# COMBAT Medical Overview

## Incorporated 2012
**Head Office - Hertfordshire**

- 2 CE Marked, Patented Products
  - BRS - HIVEC and PRS - HIPEC

## BRS - HIVEC Treatments

- Used in Treatment of Bladder Cancer in 40 countries
- 39,000 Treatments to date (as of July 2019)
- 30 NHS Hospitals

## BRS - HIVEC Treatments

- 867 Patients in Randomised Trials
- Data Published / Presented on over 1000 Patients
- Data in High Risk, BCG Failures, Peri-Operative, Neo-Adjuvant, Sequential and Intermediate Patients
- 2 new phase III trials to start. BCG Unresponsive and Neo-Adjuvant

## PRS - HIPEC Treatments + Agitation

Showing Superior Clinical Results in Peritoneal Cancer Treatments
Trials ongoing or starting in 500+ patients in Ovarian, Colo-Rectal, Pancreatic and Gastric

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**The Combined Effects of Hyperthermia and Chemotherapy are a Proven, Mutually Enhancing Solution, Widely Used in the Treatment of Many Malignancies** *(See Hyperthermia Data)*
HIVEC™ in High Risk NMIBC
BCG Vs Chemohyperthermia with Mitomycin C for High-Risk Non-Muscle Invasive Bladder Carcinoma: Preliminary Results of HIVEC-HR Randomized Clinical Trial

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

HIVEC™ in BCG Failure & BCG Unresponsive
Oncological Outcomes of BCG Unresponsive Non-Muscle Invasive Bladder Cancer Patients Treated with Postoperative Chemohyperthermia: A Multicentre European Retrospective Analysis

HIVEC™ Neo-Adjuvant Setting
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

HIVEC™ in Perioperative
Prospective Randomized Clinical Trial of Chemohyperthermia 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

HIVEC™ in High Risk in a Sequential Therapy Regime with BCG
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 Bladder Cancer (NMIBC) Patients... a BCG-Sparing Strategy

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

Hyperthermia / Heat Mapping / Scientific Data
The Effect of Conductive Hyperthermia on Mitomycin C Absorption During Intravesical Chemotherapy
Visual Summary of: BCG Vs Chemohyperthermia with Mitomycin C for High-Risk Non-Muscle Invasive Bladder Carcinoma: Preliminary Results of HIVEC-HR Randomized Clinical Trial

Félix Guerrero-Ramos*, Daniel Antonio González-Padilla, Alejandro González-Díaz, José Manuel Duarte-Ojeda, Natalia Miranda-Utrera, Felipe Villacampa-Aubá, Federico de la Rosa-Kehrmann, Madrid, Spain


Conclusions: According to our trial preliminary results, CHT (HIVEC) in high risk NMIBC patients seems not to be inferior to BCG in terms of efficacy. Moreover, patients under CHT have a higher therapeutic adherence than those under BCG treatment.

BCG (TICE STRAIN)
50mg in 50ml
1 weekly x 6 weeks
(SWOG MAINTENANCE)

HIVEC (CHT)
40mg MMC in 40ml @43°C
1 weekly x 6 weeks
(MAINTENANCE 1 PER MONTH X 6 MONTHS)

Randomisation

50 Median Follow Up
12.3 months

5 Recurrences

4 Progressions to T2

0 Recurrences

1 Progressions to T2

Click Through to Full Abstract
Visual Summary of: Chemohyperthermia with Mitomycin C (MMC) and COMBAT System in High Risk Non Muscle Invasive Bladder Cancer (HR NMIBC): A New Alternative?


**145** HR Patients

COMBAT HIVEC TREATMENT

Mean Follow Up 21 Months

14 Centres Across Europe

RFS 82%

PFS TO T2 98%

Conclusions: CHT (HIVEC) with 6 weekly induction 40mg MMC using the COMBAT system represents an attractive alternative to intravesical BCG therapy. RFS and PRS at 12 months are comparable to EORTC nomograms.

