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Clinical Evidence Visual Summary

HIVEC®
Targeting Bladder Cancer

COMBAT Medical Overview

HIVEC® Targeting Bladder Cancer

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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
- 50,000+ Treatments to date (as of June 2020)
- 250 Centres Worldwide

BRS - HIVEC Treatments

- 867 Patients in Randomsied 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 Recurrent Intermediate Risk

PRS+ - HIPEC Treatments + Agitation

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

The Combined Effects of Hyperthermia and Chemotherapy are a Proven, Mutually Enhancing Solution, Widely Used in the Treatment of Many Malignancies

See Hyperthermia Data

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Visual Summary of: 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. 4S | May 2020

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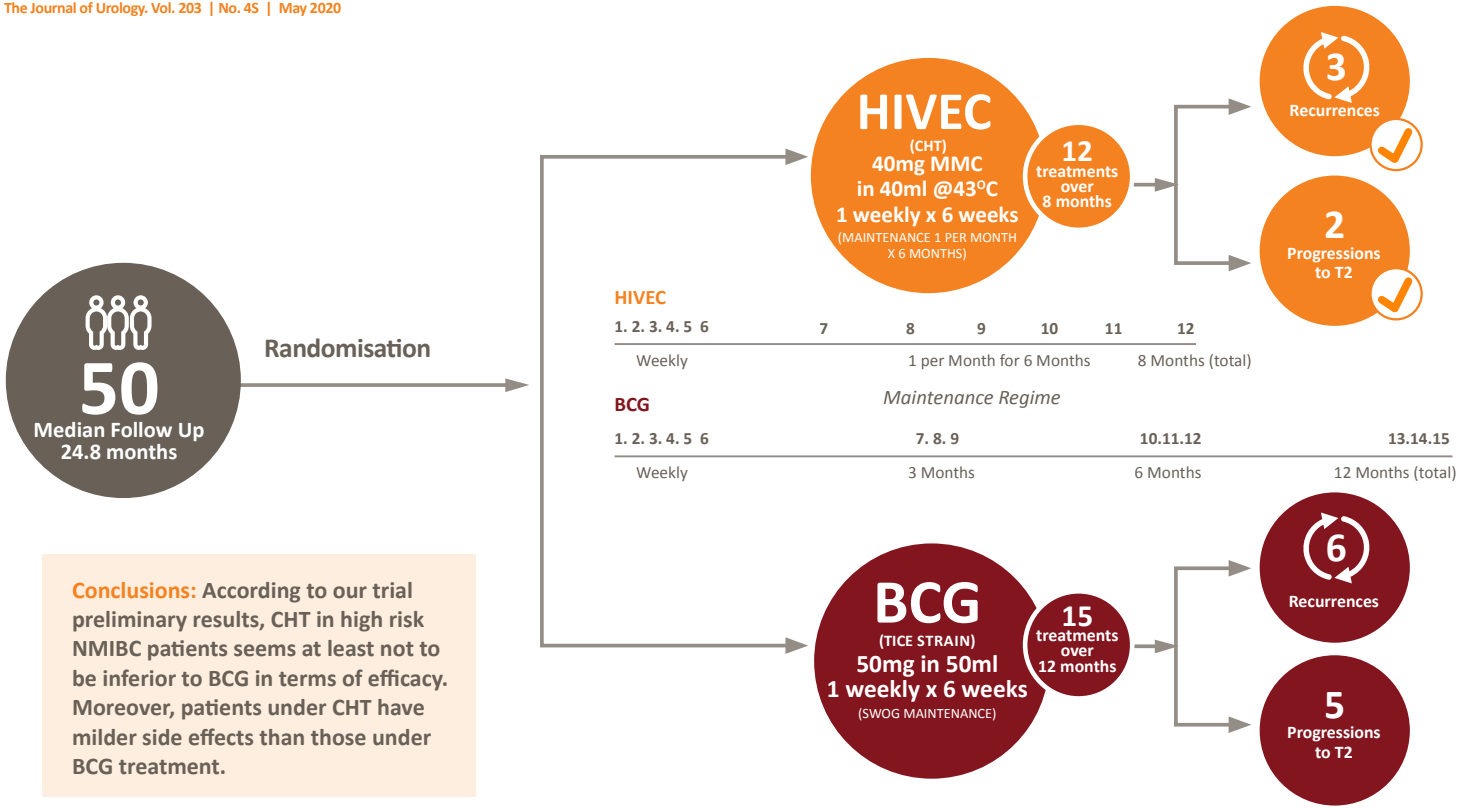

Conclusions: According to our trial preliminary results, CHT in high risk NMIBC patients seems at least not to be inferior to BCG in terms of efficacy. Moreover, patients under CHT have milder side effects than those under BCG treatment.

