“Our mission is to drive change in order 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

COMBAT provides the following:

- Five ongoing multicentre, randomised controlled clinical trials with 867 patients in UK and Spain. Data release 2019 onwards.
- A further series of High Risk trials to be announced by the end of 2018.
- HIVEC E – a real world data registry sponsored by Combat controlled by a Data Monitoring Committee (DMC).
  Dedicated HIVEC website [www.hivec.co.uk](http://www.hivec.co.uk).
- Patient Information.
COMBAT Medical

COMBAT Medical is an innovative company committed to investing in research and development, clinical trials and evidence-based studies to demonstrate the effectiveness of our technology and create a solid foundation for its use.

COMBAT is continuously adding to its HIVEC™ (Hyperthermic Intra-VEsical Chemotherapy) bibliography of evidence in Non-Muscle Invasive Bladder Cancer (NMIBC).

In use since 2010 the COMBAT BRS (Bladder Recirculation System) is a technically advanced, easy to use and affordable system that optimises the intravesical instillation of chemotherapy to achieve real, measurable results. In 2018 we are now used in 35 countries, have been used in over 20,000 treatments to date, have presented real world data on over 500 patients and have 867 patients in controlled randomised clinical trials.

Clinical Trials

COMBAT has invested in the following trials and is due to announce the start of recruitment for a further series of new High Risk trials by the end of 2018. 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 2019.

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.combat-medical.com
Targeting NMIBC with HIVEC™
Hyperthermic IntraVESical Chemotherapy

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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 40 mg 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.
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, pT1 in 10, 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.
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.
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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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 therapeutc bladder preserving option in high risk patients with superficial TCC. It is of note that thermochemotherapy has now been included in the European Guidelines.
The Role of Conductive Hyperthermia with Mitomycin C in High Risk Non Muscle Invasive Bladder Cancer that has Failed BCG Therapy

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Introduction and objective: The standard management of high risk non muscle invasive bladder cancer (HR NMIBC) is BCG intravesical therapy with radical cystectomy (RC) reserved for BCG ‘failures’, a term that encapsulates all patients who are either intolerant to or unresponsive to BCG or who relapse following treatment. However there remains a significant group of patients who are unfit for or unwilling to undergo RC. Until recently therapeutic options in such patients were limited and included re-exposure to further BCG or endoscopic management. We report our experience of the use of conductive hyperthermia in the management of patients with HR NMIBC who have are unfit for or have refused RC.

Materials and Methods: Patients with BCG ‘failure’ who were deemed unfit for or unwilling to undergo RC were referred to a tertiary bladder cancer referral centre. Patients underwent an induction therapy with a 6-week course of weekly hyperthermic mitomycin (HT-MMC) using a conductive heating system heated to 43 degrees centigrade for 1 hour. If the patient tolerated the induction course and were disease free at follow up cystoscopy they went on to have maintenance HT-MMC at 3 monthly intervals for one year.

Results: Over a 26-month period a total of 26 patients with HR NMIBC were referred for HT-MMC. Mean age was 73.5 (Range 59-82). 1/3 of patients had CIS. 18 patients were BCG relapsed, 4 patients were BCG intolerant and 4 patients were referred during the BCG shortage. 60% of patients completed the full induction course of 6 HT-MMC treatments. The mean treatment length was 55 minutes and the mean number of HT-MMC treatments was 5.2. The commonest side effects were Bladder spasm in 5 (20%) and Skin rash in 5 (20%). In the BCG relapse group of 18 patients, with a median follow up of 19 months, 3 patients had been lost to f/up and one patient had died of unknown causes. 12 patients remained recurrence free giving an overall response rate of 66%. In the BCG intolerant group of 4 patients with a median follow up of 26 months, 3 patients remained recurrence free giving an overall response rate of 75%. In the BCG naive/shortage group of 4 patients with a median follow up of 19 months, 3 patients remained recurrence free giving an overall response rate of 75%.

Conclusions: Conductive hyperthermia with MMC seems an effective option in patients who have are intolerant to or relapsed on BCG therapy who are unfit or unwilling to undergo RC. Randomised trials are required to evaluate this promising option further.
Objective: To assess the efficacy of hyperthermic intravesical chemotherapy (HIVEC™) with mitomycin-C (MMC) in BCG unresponsive or BCG ineligible intermediate and high-risk non-muscle invasive bladder cancer (NMIBC) patients.

Methods: From January 2015 to February 2017 intermediate and high-risk NMIBC patients received HIVEC™ treatment, which consisted of 10 intravesical instillations (4 instillations weekly + 6 monthly). Only patients who had a minimum of 5 HIVEC™ instillations were included in the present analysis and all data were prospectively collected. Patients were followed by cystoscopy and cytology every three months and CT-scan once a year. The primary outcome was the recurrence-free survival (RFS). Questionnaires on micturition were completed before and after treatment. The Common Terminology Criteria for Adverse Events was used for the assessment of side-effects.

