Hyperthermia
Bladder Cancer
Mitomycin C
Synergistic Effects of Hyperthermia

Overview:

Thermal Tolerance:

Immune Adaptation:

Angiogenesis Inhibition:

DNA Damage:

Thermodynamic activation:

Hyperthermia and Bladder Cancer:
Edward N Rampersaud, Zeljko Vujaskovic and Brant a Inman, “Hyperthermia as a Treatment for Bladder Cancer.,” Oncology (Williston Park, N.Y.), 24 (2010), 1149–55
Richmond a Owusu, Michael R Abern and Brant a Inman, “Hyperthermia as Adjunct to Intravesical Chemotherapy for Bladder Cancer.,” BioMed research international, 2013 (2013), 262313
BCG Failures:


High Grade & CIS:


Adjuvant Therapy – Intermediate to High Risk:


Neoadjuvant Therapy - Intermediate to High Risk:


Abstract:

There is a clear rationale for using hyperthermia in cancer treatment. Treatment at temperatures between 40 and 44 degrees C is cytotoxic for cells in an environment with a low pO(2) and low pH, conditions that are found specifically within tumour tissue, due to insufficient blood perfusion. Under such conditions radiotherapy is less effective, and systemically applied cytotoxic agents will reach such areas in lower concentrations than in well perfused areas. Therefore, the addition of hyperthermia to radiotherapy or chemotherapy will result in at least an additive effect. Furthermore, the effects of both radiotherapy and many drugs are enhanced at an increased temperature. Hyperthermia can be applied by several methods: local hyperthermia by external or internal energy sources, regional hyperthermia by perfusion of organs or limbs, or by irrigation of body cavities, and whole body hyperthermia. The use of hyperthermia alone has resulted in complete overall response rates of 13%. The clinical value of hyperthermia in addition to other treatment modalities has been shown in randomised trials. Significant improvement in clinical outcome has been demonstrated for tumours of the head and neck, breast, brain, bladder, cervix, rectum, lung, oesophagus, vulva and vagina, and also for melanoma. Additional hyperthermia resulted in remarkably higher (complete) response rates, accompanied by improved local tumour control rates, better palliative effects and/or better overall survival rates. Generally, when combined with radiotherapy, no increase in radiation toxicity could be demonstrated. Whether toxicity from chemotherapy is enhanced depends on sequence of the two modalities, and on which tissues are heated. Toxicity from hyperthermia cannot always be avoided, but is usually of limited clinical relevance. Recent developments include improvements in heating techniques and thermometry, development of hyperthermia treatment planning models, studies on heat shock proteins and an effect on anticancer immune responses, drug targeting to tumours, bone marrow purging, combination with drugs targeting tumour vasculature, and the role of hyperthermia in gene therapy. The clinical results achieved to date have confirmed the expectations raised by results from experimental studies. These findings justify using hyperthermia as part of standard treatment in tumour sites for which its efficacy has been proven and, furthermore, to initiate new studies with other tumours. Hyperthermia is certainly a promising approach and deserves more attention than it has received until now.
Status of Clinical Hyperthermia.
Dahl, O, R Dalene, B C Schem, and O Mella,
Acta oncologica (Stockholm, Sweden), 38 (1999), 863–73

Introduction:
The expectations of rapid clinical benefits from hyperthermia were high 20 years ago but progress has not been quite as brilliant as projected, despite a substantial effort by many centres. The Scandinavian activities have previously been reviewed (1). Today there is a renewed interest in clinical use of hyperthermia, mostly based upon the results from randomized phase III studies from Europe, but also because of the limited success of other strategies. The aim of this paper is to present the current status of clinical hyperthermia in Western Europe with reference to international papers of major impact on the field.

Conclusion:
Hyperthermia remains one of the most powerful modalities in improving the clinical outcome of radiation therapy and anticancer drugs. From a period of uncritical administration of hyperthermia in far-advanced cases, patients with some locally advanced tumours are now being seriously considered as candidates for hyperthermia in order to obtain better tumour control. With careful selection of suitable patients and the use of more advanced hyperthermia machines by a well-trained staff, hyperthermia is a viable option on the edge of established therapy for some groups of patients.
The Cellular and Molecular Basis of Hyperthermia.