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?

Plata Bello A. et al **Presented:** AUA 18-21 May 2018 San Francisco, CA, USA. The Journal of Urology, Vol. 199, Issue 4, e1119, April 2018

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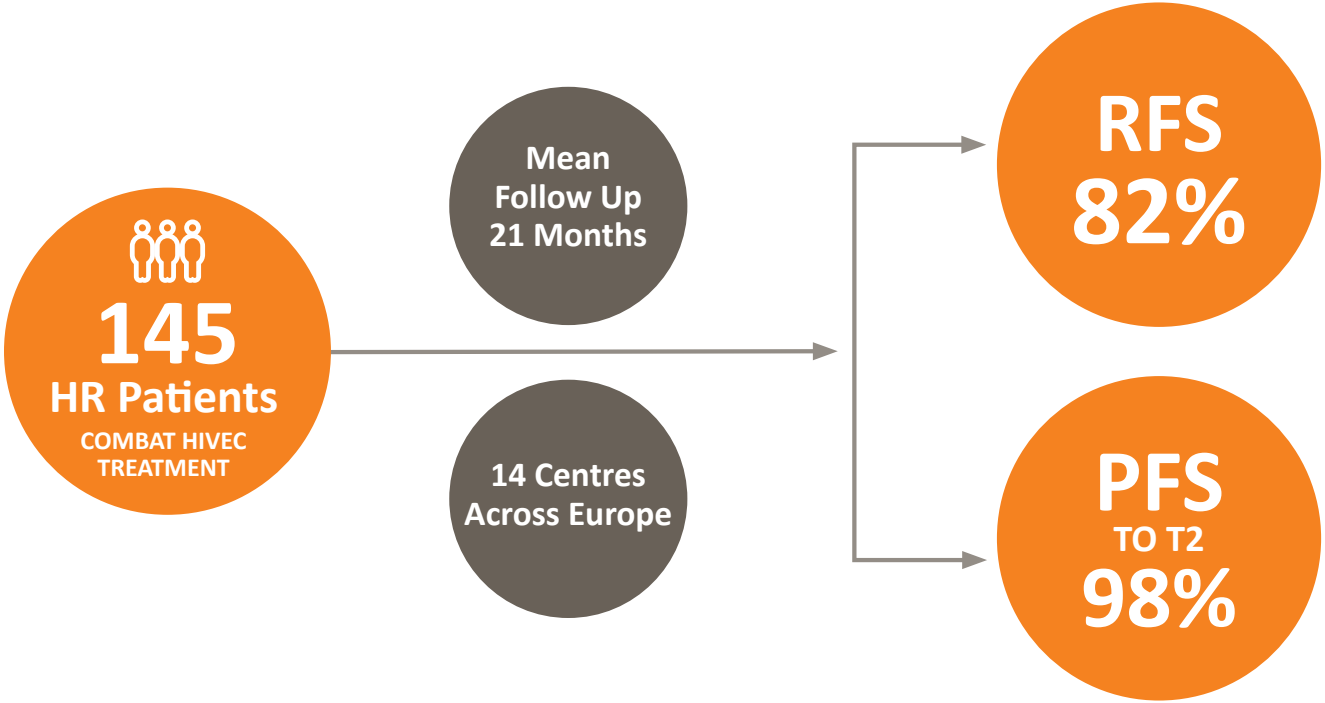

Conclusions: CHT (HIVEC) with 6 weekly induction 40mg MMC using the COMBAT system represents an attractive alternative to intravesical BCG therapy. RFS and PRS at 12 months are comparable to EORTC nomograms.

