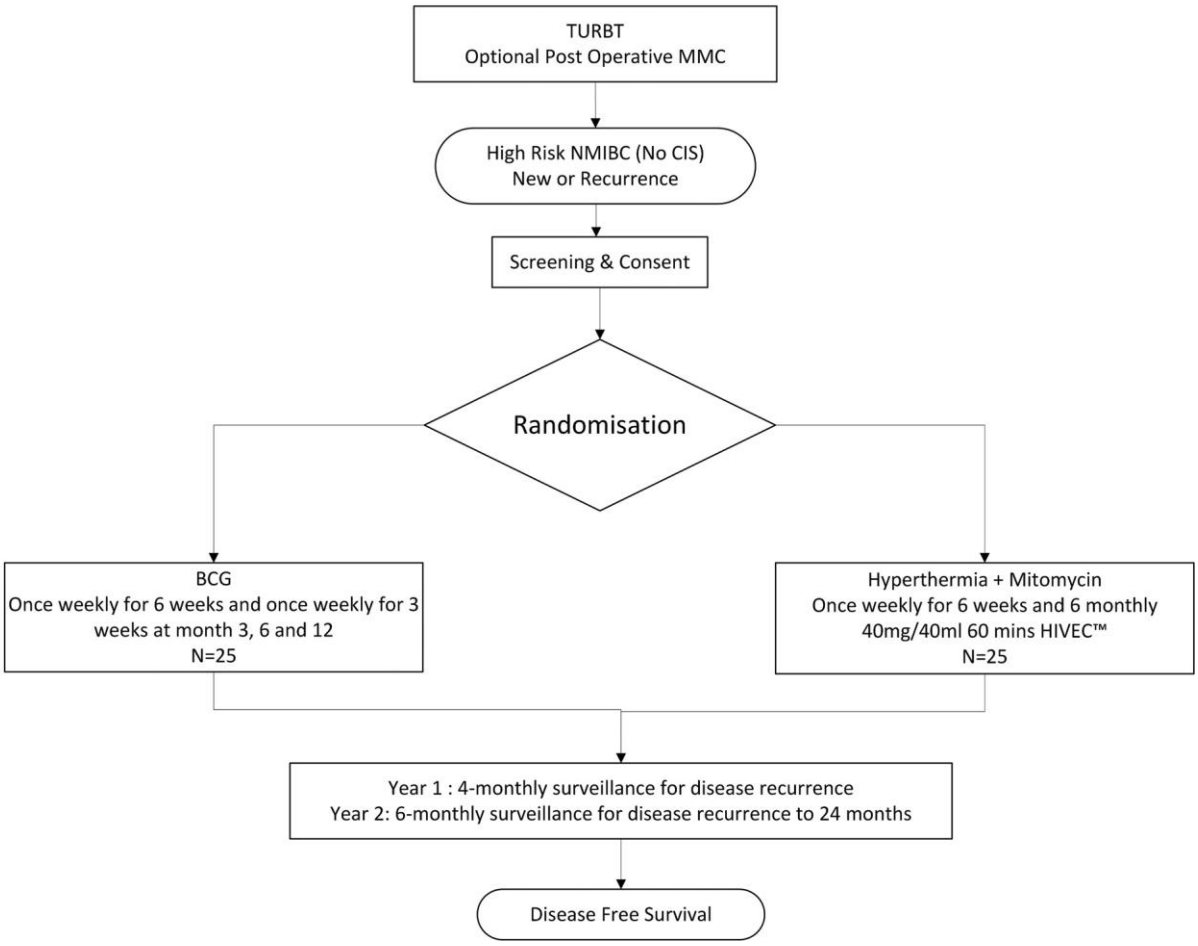
HIVEC®-II



HIVEC®-R


Intermediate & High Risk NMIBC
New or Recurrence
Screening & Consent
Randomisation
Control Arm
Standard Treatment
N=34
Hyperthermia + Mitomycin
Once weekly for 8 weeks
80mg/50ml 60 mins HIVEC™
N=34
Cystoscopy
Progression
Complete, Partial, No Response
Hyperthermia + Mitomycin
Once weekly for 8 weeks
80mg/50ml 60 mins HIVEC™
No Response
Partial Response
Complete Response
TURBT
Optional Post Operative MMC
Mitomycin
Once weekly for 4 weeks and 11 monthly
40mg/50ml Room Temperature
Year 1 : 4-monthly surveillance for disease recurrence
Year 2: 6-monthly surveillance for disease recurrence to 24 months
Disease Free Survival
TURBT
Optional Post Operative MMC
Mitomycin
Once weekly for 4 weeks and 11 monthly
40mg/50ml Room Temperature
Year 1 : 4-monthly surveillance for disease recurrence
Year 2: 6-monthly surveillance for disease recurrence to 24 months
Disease Free Survival