Hildebrandt, Bert, Peter Wust, Olaf Ahlers, Annette Dieing, Geetha Sreenivasa, Thoralf Kerner, et al

Critical reviews in oncology/hematology, 43 (2002), 33–56

Abstract:

In oncology, the term ‘hyperthermia’ refers to the treatment of malignant diseases by administering heat in various ways. Hyperthermia is usually applied as an adjunct to an already established treatment modality (especially radiotherapy and chemotherapy), where tumor temperatures in the range of 40-43 degrees C are aspired. In several clinical phase-III trials, an improvement of both local control and survival rates have been demonstrated by adding local/regional hyperthermia to radiotherapy in patients with locally advanced or recurrent superficial and pelvic tumors. In addition, interstitial hyperthermia, hyperthermic chemoperfusion, and whole-body hyperthermia (WBH) are under clinical investigation, and some positive comparative trials have already been completed. In parallel to clinical research, several aspects of heat action have been examined in numerous pre-clinical studies since the 1970s. However, an unequivocal identification of the mechanisms leading to favorable clinical results of hyperthermia have not yet been identified for various reasons. This manuscript deals with discussions concerning the direct cytotoxic effect of heat, heat-induced alterations of the tumor microenvironment, synergism of heat in conjunction with radiation and drugs, as well as, the presumed cellular effects of hyperthermia including the expression of heat-shock proteins (HSP), induction and regulation of apoptosis, signal transduction, and modulation of drug resistance by hyperthermia.
Abstract:

The blood flow in tumors varies considerably among different tumor types. Even in the same tumor, the distribution of vasculature and blood flow is quite heterogeneous. The tumor blood flow generally decreases as the tumors grow larger, owing partially to progressive deterioration of vascular beds and to the rapid growth of tumor cell population relative to vascular beds. Contrary to the general notion that blood flow is less in tumors than in normal tissues, blood flow in many tumors, particularly in small tumors, is actually greater than that in surrounding normal tissues at normothermic conditions. Compared to the normal tissue blood flow, however, the capacity of tumor blood flow to increase upon heating appears to be rather limited. Consequently, the heat dissipation by blood flow in tumors is slower than that in normal tissues, and thus the temperature of tumor rises higher than that in normal tissue during heating. Preferential heating of tumors, however, may not be achieved all the time because the relative blood perfusion in some tumors remains greater than that in the surrounding normal tissues despite the profound increase in normal tissue blood flow during heating. The vasculature in tumor can be significantly damaged at temperatures which may alter but do not damage the vasculature of normal tissue. Upon heating, the intratumor environment becomes acidic, hypoxic, and nutritionally deprived due probably to vascular damage. Such a suboptimal environment in the heated tumors potentiates the response of tumor cells to hyperthermia, inhibits the repair of thermal damage, and also interferes with the development of thermal tolerance. The acidic environment also appears to potentiate the response of tumor cells to certain drugs at elevated temperatures. The changes in oxygenation of tumors and normal tissues caused by the changes in blood flow may have significant implications in the effectiveness of different sequences of hyperthermia and radiotherapy in the combined use of these two modalities. Changes in the distribution of drugs in tumors and normal tissues due to changes in blood flow will also determine the optimal use of hyperthermia in conjunction with chemotherapy.
Old and New Facts about Hyperthermia-Induced Modulations of the Immune System.