Click Through to Full Abstract

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

1. Tan WS, University College London, London, UK et al

EAU20 Virtual 17-26 July

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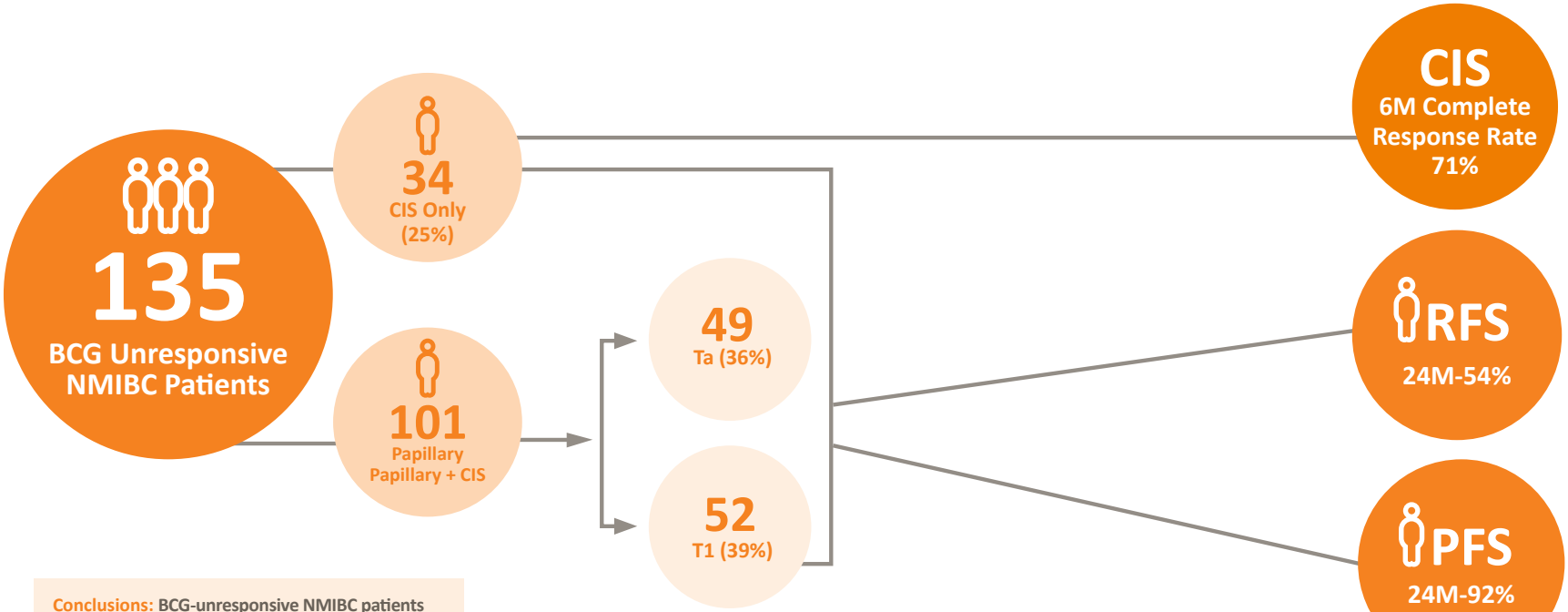

Conclusions: BCG-unresponsive NMIBC patients who are treated with CHT had a 24-month DFS of 53.9% and PFS of 92.1%. CHT seems a valid treatment option for BCG unresponsive NMIBC patients who are unsuitable for radical cystectomy.