Wei Shen Tan et al

87 BCG Unresponsive NMIBC Patients

- 23 CIS Only
- 64 Papillary Papillary + CIS
- 29 T1 (45%)

35 Ta (55%)

14 Centres

MEDIAN Follow up 15 months (IQR: 8-29 Months)

RFS

12M-55%
24M-48%

PFS

24M 95%

Conclusions: BCG-unresponsive NMIBC patients who are treated with CHT delivered using the Combat BRS system had a 24-month PFS of 48% and PFS of 95%. CHT may be an option in NMIBC patients who are unresponsive to BCG.
**Visual Summary of:** 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

Dr. Daniel Sousa et al

**Neoadjuvant HIVEC Treatment:**
- 80mg/50ml
- 1 hour - weekly
- x 8 weeks

- **TURB:** 2 Weeks Post HIVEC

- **Neo Adjuvant Setting:**
- 2009-2017
- HIVEC performed before TURB, could generate a tumor ICD that would improve immunological activation and clinical response, functioning theoretically as a self-vaccine

- **Complete Response:** 63% (27 patients)
- **Partial Response:** 30% (13 patients)
- **No Response:** 7% (2 patients)

- **Total Series PFS:** 81%
- Median Follow up 52 Months

**Conclusions:** Treatment with neo-adjuvant HIVEC resulted in a CR of 63% and was associated with a durable PFS 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 PFS index.
**Visual Summary of:** Prospective Randomized 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

García Álvarez C.; Plata Bello A.C.; Plata Bello J.; Tamayo Jover M.A.; Cabral Fernández, A.V.; Cereijo Tejedor, D.; Navarro Galmés, M.A.; Fernández Cranz, N.; Concepción Masip, T.

Hospital Universitario de Canarias.


**Objectives:** Evaluate early recurrence rate of low to intermediate Risk NMIBC with HIVEC instillation prior to TURBT compared to single immediate IPOP MMC

152

HIVEC 50%
(76 Patients)

Safe & Well Tolerated

100% Patients Treated

12 Months Mean Follow Up Equivalent Recurrence Rates

HIVEC - A Safe and Well Tolerated Alternative

MMC IPOP 50%
(76 Patients)

30% Patients Not Suitable for I-POP

67% Patients Treated 33% unsuitable due to deep resections and hematuria

Click Through to Full Abstract
Visual Summary of: 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 Bladder Cancer (NMIBC) Patients... a BCG-Sparing Strategy

University Hospitals of Leicester, Dept. of Urology, Leicester, United Kingdom

50 HR NMIBC
CIS in 40%
T1 in 62%

2 YEAR Follow up

46 92% Cystectomy Free

4  Cystectomies, no upstaging to T2

38 76% Disease Free

47 94% Progression Free

HIVEC™ in High Risk in a Sequential Therapy Regime with BCG

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 utilised heated MMC using the Combat BRS device. In this non-selected HR NMIBC series, the low progression rates and good tolerability are reassuring.
Visual Summary of: 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


Conclusions: HM (HIVEC) 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 (HIVEC) represents a safe and well tolerated intravesical treatment for NMIBC.
Visual Summary of: The Effect of Conductive Hyperthermia on Mitomycin C Absorption During Intravesical Chemotherapy

Wei Phin Tan*, Andrew Chang, Gregory Barton, Wiguins Etienne, Brant A Inman, Durham, NC

Female Swine
(Refer to full abstract for methods)

<table>
<thead>
<tr>
<th>MMC dose &amp; dwell time</th>
<th>Bladder wall Mitomycin C concentration (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Room Temperature</td>
</tr>
<tr>
<td></td>
<td>Median</td>
</tr>
<tr>
<td>40mg (1 hour)</td>
<td>329</td>
</tr>
<tr>
<td>80mg (1 hour)</td>
<td>617</td>
</tr>
</tbody>
</table>

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 saturate drug delivery and allow lower doses. These data support the use of the Combat BRS device to improve MMC penetration into the bladder wall.
Combined Effects of Hyperthermia in NMIBC

Clinical hyperthermia is defined as the therapeutic use of temperature between 41°C to 44°C. The introduction of thermal energy affects the cancer cells more because of their inability to manage the heat as well as healthy cells. Mitomycin C (MMC) is stable at temperatures up to 50°C, but has shown to be 1.4 times more active at 43°C. Hyperthermia inhibits the formation of new blood vessels (angiogenesis) by the tumour mass. At 43°C the cytotoxicity increases by 10 times, without any increase in the toxicity to the patient. 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. 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 surface. 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

Hyperthermia

Cancer cell with Mitomycin C
Delivered at 43°C

References:

COMBAT BRS

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

Peristaltic Pump
Maintains accurate and continuous recirculation and flow rates.