Abstract:

Hyperthermia (HT) is a potent sensitiser for radiotherapy (RT) and chemotherapy (CT) and has been proven to modulate directly or indirectly cells of the innate and adaptive immune system. We will focus in this article on how anti-tumour immunity can be induced by HT. In contrast to some in vitro assays, in vivo examinations showed that natural killer cells and phagocytes like granulocytes are directly activated against the tumour by HT. Since heat also activates dendritic cells (DCs), HT should be combined with further death stimuli (RT, CT or immune therapy) to allocate tumour antigen, derived from, for example, necrotic tumour cells, for uptake by DCs. We will outline that induction of immunogenic tumour cells and direct tumour cell killing by HT in combination with other therapies contributes to immune activation against the tumour. Studies will be presented showing that non-beneficial effects of HT on immune cells are mostly timely restricted. A special focus is set on immune activation mediated by extracellular present heat shock proteins (HSPs) carrying tumour antigens and further danger signals released by dying tumour cells. Local HT treatment in addition to further stress stimuli exerts abscopal effects and might be considered as in situ tumour vaccination. An increased natural killer (NK) cell activity, lymphocyte infiltration and HSP-mediated induction of immunogenic tumour cells have been observed in patients. Treatments with the addition of HT therefore can be considered as a personalised cancer treatment approach by specifically activating the immune system against the individual unique tumour.
Abstract:

OBJECTIVE: Hyperthermia has been clinically applied to some types of brain tumors. However, the detailed mechanisms of this growth inhibition are not clear. The effect of mild hyperthermia on cultured human glioblastoma cell line, A172, was studied.

METHODS: A172 cells were heat treated (43-44.5 degrees C) for 1 hour in the growing phase. Cell viability was assessed by trypan blue dye exclusion assay. The presence of apoptosis was determined by the morphological changes observed using phase contrast microscopy and nuclear changes observed using HOECHST 33342 stain. For the evaluation of cellular deoxyribonucleic acid fragmentation, the TUNEL method was used. The expression of p53 and bax proteins was evaluated by Western blot, and the bax messenger ribonucleic acid was detected by Northern blot.

RESULTS: Heat treatment induced cell death in time- and temperature-dependent manners. The nuclear staining with HOECHST 33342 demonstrated morphological changes consistent with apoptosis. The TUNEL stain also demonstrated damages in the deoxyribonucleic acid. These morphological changes were accompanied by the accumulation of p53 protein, bax protein, and messenger ribonucleic acid.

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Hyperthermia-Induced DNA Repair Deficiency Suggests Novel Therapeutic Anti-Cancer Strategies.

Abstract:
Local hyperthermia is an effective treatment modality to augment radio- and chemotherapy-based anti-cancer treatments. Although the effect of hyperthermia is pleotropic, recent experiments revealed that homologous recombination, a pathway of DNA repair, is directly inhibited by hyperthermia. The hyperthermia-induced DNA repair deficiency is enhanced by inhibitors of the cellular heat-shock response. Taken together, these results provide the rationale for the development of novel anti-cancer therapies that combine hyperthermia-induced homologous recombination deficiency with the systemic administration of drugs that specifically affect the viability of homologous recombination deficient cells and/or inhibit the heat-shock response, to locally sensitise cancer cells to DNA damaging agents.
Enhancement by Hyperthermia of the in Vitro Cytotoxicity of Mitomycin C toward Hypoxic Tumor Cells.
Teicher, Beverly A, Charles D Kowal, Katherine A Kennedy, and Alan C Sartorelli.

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 μM) at 37° or at elevated temperatures (41, 42, and 43°) for durations of 1, 2, 3, and 6 hr. At 42°, 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 μM mitomycin C at 43° for 6 hr of exposure. Under most conditions, additivity was observed for the antibiotic and heat in oxygenated cells, except at 43° with 0.01 and 0.1 μM 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 alkylating 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.
Effect of Local Hyperthermia of the Bladder on Mitomycin C Pharmacokinetics during Intravesical Chemotherapy for the Treatment of Superficial Transitional Cell Carcinoma.


Abstract:

AIMS: To assess the effect of local hyperthermia on the systemic absorption of mitomycin C (MMC) during intravesical chemotherapy for the treatment of superficial transitional cell carcinoma of the bladder, and to establish the likely safety of this procedure.