Click Through to Full Abstract

Visual Summary of: 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

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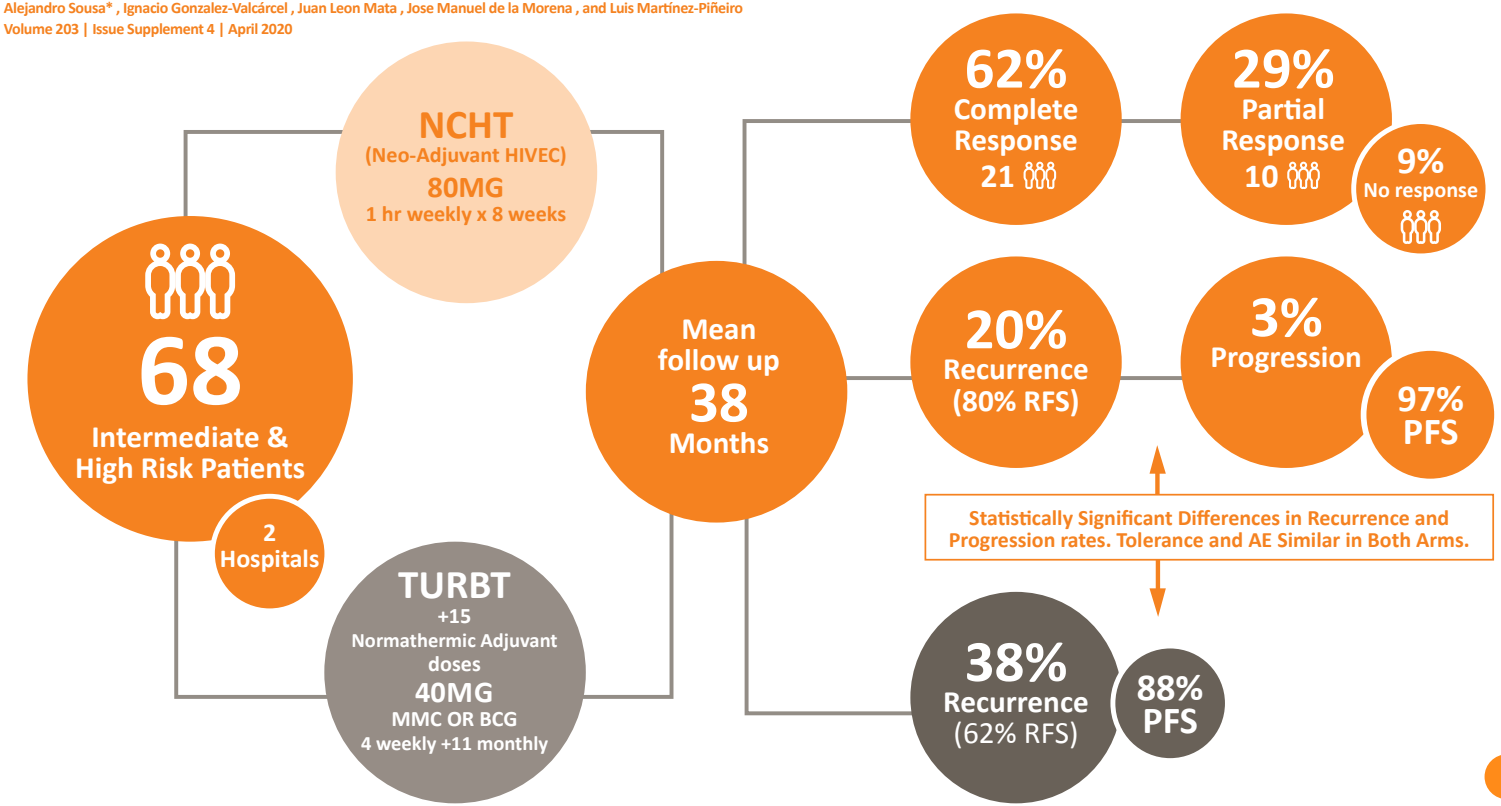

Conclusions: In the preliminary analysis, 60% of patients showed complete response after NCHT and the recurrence and progression rates after a mean follow up of 3 years were significantly better in the NCHT arm vs. standard TURBT and adjuvant therapy. Further studies are needed to confirm a protective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