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

Catheter
Flexible soft 16F 3-way catheter with coude tip to help ease of insertion.

Safety Alarms
Audible and visible alarms for high and low temperature, and over and under pressure.

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

Pressure Sensor
In line pressure transducer detects excess and low pressure situations with automated cut off to ensure patient safety and comfort.

Combined Effects of Hyperthermia & COMBAT BRS
COMBAT clinical specialists work with healthcare professionals worldwide to ensure HIVEC is available in hospitals as an alternative treatment option. HIVEC is already reimbursed in many countries. Please contact us for more information.

BRS V5

Equipment external dimensions:
Height 400 mm Width 250 mm Depth 255 mm

Equipment weight:
BRS system 8 Kg plus optional portable stand

Safety alarms:
High & low temperature alarms
High & low pressure alarms
Auto safety cut off
End of treatment alarm & auto stop

Electrical risk classification:
Class I, Type B

Fluid ingress protection:
IPX2

Function mode:
Continuous delivery at set temperature between 41 – 44°C ± 0.2°C

Certification:
IEC/UL 60601 - 1; IEC 60601 - 1 - 2; EN 55011; CAN/CSA - C22.2; CE 0086

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Twitter: @CombatCancer
Introduction: After the BCG shortage happened several years ago, there is an increasing interest in finding a valid alternative for patients with non-muscle invasive bladder cancer (NMIBC). HIVEC-HR is a pilot study 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 randomized 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 43°C using COMBAT recirculation system for 60 minutes, one weekly instillation for 6 weeks and one monthly instillation for 6 months.

Follow-up was carried out with cytology and 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 were to evaluate safety, progression rate, overall survival and quality of life.

*continued on page 2*
Results: Fifty patients have been randomized (100% recruitment completed), with 48 finally starting treatment. Median age is 73 years old, 87.6% were males and 83% were primary tumours. Baseline characteristics were comparable in both groups. Median follow-up is 12.3 months from TURBT. For the BCG group, 5 recurrences and 4 progressions to T2 were reported, and only 1 progression happened in the CHT group with no recurrences.

Regarding safety profile, adverse events (AE) appeared in 11 patients in the CHT group and 9 in the BCG group. In relation to the severity of these AEs, 4 patients in each group presented CTCAE grade 3 complications, although 3/4 in the CHT group were treatment withdrawals due to MMC allergy. More patients in the BCG group had to discontinue due to AE (6 vs 4). Four patients have died so far, none of them related with their bladder cancer.

Conclusions: According to our trial preliminary results, CHT in high risk NMIBC patients seems not to be inferior to BCG in terms of efficacy. Moreover, patients under CHT have a higher therapeutic adherence than those under BCG treatment. Primary endpoint was recurrence-free survival at 24 months. Secondary objectives were to evaluate safety, progression rate, overall survival and quality of life.

Note: Similar data also presented at EAU 2019. To request a copy of the specific abstract and poster please contact us or see the website.
Chemohyperthermia with Mitomycin C (MMC) and COMBAT System in High Risk Non Muscle Invasive Bladder Cancer (HR NMIBC): A New Alternative?

Plata Bello A.¹, Garcia Alvarez C.¹, Villacampa F.², Gonzalez D.³, Llanes L.³, Diaz Goizueta J.³, Rios E.³, Rimington P.⁴, Castillo JM.⁵, Castillo Dj.⁶, Pontones JL.⁷, Nze A.⁷, Brisuca A.⁷, Leon J.⁸, Sousa A.⁹, Chiancone F.¹⁰, Fedelini P.¹¹, Hendriksen K.¹², Vogeli TA.¹³.