METHODS: Group 1 (n = 12) received 20 mg intravesical MMC plus local hyperthermia, group 2 (n = 13) 20 mg MMC alone, group 3 (n = 16) 40 mg MMC plus local hyperthermia and group 4 (n = 10) 40 mg MMC alone. Patients in groups 1, 2, and 4 underwent post-tumour resection adjuvant treatment, whereas those in group 3 still had tumour present and were treated to eradicate it. Intravesical instillation lasted 60 min, with the solution (50 ml) being replaced after the first 30 min. Blood samples were taken before, and every 15 min during instillation. MMC concentrations in plasma and in urine were determined by h.p.l.c.

RESULTS: The highest MMC plasma concentration (67.9 ng ml(-1)) occurred in a patient in group 3. This value was well below the threshold concentration (400 ng ml(-1)) for myelosuppression. Local hyperthermia associated with the intravesical chemotherapy enhanced plasma MMC concentrations at 30, 45 and 60 min compared with chemotherapy alone (Group 1 vs 2, P ≤ 0.008). Systemic exposure to MMC was not significantly increased by doubling the intravesical dose when intravesical chemotherapy alone was administered. Patients in group 3 displayed the highest degree of MMC absorption and the greatest variability in pharmacokinetics between patients.

CONCLUSIONS: Local hyperthermia enhances the systemic absorption of MMC during intravesical chemotherapy for bladder cancer. In the doses used, plasma MMC concentrations were always more than six times lower than those shown to cause toxicity.
Abstract:

Modern cancer care is characterized by a focus on organ-sparing multi-modal treatments. In the case of non-muscle-invasive bladder cancer this is particularly true; treatment is focused on reducing the frequency of low-risk recurrences and preventing high-risk progression. Deep regional hyperthermia is an oncologic therapeutic modality that can help achieve these two goals. The combination of hyperthermia with chemotherapy and radiotherapy has improved patient outcomes in several tumor types. In this review, we highlight the biology of therapeutic fever-range hyperthermia, discuss how hyperthermia is administered and dosed, demonstrate how heat can be added to other treatment regimens, and summarize the data supporting the role of hyperthermia in the management of bladder cancer.
Hyperthermia as Adjunct to Intravesical Chemotherapy for Bladder Cancer.
Owusu, Richmond a, Michael R Abern, and Brant a Inman,
BioMed research international, 2013 (2013), 262313

Abstract:
Nonmuscle 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.
Intravesical Hyperthermia and Mitomycin-C for Carcinoma in Situ of the Urinary Bladder: Experience of the European Synergo Working Party.

Alfred Witjes, J, Kees Hendrickxen, O Gofrit, O Risi, and O Nativ,
World journal of urology, 27 (2009), 319–24

Abstract:

OBJECTIVES: To study the results of chemotherapy combined with intravesical hyperthermia in patients with mainly BCG-failing carcinoma in situ (CIS).

METHODS: Patients with histologically confirmed CIS were included retrospectively. Outpatient thermochemotherapy treatment was done with mitomycin-C (MMC) and the Synergo system SBTS 101 (temperature range between 41 and 44 degrees C), weekly for 6-8 weeks, followed by 4-6 sessions every 6-8 weeks.

RESULTS: Fifty-one patients were treated between 1997 and 2005 from 15 European centers. Thirty-four were pre-treated with BCG. Mean age was 69.9 years. Twenty-four patients had concomitant papillary tumors. The mean number of hyperthermia/MMC treatments per patient was 10.0. Of the 49 evaluable patients 45 had a biopsy and cytology proven complete response. In two patients CIS disappeared, but they had persistent papillary tumors. Follow-up of 45 complete responders showed 22 recurrences after a mean of 27 months (median 22): T2 (4), T1 (4), T1/CIS (1), CIS (5), Ta/CIS (2), Ta (5) and Tx (1). Side effects (bladder complaints) were generally mild and transient.

CONCLUSIONS: In patients with primary or BCG-failing CIS, treatment with intravesical hyperthermia and MMC appears a safe and effective treatment. The initial complete response rate is 92%, which remains approximately 50% after 2 years.
Combined Thermo-Chemotherapy for Recurrent Bladder Cancer after Bacillus Calmette-Guerin.