Results: A total of 27 NMIBC patients (30% intermediate- and 70% high-risk) were recruited. Twenty-five patients underwent ≥5 HIVEC™ treatments and were analyzed for recurrence. Patients were classified as: BCG-unresponsive in 17, 4 patients had received an unknown number of BCG installations, and 6 patients were BCG naïve. The median follow-up was 10.4 months [IQR 4.4-16.7] and the overall relapse rate was 52%. The mean RFS was 15.3 months [SE 2.12]. In BCG-unresponsive patients, the relapse rate was 56% and the RFS was 13.8 months [SE 2.67]. No severe side-effects were reported nor were changes in voiding diary observed. Five out of 14 carcinoma in situ (CIS) positive patients (10 CIS only and 4 concomitant CIS) had a recurrence.

Conclusions: In BCG-unresponsive or BCG ineligible intermediate - or high-risk NMIBC patients, treatment with HIVEC™ resulted in a RFS of >1 year, potentially avoiding or postponing the need for radical surgery.
Intravesical Thermo-Chemotherapy using the Combined Antineoplastic Thermotherapy Bladder Recirculation System (COMBAT BRS) for Patients with High Risk, Non-Muscle Invasive Bladder Cancer – Early Results

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BAUS 2017 Abstracts: Journal of Clinical Urology 10(2S)

Introduction: EUA guidelines recommend that patients with high-risk, superficial TCC of the bladder are treated with either intravesical BCG or, in highest risk tumours, radical cystectomy. However when patients fail BCG treatment (or as in recent times it is unavailable) and they are unfit for cystectomy then treatment options are limited. We set out to assess the efficacy of intravesical thermochemotherapy, using the COMBAT BRS device, in a group of such patients.

Methods: Between June 2015 and August 2016, 26 patients (mean age 74, range 53-88) with high grade, superficial bladder cancer were referred for a six-week course of intravesical mitomycin with hyperthermia, using the COMBAT BRS. They then underwent rigid cystoscopy six weeks later. Of the 26 patients, 14 (54%) had failed BCG, seven (27%) were eligible for BCG but it was not available, and five (19%) were referred on specific consultant recommendation.

Results: 24 of the 26 patients completed the six-week course. Two patients discontinued treatment early due to pain. At the six week check cystoscopy, 20 (77.0%) were recurrence free, three (11.5%) patients had recurrent disease, two (7.7%) patients had progressive disease and one failed access (3.8%). Subsequently three recurrences were found, two at six months and one at nine months. To date, nine patients remain recurrence free at 15 months and four are recurrence free at 18 months.

Conclusions: Early results from this small group suggest that thermo-chemotherapy is well tolerated and could be a promising treatment option in this sub-set of patients.
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

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.
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 ≤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.
Recirculant Hyperthermic IntraVesical Chemotherapy (HIVEC)
in Intermediate – High Risk Non-Muscle Invasive Bladder Cancer

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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 HIVEC™ treatment with a COMBAT BRS system. Of these patients, 24 received neoadjuvant HIVEC™ treatment (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.
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 anesthetized 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.
“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.16 - 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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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.
Enhancement by Hyperthermia of the in Vitro Cytotoxicity of Mitomycin C Toward Hypoxic Tumor Cells

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Abstract
Mitomycin C and hyperthermia are both toxic to chronically hypoxic EMT6 tumor cells. Combinations of this drug and heat were tested in vitro in normally aerated and chronically hypoxic EMT6 mouse mammary tumor cells to establish whether greater than additive cytotoxicity could be achieved by combined treatment. Cell survival was measured at four concentrations of mitomycin C (0.01, 0.1, 1.0, and 10 microM) at 37 degrees or at elevated temperatures (41, 42, and 43 degrees) for durations of 1, 2, 3, and 6 hr. At 42 degrees, exposure to mitomycin C for 3 and 6 hr produced a 2- to 3-fold increase in hypoxic tumor cell kill at all drug concentrations over that expected for strict additivity. A 15-fold enhancement in the kill of hypoxic tumor cells was obtained at 1.0 and 10 microM mitomycin C at 43 degrees for 6 hr of exposure. Under most conditions, additivity was observed for the antibiotic and heat in oxygenated cells, except at 43 degrees with 0.01 and 0.1 microM mitomycin C following 3 and 6 hr of treatment, conditions under which a 5- to 10-fold potentiation of tumor cell kill was obtained. The rate of formation of reactive metabolites from mitomycin C under anaerobic conditions in EMT6 cell-free preparations was measured. A 30 to 50% increase in alkylation activity was observed at elevated temperatures, suggesting that the enhanced cytotoxicity of mitomycin C with heat toward hypoxic cells may, in part, be due to an increase in activation of the drug.
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.
COMBAT BRS

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

**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.

**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.
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.
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.

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

<table>
<thead>
<tr>
<th>Temp.</th>
<th>Solvent</th>
<th>Parameter</th>
<th>Storage Period</th>
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<th>1 hr</th>
<th>3 hr</th>
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<td>91.3</td>
<td>90.2</td>
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</table>

*0 hr : immediately after reconstitution.
Appendix: Clinical Trial Protocol Flow Charts
HIVEC-R Targeting Bladder Cancer

Intermediate & High Risk NMIBC New or Recurrence

Screening & Consent

Randomisation

Control Arm
Standard Treatment
N=34

Hyperthermia + Mitomycin
Once weekly for 4 weeks
80mg/50ml 60 mins HIVEC™
N=34

Cystoscopy

Complete, Partial, No Response

Progression

Hyperthermia + Mitomycin
Once weekly for 4 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

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
References:


f. Adapted from Company Data Kyowa http://www.mitomycin.net/professionals/about03.html