HIVEC®-HR


TURBT
Optional Post Operative MMC
High Risk NMIBC (No CIS)
New or Recurrence
Screening & Consent
Randomisation
BCG
Once weekly for 6 weeks and once weekly for 3 weeks at month 3, 6 and 12
N=25
Hyperthermia + Mitomycin
Once weekly for 6 weeks and 6 monthly
40mg/40ml 60 mins HIVEC™
N=25
Year 1 : 4-monthly surveillance for disease recurrence
Year 2: 6-monthly surveillance for disease recurrence to 24 months
Disease Free Survival

HIPEC + Agitation for Treating Peritoneal Cancers

Developed in collaboration with surgeons to optimise **Efficacy, Safety** and **Delivery** of the **HIPEC** technique.

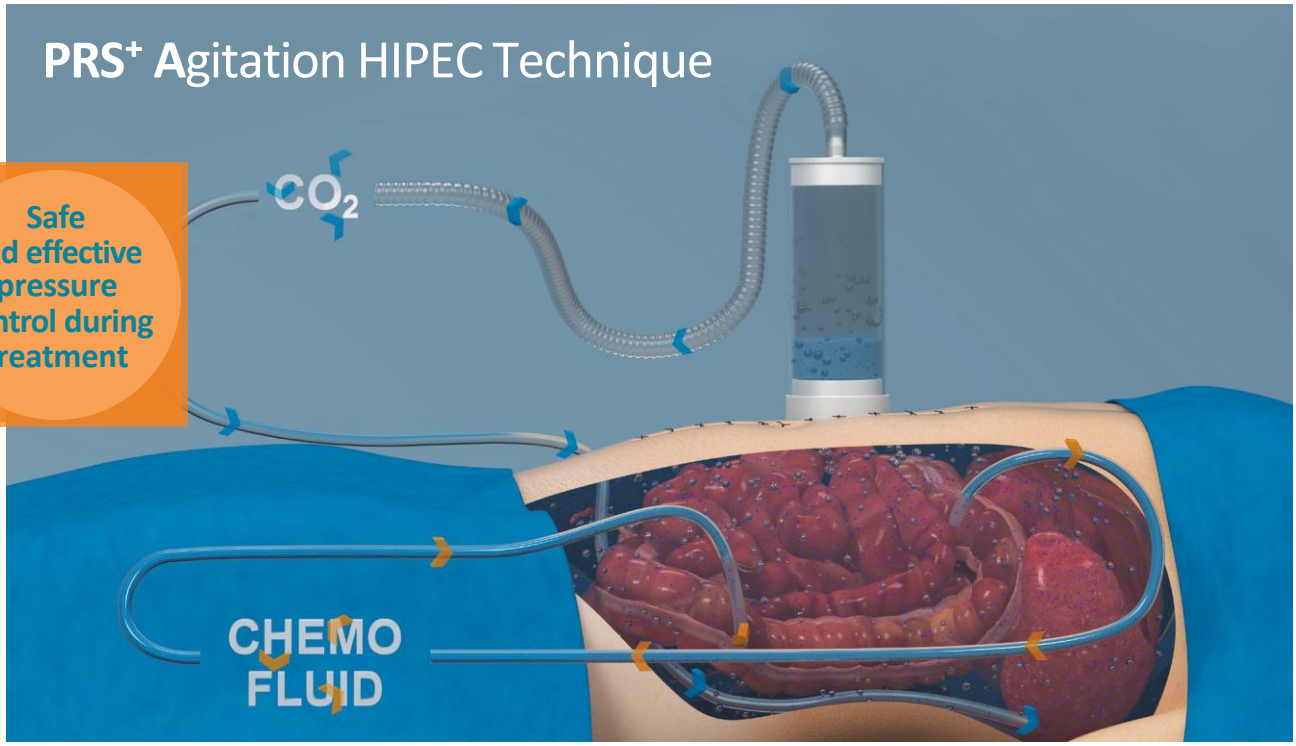
The **COMBAT PRS+** unique, patented agitation system optimises the heat and drug distribution in the abdominal cavity to improve drug penetration into the tumour and peritoneum.[1]

Agitation with CO_2 improves drug and heat distribution

Trials are ongoing in:

- **Ovarian Cancer** (NCT02681432). Interim presented results showed a increased DFS in the HIPEC Group compared to the non HIPEC group [2]
- **Colo-Rectal** (HIPECT4-NCT02614534)
- **Pancreatic** (Euradact-2016-004298-41)

The PRS Registry has collated and evaluated data from over 500 patients with 6 types of peritoneal cancer. Data is constantly being presented and published. Please contact us to find out more and request a copy of the clinical evidence.



Safe and effective pressure control during treatment

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