Nativ, Ofer, J Alfred Witjes, Kees Hendrickxen, Michael Cohen, Daniel Kedar, Ami Sidi, et al
The Journal of urology, 182 (2009), 1313–7

Abstract:

PURPOSE: Despite an initial adequate response many patients with nonmuscle invasive urothelial cell carcinoma of the bladder eventually have recurrence after intravesical bacillus Calmette-Guerin treatments. We evaluated the efficacy of combined bladder wall hyperthermia and intravesical mitomycin C instillation (thermo-chemotherapy) in cases of recurrence after bacillus Calmette-Guerin.

MATERIALS AND METHODS: A total of 111 patients with recurrent papillary nonmuscle invasive urothelial cell carcinoma of the bladder after previous bacillus Calmette-Guerin treatment underwent complete bladder tumor resection and were referred for prophylactic adjuvant treatment with thermo-chemotherapy. Treatment was received on an outpatient basis weekly for 6 weeks, followed by 6 maintenance sessions at 4 to 6-week intervals. Each treatment included 2, 30-minute cycles of 20 mg mitomycin C and bladder wall hyperthermia to 42℃ ± 2℃. Cystoscopy and urine cytology were performed after the completion of induction treatment and every 3 months thereafter.

RESULTS: The Kaplan-Meier estimated disease-free survival rate was 85% and 56% after 1 and 2 years, respectively. No maintenance treatment was associated with decreased efficacy, that is the recurrence rate was 61% at 2 years vs 39% in those with maintenance treatments (p = 0.01). The progression rate was 3%.

CONCLUSIONS: Thermo-chemotherapy may be effective for papillary nonmuscle invasive urothelial cell carcinoma of the bladder that recurs after BCG treatment without increasing the risk of tumor progression. Maintenance therapy is important and improves the outcome.
Preliminary European Results of Local Microwave Hyperthermia and Chemotherapy Treatment in Intermediate or High Risk Superficial Transitional Cell Carcinoma of the Bladder.
European urology, 46 (2004), 65–71; discussion 71–2

Abstract:

INTRODUCTION: Superficial bladder cancer can be treated by transurethral resection (TUR) and adjuvant intravesical therapy. Intravesical bacillus Calmette-Guérin (BCG) has been proven to be more efficacious with respect to recurrence prevention than intravesical chemotherapy, although at the cost of more severe side effects. There is a need for a new treatment modality with higher efficacy and less toxicity. The subject of this study is the efficacy of local microwave hyperthermia and chemotherapy treatment in intermediate or high risk superficial transitional cell carcinoma (TCC) of the bladder.

PATIENTS AND METHODS: Ninety eligible patients received adjuvant treatment with a combination of mitomycin-C (MMC) and local microwave hyperthermia. All patients had multiple or recurrent Ta or T1 TCC of the bladder and were classified as intermediate or high risk according to EAU criteria. In total, 41 patients were BCG failures. The treatment regimen included 6 to 8 weekly sessions followed by 4 to 6 monthly sessions. Follow-up consisted of video-cystoscopy and urine cytology every 3 months. All patients were observed for 2 years.

RESULTS: Kaplan-Meier analyses of the total group (N = 90) indicated that 1 year after treatment only 14.3% (SE 4.5%) of all patients experienced a recurrence. After 2 years of follow-up the risk of recurrence was 24.6% (SE 5.9%). No progression in stage and grade was observed.

CONCLUSION: Microwave induced hyperthermia combined with MMC has promising value in intermediate or high risk superficial bladder cancer patients compared to literature data of BCG and/or intravesical chemotherapy, particularly where other treatments, i.e. BCG, have failed.
Combined Local Bladder Hyperthermia and Intravesical Chemotherapy for the Treatment of High-Grade Superficial Bladder Cancer.

Abstract:

OBJECTIVES: To evaluate the effectiveness of combined local bladder hyperthermia and intravesical chemotherapy for the treatment of patients with high-grade (G3) superficial bladder cancer.