Click Through to Full Abstract

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

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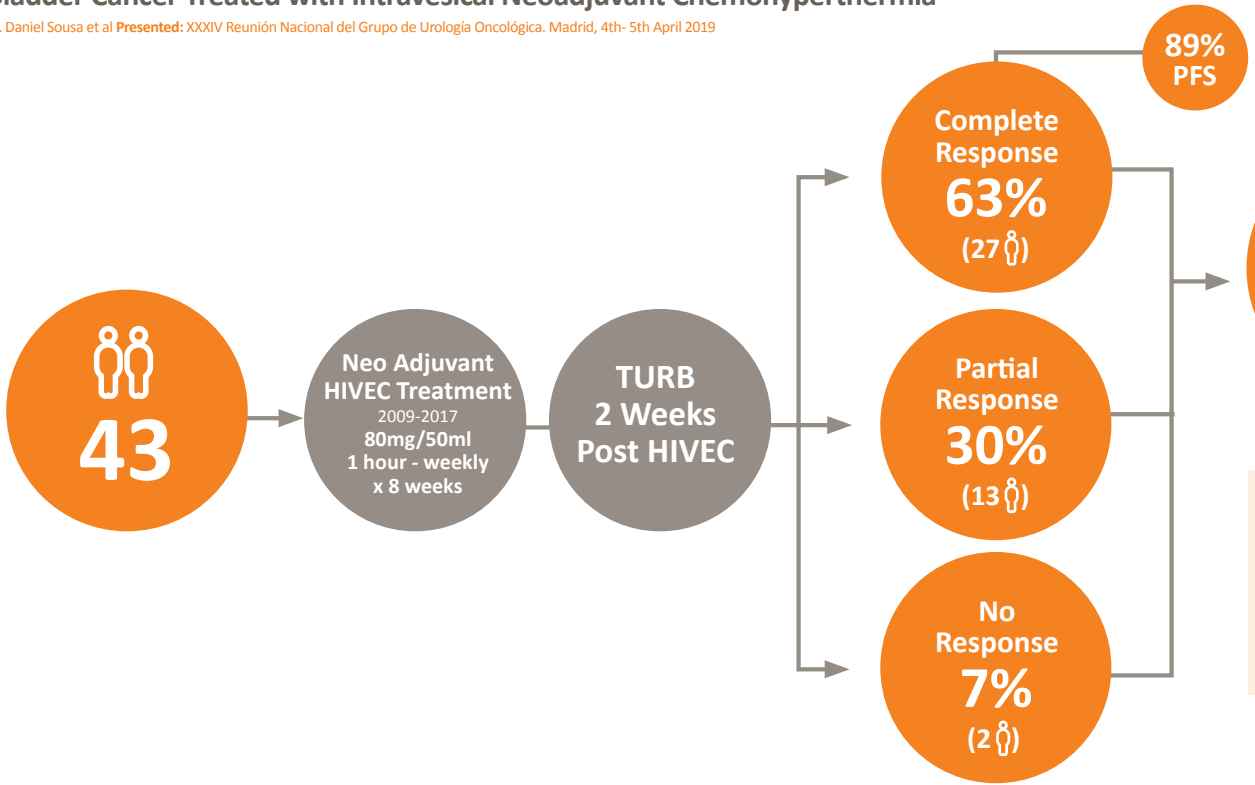
HIVEC® Neo-Adjuvant Setting



HIVEC performed before TURB, could generate a tumor ICD that would improve immunological activation and clinical response, functioning theoretically as a self-vaccine

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.

Click Through to Full Abstract

Visual Summary of: 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 | April 2020

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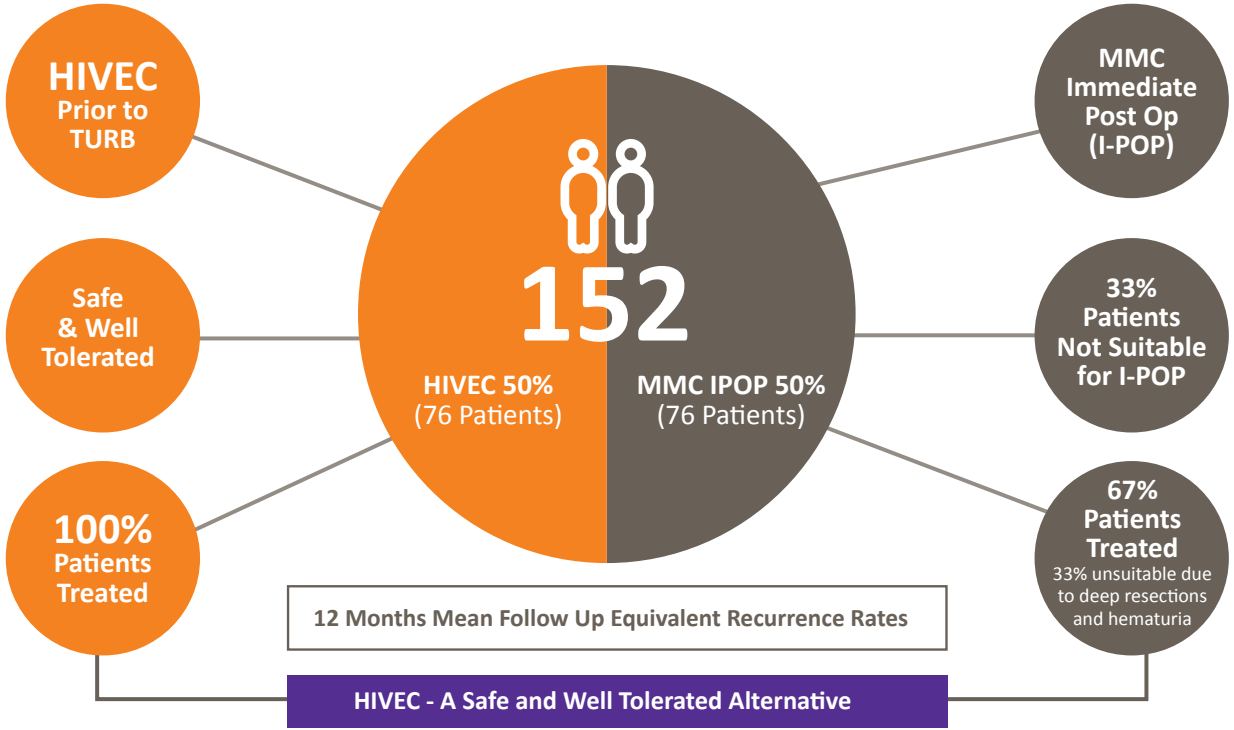