Institutes: ¹ Universitario de Canarias, Tenerife, Spain; ² Hospital Universitario 12 de Octubre, Madrid, Spain; ³ Universitario Torrejón, Madrid, Spain; ⁴ Hospital Universitario Infanta Sofia, Madrid, Spain; ⁵ East Sussex NHS Trust, Eastbourne, UK; ⁶ Hospital Comarcal Vinaroz, Castellón, Spain; ⁷ Hospital Universitario La Fe, Valencia, Spain; ⁸ St Barbara Hospital, Gladbeck, Germany; ⁹ Motole Hospital, Prague, Czech Republic; ¹⁰ Hospital de Momporgte, Lugo, Spain; ¹¹ Hospital Cardarelli, Naples, Italy; ¹² Netherlands Cancer Institute, Amsterdam, Netherlands; ¹³ Uniklinik RWTH Aachen, Aachen, Germany; ¹⁴ Queen Alexandra Hospital, Portsmouth, UK.


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% pT1 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 PFR at 12 months are comparable to EORTC nomograms. Randomised controlled trials are eagerly awaited.
Oncological Outcomes of BCG Unresponsive Non-Muscle Invasive Bladder Cancer Patients Treated with Postoperative Chemohyperthermia: A Multicentre European Retrospective Analysis

Wei Shen Tan*, London, United Kingdom, Kees Hendricksen, Amsterdam, Netherlands, Dan Wilby, Portsmouth, United Kingdom, Cajetan Nzeh, Gladbeck, Germany, Javier Goizueta, Madrid, Spain, Wolfgang Vilmar, Nuremberg, Germany, Ana Bello, Tenerife, Spain, Alejandro Sousa, Lugo, Spain, J Morena, Madrid, Spain, Jose Pontones, Valencia, Spain, Felix Guerrero, Madrid, Spain, Iliya Kalchev, Sofia, Bulgaria, Eric Frank, Aachen, Germany, Joost Boormans, Rotterdam, Netherlands


Introduction: Intravesical BCG with maintenance is recommended for patients with high-risk non-muscle invasive bladder cancer (NMIBC). However, there remains no bladder sparing option in patients with persistent or early recurrent disease following adequate BCG treatment. We report oncological outcomes of patients with BCG unresponsive disease who were treated with conductive chemohyperthermia (CHT) (HIVEC).

Methods: We utilised a multicentre European retrospective patient cohort of patients treated with the Combat BRS system. Each treatment instillation comprised of MMC with hyperthermia delivered at 43°C, over 60 minutes. BCG-unresponsive NMIBC (urothelial carcinoma) 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 12-month recurrence-free survival (RFS) and the progression-free survival (PFS).

Results: A total of 87 patients from 14 European institutions met the criteria for BCG-unresponsive disease. Median patient age was 73.3 years (64.0-79.1) with male patients comprising of 77 patients (88.5%). A total of 23 patients (26.4%) had CIS only disease, 52 patients (59.8%) with papillary only disease and 12 patients (13.8%) with concurrent CIS and papillary disease. Of the 64 patients with papillary disease, 35 patients (54.7%) had Ta and 29 patients (45.3%) T1 NMIBC. Sixty-six patients (75.9%) had high-risk disease. With a median follow-up of 15 (IQR: 8-29) months, 44 patients developed disease recurrence. RFS at 12 months was 55% and at 24 months was 48%. PFS at 24 months was 95%. In patients with CIS disease, 6-month complete response rate was 57% and only one patient had disease progression.

Conclusions: BCG-unresponsive NMIBC patients who are treated with CHT delivered using the Combat BRS system had a 24-month DFS of 48% and PFS of 95%. CHT may be an option in NMIBC patients who are unresponsive to BCG.
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

Dr. Daniel Sousa, Dr. Alejandro Sousa, Dr. Juan León, Dr. Andrés Blanco

Urology Department, Comarcal Hospital de Monforte. Epidemiology Unit. Fundacion Institute of Sanitary Investigation of Santiago de Compostela (FIDIS). Spain.

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.
Prospective Randomized Clinical Trial of Chemohyperthermia 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

García Álvarez C.; Plata Bello A.C.; Plata Bello J.; Tamayo Jover M.A.; Cabral Fernández, A.V.; Cereijo Tejedor, D.; Navarro Galmés, M.A.; Fernández Craz, N.; Concepción Masip, T.