METHODS: Patients with G3 bladder tumors (Stage Ta or T1) were treated with combined intravesical chemotherapy with mitomycin-C and local radiofrequency hyperthermia of the bladder wall. The patients were treated with either a prophylactic protocol (40 mg mitomycin-C) after complete transurethral resection of all tumors or with an ablative protocol (80 mg mitomycin-C) when visible tumor was seen on video-cystoscopy or bladder biopsies were positive for carcinoma in situ.

RESULTS: Combined chemo-thermotherapy was administered to 52 patients with high-grade superficial bladder cancer (40 patients with Stage T1 tumor, 11 with Ta, and 3 with concomitant or isolated carcinoma in situ). At a median follow-up of 15.2 months (mean 23, range 6 to 90), no stage progression to T2 or disease-related mortality had occurred. The bladder preservation rate was 86.5%. The prophylactic protocol was administered to 24 patients. After a mean follow-up of 35.3 months, 15 patients (62.5%) were recurrence free. The bladder preservation rate was 95.8%. The ablative protocol was administered to 28 patients. Complete ablation of the tumor was accomplished in 21 patients (75%). After a mean follow-up of 20 months, 80.9% of these patients were recurrence free. The bladder preservation rate for the ablative group was 78.6%.

CONCLUSIONS: Combined local bladder hyperthermia and intravesical chemotherapy has a beneficial prophylactic effect in patients with G3 superficial bladder cancer. Ablation of highgrade bladder tumors is feasible, achieving a complete response in about three quarters of the patients.
The Role of a Combined Regimen with Intravesical Chemotherapy and Hyperthermia in the Management of Non-Muscle-Invasive Bladder Cancer: A Systematic Review.


Abstract:

CONTEXT: Due to the suboptimal clinical outcomes of current therapies for non-muscle-invasive bladder cancer (NMIBC), the search for better therapeutic options continues. One option is chemohyperthermia (C-HT): microwave-induced hyperthermia (HT) with intravesical chemotherapy, typically mitomycin C (MMC). During the last 15 yr, the combined regimen has been tested in different clinical settings.

OBJECTIVE: To perform a systematic review to evaluate the efficacy of C-HT as a treatment for NMIBC.

EVIDENCE ACQUISITION: The review process followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. An electronic search of the Medline, Embase, Cochrane Library, CancerLit, and ClinicalTrials.gov databases was undertaken. Relevant conference abstracts and urology journals were also searched manually. Two reviewers independently reviewed candidate studies for eligibility and abstracted data from studies that met inclusion criteria. The primary end point was time to recurrence. Secondary end points included time to progression, bladder preservation rate, and adverse event (AE) rate.

EVIDENCE SYNTHESIS: A total of 22 studies met inclusion criteria and underwent data extraction. When possible, data were combined using random effects meta-analytic techniques. Recurrence was seen 59% less after C-HT than after MMC alone. Due to short follow-up, no conclusions can be drawn about time to recurrence and progression. The overall bladder preservation rate after C-HT was 87.6%. This rate appeared higher than after MMC alone, but valid comparison studies were lacking. AEs were higher with C-HT than with MMC alone, but this difference was not statistically significant.

CONCLUSIONS: Published data suggest a 59% relative reduction in NMIBC recurrence when C-HT is compared with MMC alone. C-HT also appears to improve bladder preservation rate. However, due to a limited number of randomized trials and to heterogeneity in study design, definitive conclusions cannot be drawn. In the future, C-HT may become standard therapy for high-risk patients with recurrent tumors, for patients who are unsuitable for radical cystectomy, and in cases for which bacillus Calmette-Guérin treatment is contraindicated.

Abstract:

OBJECTIVE: To present long-term efficacy data of intravesical thermochemotherapy vs chemotherapy alone with mitomycin-C (MMC) randomly administered to patients with non-muscle-invasive bladder cancer (NMIBC) as an adjuvant treatment after complete transurethral resection.