Objectives: Evaluate early recurrence rate of low to intermediate Risk NMIBC with HIVEC instillation prior to TURBT compared to single immediate IPOP MMC

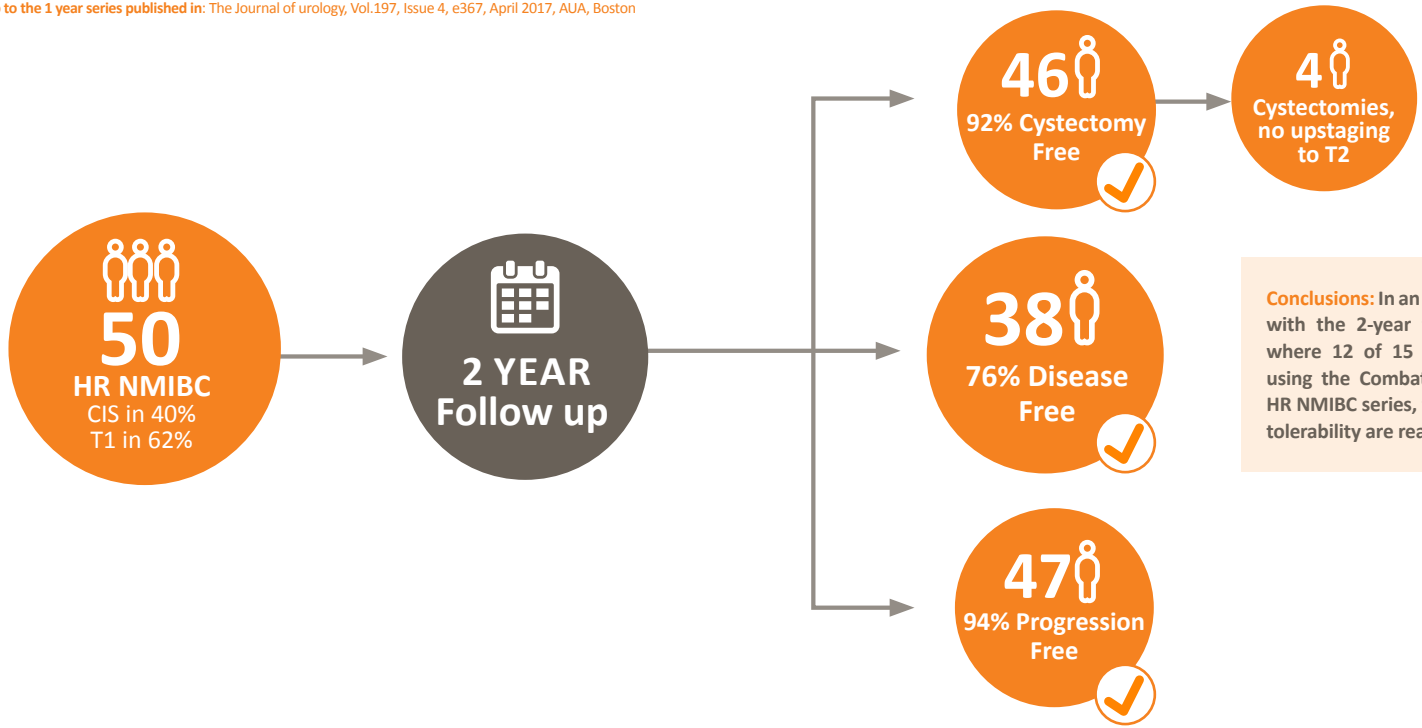
Conclusions: Chemohyperthemia treatment with Mitomycin-C pre-TURBT seems to be a safe and well tolerated alternative.
After a follow-up period of 12 months the recurrence rate in both arms seems to be equivalent.