Hospital Universitario de Canarias.

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

**Introduction:** The recurrence rate for non-muscle invasive bladder cancer (NMIBC) varies from 50-70%, with single immediate postoperative instillation (IPOP) of mitomycin-C (MMC) having been shown to be effective in preventing recurrence.

Some 30% of patients are not suitable candidates for IPOP due to macroscopic hematuria or bladder perforation. In these circumstances the use of chemohyperthermia (CH- HIVEC) immediately prior to TURBT is a safe and effective alternative to IPOP delivered normothermically, with improved penetration of MMC through the urothelium.

**Objective:** To evaluate the early recurrence rate of low to intermediate risk NMIBC with the CH (HIVEC) instillation of MMC prior to TURBT (compared to single immediate IPOP MMC) at 12, 18 and 24 months. Safety and tolerability of the experimental treatment for these patients will also be evaluated.

**Methods:** Single center prospective randomized control clinical trial.

**Inclusion Criteria:** Low to intermediate risk NMIBC, single t tumor <30mm or multiple <8 lesions and <30mm. Patients with a history of bladder TURBT <1 year were excluded.

**Primary analysis:** Safety and tolerability of pre-operative instillation of MMC in 152 patients: 76 in the control arm (CA: postoperative MMC normothermic), 76 in the experimental arm (EA: Hyperthermic pre-operative MMC).

Follow up with cystoscopy, cytology and ultrasound. Assessment tools for tolerability of the instillation procedure (pain scale analogue – visual) and global satisfaction.

**Conclusions:**
1. Chemohyperthermia treatment (HIVEC) with mitomycin-c pre-TURBT is a safe and well tolerated alternative.
2. After a follow-up period of 18 months, the recurrence rate in both arms are equivalent.

continued on page 2
### Results:

<table>
<thead>
<tr>
<th>Gender</th>
<th>Patient Number</th>
<th>Pathologic Anatomy (PA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>125 (82.2%)</td>
<td>Comply with the PA criteria for low to intermediate risk NMIBC</td>
</tr>
<tr>
<td>Female</td>
<td>27 (17.8%)</td>
<td>Do not comply with the PA criteria for low to intermediate risk NMIBC</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>90 (59.2%)</td>
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</tr>
<tr>
<td>Smoker</td>
<td>42 (27.6%)</td>
<td></td>
</tr>
<tr>
<td>Non-smoker</td>
<td>20 (13.2%)</td>
<td></td>
</tr>
</tbody>
</table>

#### Instillations

- Received instillations (pre/post operative): 127 (80.9%)
  - a) EA: MMC-CH: 76 (100%)
  - b) CA: MMC-IPOP: 51 (67.1%)

25 patients did not receive an instillation.

- 22 macroscopic hematuria
- 3 Deep resection

#### Global Tolerability to MMC-CH

- 3 patients (3.5%) with PA for low to intermediate risk NMIBC

#### Mean Follow up:

- 12 months

#### Recurrence

- 3 patients (3.5%) with PA for low to intermediate risk NMIBC

Only 1 patient received < 1-hour instillation.
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 Bladder Cancer (NMIBC) Patients... a BCG-Sparing Strategy


University Hospitals of Leicester, Dept. of Urology, Leicester, United Kingdom

**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.
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 I (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.
The Effect of Conductive Hyperthermia on Mitomycin C Absorption During Intravesical Chemotherapy

Wei Phin Tan*, Andrew Chang, Gregory Barton, Wiguins Etienne, Brant A Inman, Durham, NC


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.

<table>
<thead>
<tr>
<th>MMC dose &amp; dwell time</th>
<th>Bladder wall Mitomycin C concentration (ng/ml)</th>
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<tbody>
<tr>
<td></td>
<td>Room Temperature</td>
</tr>
<tr>
<td></td>
<td>Median</td>
</tr>
<tr>
<td>40mg (1 hour)</td>
<td>329</td>
</tr>
<tr>
<td>80mg (1 hour)</td>
<td>617</td>
</tr>
<tr>
<td>120mg (30 mins)</td>
<td>3970</td>
</tr>
<tr>
<td>120mg (1 hour)</td>
<td>6636</td>
</tr>
</tbody>
</table>

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