PATIENTS AND METHODS: In all, 83 patients with intermediate-/high-risk NMIBC, following complete transurethral resection, were randomly assigned to receive either intravesical thermochemotherapy by means of Synergo® (Medical Enterprises, Amsterdam, The Netherlands) or intravesical chemotherapy alone, for prophylaxis of tumour recurrence. Two doses of MMC (20 mg dissolved in 50 mL distilled water administered throughout two consecutive sessions) was used as the chemotherapeutic agent in both arms. In all, 75 patients completed the original study (35 of 42 in the treatment arm, 40 of 41 in the control arm), whose results at minimum 2-year follow-up have already been published. Recently, the files of these patients have been updated for long-term outcome definition. Data on general health, follow-up examinations, tumour relapse or progression, and cause of death were collected and analysed.

RESULTS: Updated complete data collection was available for 65/75 (87%) of the original patients. The median follow-up for tumour-free patients was 91 months. The 10-year disease-free survival rate for thermochemotherapy and chemotherapy alone were 53% and 15%, respectively (P < 0.001). An intent-to-treat analysis performed to overcome the potential bias introduced by the asymmetrical discontinuation rate still showed a significant advantage of the active treatment over the control treatment. Bladder preservation rates for thermochemotherapy and chemotherapy alone were 86% and 79%, respectively.

CONCLUSION: This is the first analysis of long-term follow-up of patients treated with intravesical thermochemotherapy. The high rate (53%) of patients who were tumour-free 10 years after treatment completion, as well as the high rate (86%) of bladder preservation, confirms the efficacy of this adjuvant approach for NMIBC at long-term follow-up, even in patients with multiple tumours.
A Clinical Trial of Neoadjuvant HIVEC (Hyperthermic IntraVESical Chemotherapy) for Treating Intermediate and High-Risk Non-Muscle Invasive Bladder Cancer.


Abstract:

PURPOSE: To report a pilot/feasibility trial of neoadjuvant hyperthermic intravesical chemotherapy (HIVEC) prior to transurethral resection of bladder tumor (TURBT) for nonmuscle invasive bladder cancer (NMIBC).

MATERIALS AND METHODS: A pilot/feasibility clinical trial was performed and 15 subjects with intermediate to high-risk NMIBC received HIVEC prior to TURBT. HIVEC consisting of 8 weekly instillations of intravesical MMC (80 mg in 50 mL) delivered with the novel Combat BRS® system at a temperature of 43°C for 60 min. Treatment-related adverse effects were measured and subjects were followed for 2 years for disease recurrence.

RESULTS: A total of 119 HIVEC treatments occurred. Grade 1 adverse events consisted of irritative bladder symptoms (33%), bladder spasms (27%), pain (27%), hematuria (20%) and UTI (14%). Grade 2 adverse events were bladder calcification (7%) and reduced bladder capacity (7%). No grade 3 or higher toxicity was observed. At TURBT 8 (53%) subjects were complete responders (pT0) while 7 (47%) were partial responders. With a median follow-up of 29 months, the 3-year cumulative incidence of recurrence was 15%.

CONCLUSIONS: The Combat BRS® system achieved target bladder temperatures and delivered HIVEC with a favorable side-effect profile. Our pilot trial also provides preliminary evidence of treatment efficacy.
A New Approach Using Local Combined Microwave Hyperthermia and Chemotherapy in Superficial Transitional Bladder Carcinoma Treatment.


Abstract:

For some time hyperthermia, alone or in combination with radiotherapy or chemotherapy, has proved to be a promising method for treating several kinds of solid tumors. After intensive laboratory investigations a new device, based on a microwave source delivering local bladder hyperthermia together with intravesical mitomycin C chemotherapy has been clinically tested as a neoadjuvant approach in 44 patients suffering from superficial cancer of the bladder. The combined approach was administered on an outpatient basis without major complications and with acceptable local toxicity. Endoscopic and histological evaluations proved that combined local hyperthermia and chemotherapy can induce necrosis of transitional tumors. The overall response rate was 90.8%, with 70.4% complete and 20.4% partial, leaving 4 patients (9.2%) nonrespondent. Clinical and histological evaluations have confirmed the feasibility and safety of this combined treatment. Further multicentric studies have been initiated.
Local Microwave Hyperthermia and Intravesical Chemotherapy as Bladder Sparing Treatment for Select Multifocal and Unresectable Superficial Bladder Tumors.