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

Griffiths T.R.L., Grice P.T., Green W.J.F., Goddard J.C., Kockelbergh R.C.
University Hospitals of Leicester, Dept. of Urology, Leicester, United Kingdom

Follow up to the 1 year series published in: The Journal of urology, Vol.197, Issue 4, e367, April 2017, AUA, Boston



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.

Click Through to Full Abstract

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

Presented: European Urology Supplements, Vol. 16, Issue 3, e1150–e1151, March 2017

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Safety & Tolerability & Quality of Life

307

89%
Completed Inductive Therapy
No statistical difference in AE between Hyperthermic MMC (HIVEC) & MMC

Drug allergy
Main reason for stopping in both arms

Only low grade (GI & GII) adverse events both arms

No urethral strictures - either arm

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.**

Click Through to Full Abstract

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

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

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40
Female Swine
(Refer to full abstract for methods)

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

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.

Click Through to Full Abstract

Combined Effects of Hyperthermia in NMIBC

Clinical hyperthermia is defined as the therapeutic use of temperature between 41°C to 44°C[a]. The introduction of thermal energy affects the cancer cells more because of their inability to manage the heat as well as healthy cells[b]. Mitomycin C (MMC) is stable at temperatures up to 50°C[f], 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 mass[d]. At 43°C the **cytotoxicity increases by 10 times,** without any increase in the toxicity to the patient[c]. 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 surface[e]. 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.**

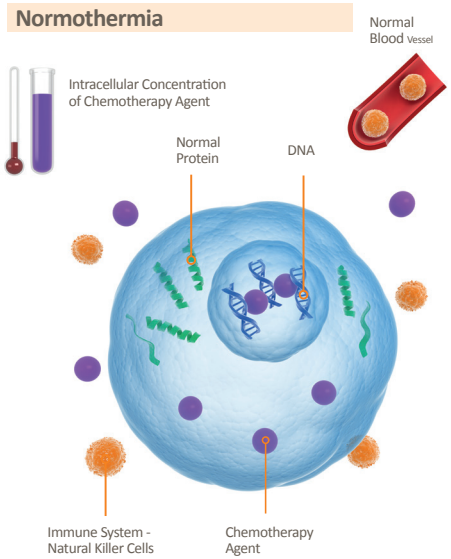
Based on the body of evidence, and real world experience from urology teams using HIVEC, it is recommended to achieve the best results with the COMBAT BRS, that intermediate risk patients receive a minimum of 6 weekly induction treatments plus an additional 1 year maintenance for high risk patients.

COMBAT HIVEC treatment given in day urology unit setting

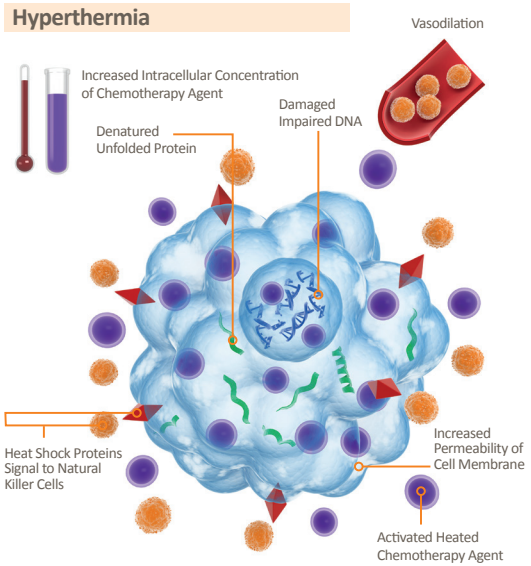
Scroll down for more Hyperthermia data

Cell Diagram

Cancer cell with Mitomycin C
Delivered at room temperature



Cancer cell with Mitomycin C
Delivered at 43°C

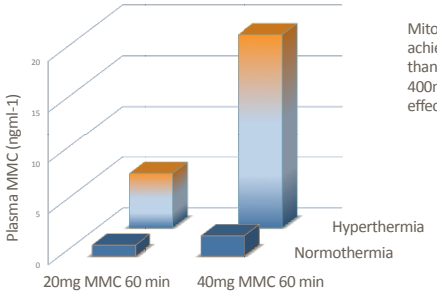


Effect of hyperthermia on alkylating agents
Teicher et al (1981) demonstrated activation rates 1.3 – 1.4 times higher at 41°C, 42°C, and 43°C compared to 37°C[c].

Mitomycin C remains stable at higher temperatures[f].

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 myelosuppression[h].

References:

a. Dahl, O., Dalene, R., Schem, B. C. & Mella, O. Status of clinical hyperthermia. Acta Oncol. 38, 863–73 (1999). **b.** Song, C. W. Effect of Local Hyperthermia on Blood Flow and Microenvironment : A Review. Cancer Res. 44, 4721s – 4730s (1984). **c.** Teicher, B. A., Kowal, C. D., Kennedy, K. A. & Sartorelli, A. C. Enhancement by Hyperthermia of the in Vitro Cytotoxicity of Mitomycin C toward Hypoxic Tumor Cells. Cancer Res. 41, 1096–1099 (1981). **d.** Fajardo, L., Prionas, S., Kowalski, J. & Kwan, H. Hyperthermia inhibits angiogenesis. Radiat Res 114, 297–306 (1988). **e.** Fuse, T., Yoon, K., Kato, T. & Yamada, K. Heat-induced apoptosis in human glioblastoma cell line A172. Neurosurgery 42, 843–9 (1998). **f.** Adapted from Company Data Kyowa http://www.mitomycin.net/professionals/about03.html **g.** Paroni, R. et al. Efect of local hyperthermia of the bladder on mitomycin C pharmacokinetcs during intravesical chemotherapy for the treatment of superfcial transitonal cell carcinoma. Br. J. Clin. Pharmacol. 52, 273–8 (2001).**h**. Crooke, S. T., Henderson, M., Samson, M. & Baker, L. H. Phase I study of oral mitomycin C. Cancer Treat. Rep. 60, 1633–6 (1976).

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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.

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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.

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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.[2], Llanes L.[3], Diaz Goizueta J.[3], Rios E.[4], Rimington P.[5], Castillo JM.[6], Castillo DJ.[6], Pontones JL.[7], Nzeh C.[8], Brisuda A.[9], León J.[10], Sousa A.[10], Chiancone F.[11], Fedelini p.[11], Hendricksen K.[12], Vögeli TA.[13], Frank E.[13], Wilby D.[14]

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 Univeritario La Fe, Valencia, Spain; [8] St Barbara Hospital, Gladbeck, Germany; [9] Motole Hospital, Prague, Czech Republic; [10] Hospital de Monforte, Lugo, Spain; [11] Hospital Cardarelli, Napel, Italy; [12] Netherlands Cancer Institute, Amsterdam, Netherlands; [13] UnikliniK RWTH Aachen, Aachen, Germany; [14] Queen Alexandra Hospital, Portsmouth, UK.

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.

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

1. **Tan WS, University College London, London, UK**. [2]. Chiancone F, Cardarelli Hospital, Naples, Italy [3]. Fedelini P, Cardarelli Hospital, Naples, Italy. [4]. Boormans JL, Erasmus MC, Rotterdam, The Netherlands. [5]. de Jong J.J, Erasmus MC, Rotterdam, The Netherlands. [6]. Wilby D, Queen Alexandra Hospital, Portsmouth, UK. [7]. Robinson R, Queen Alexandra Hospital, Portsmouth, UK. [8]. Poggio M, San Luigi Hospital Orbassano, Turin, Italy. [9]. Calleja Escudero J, Hospital Clínico Universitario de Valladolid, Valladolid, Spain. [10]. Díaz goizueta FJ, Hospital Universitario de Torrejón, Madrid, Spain. [11]. Plata Bello A, Hospital Universitario de Canarias, Canary Islands, Spain. [12]. Vögeli TA, Universitätsklinik RWTH Aachen, Germany. [13]. Sousa Escandón A, Hospital Monforte de Lemos, Lugo, Spain. [14]. Nzeh C, St. Barbara Hospital, Gladbeck, Germany. [15]. de la Morena JM, Hospital Universitario Infanta Sofía, Madrid, Spain. [16]. Pontones Moreno JL, Hospital Universitario La Fe, Valencia, Spain.[17]. Guerrero F, Hospital Universitario 12 Octubre, Madrid, Spain. [18]. Montero Torres J, Hospital Universitario de Burgos, Burgos, Spain. [19]. Hendricksen K, Netherlands Cancer Institute, The Netherlands.

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.

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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.

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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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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.

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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

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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.

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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.

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

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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.

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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

COMBAT clinical specialists work with healthcare professionals worldwide to ensure HIVEC is available in hospitals as a bladder sparing option with proven cost savings. HIVEC is reimbursed in many countries and national tariff codes are available, ensuring cost effective clinical benefits. Support is available for business case preparation and comprehensive device training provided.

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

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