Abstract:

PURPOSE: The role of a combined regimen of local hyperthermia and topical chemotherapy in patients with multifocal and recurrent superficial bladder tumors not curable by transurethral resection was evaluated in a neoadjuvant organ sparing clinical study.

MATERIALS AND METHODS: A total of 19 patients with multifocal, superficial grades 1 to 3 bladder tumors that recurred after intravesical chemoprophylaxis or immunoprophylaxis underwent local combined administration of microwave induced hyperthermia and intravesical chemotherapy as a debulking approach. Due to extensive superficial involvement of the bladder walls complete transurethral resection of all tumors seemed technically unfeasible in all cases and radical cystectomy was considered the treatment of choice. Endovesical hyperthermia at 42.5 to 46°C was delivered using the SB-TS 101 system, based on a microwave transurethral applicator that irradiates the bladder filled with a circulating solution of mitomycin C. Patients underwent 8 weekly 1-hour sessions on an outpatient basis without anesthesia. When possible, after treatment patients underwent transurethral resection of residual tumors and all suspicious areas.

RESULTS: After treatment transurethral resection appeared to be feasible and curative in 16 patients (84%). Histological study revealed complete and partial responses in 9 (47%) and 7 (37%) cases, respectively. Due to extensive residual tumors radical cystectomy was performed in 3 patients (16%). At a median 33-month followup 8 superficial transitional tumor recurrences were documented and easily eradicated by transurethral resection or laser therapy in patients in whom the bladder had been saved.

CONCLUSIONS: Microwave induced hyperthermia combined with intravesical mitomycin C seems to be a feasible, safe and elective approach for conservative treatment of multifocal and recurrent superficial bladder tumors when other treatment strategies have failed.
Synergistic effects of hyperthermia

Clinical hyperthermia is defined as the therapeutic use of temperature between 40°C to 44°C. The introduction of thermal energy at these temperatures into cancer tumours affects the cancer cells more because of their inability to manage the heat as well as good cells. **Mitomycin C (MMC)** an alkylating chemotherapy agent is stable at temperatures up to 50°C, but importantly it 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 cytototoxicity increases by 10 times, importantly 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, resulting in higher intracellular concentration of the chemotherapy agent. Direct affects on the DNA include; **strand breaking**, **impaired transcription** (production of messenger RNA for protein synthesis), **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 of all these actions on the cancer cells is that they actively participate in their own demise through the natural process of **apoptosis**.

Chemo-hyperthermia multifactorial modes of action create a strong synergistic 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 has the potential to be 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 or increasing resources required.

Based on the strong body of evidence cited above to achieve the best results with the Combat BRS system in adjuvant treatment it should be used at a temperature setting of 43°C for 1 hour using 40 mg dose of Mitomycin C.

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**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 400 ng/ml associated with systemic side effects like myelosuppression.

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**Mitomycin C remains stable at higher temperatures**

<table>
<thead>
<tr>
<th>Temp.</th>
<th>Solvent</th>
<th>Parameter</th>
<th>Storage Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>37°C</td>
<td>5 ml water</td>
<td>Content %</td>
<td>0 hr* 1 hr 3 hr 6 hr</td>
</tr>
<tr>
<td></td>
<td>5 ml of saline</td>
<td>Content %</td>
<td>100.0 94.9 92.8 91.6</td>
</tr>
<tr>
<td>50°C</td>
<td>5 ml water</td>
<td>Content %</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5 ml of saline</td>
<td>Content %</td>
<td>100.0 91.0 88.0 87.3</td>
</tr>
</tbody>
</table>

* o hr : immediately after reconstitution.