In this article, Sari Prutchi Sagiv, PhD, Marketing Director at TheraCoat, explains why longer chemotherapy dwell-time is critical for the optimal treatment of bladder cancer, and how this can be achieved via a simple yet sophisticated drug delivery system.

**GREAT INVENTIONS THAT TRICK NATURE – NEW DELIVERY SYSTEM OPTIMISES BLADDER CANCER TREATMENT BY INCREASING DWELL TIME**

**INTRODUCTION**

TheraCoat’s Internal Cavity Drug Retention (ICDR) system allows for controlled and highly effective delivery of therapeutic agents into the bladder without being voided and diluted by the urine, overcoming the major drawbacks of instilled therapies. ICDR defies some natural norms regarding the behaviour of materials. Normally, gels become liquid with heat, not the other way around. Based on advanced materials technologies, the novel ICDR system stays liquid outside the body when cooled, and becomes a muco-adhesive gel only once inside the bladder. The use of the ICDR system increases drug exposure and reduces toxicity, significantly enhancing treatment potential, safety and compliance.

**BLADDER CANCER**

Bladder cancer is the fourth most frequent solid tumour cancer in men and the seventh in women, with more than 350,000 new cases diagnosed worldwide annually with a prevalence of 840,000 patients in Europe and 530,000 in the US. Most patients suffer from a non-invasive disease with a high survival rate but high recurrence rates mean lifelong treatment and monitoring.

The initial treatment of this cancer is surgical removal of the tumour, commonly known as transurethral resection of the bladder tumour (TURBT) followed by a series of periodic intravesical chemotherapy instillations which the patient is required to retain for approximately 60 minutes. Intravesical chemotherapy is used either as an adjuvant to TURBT, to delay tumour recurrence, or to control widespread disease not manageable by surgical methods. The rationale is to expose tumours to high local drug concentrations while minimising systemic exposure, enhancing treatment efficacy and reducing drug toxicity. But these traditional approaches to treating bladder cancer have largely proven to be insufficient since after intravesical instillation, drug concentration is immediately reduced and washed out due to continuous urine creation and voiding. Therefore, the cancerous tissue is not optimally exposed to the drug, allowing tumour reseeding and migration.

The improved efficacy of chemotherapy following increase in tissue exposure time (dwell time) was established by numerous in vitro models, in vivo studies and computer simulations. Schmittgen showed that tumour sensitivity increases with increasing Mitomycin...
A (MMC) exposure time. De Brujin treated bladder cancer patients with intravesical MMC using 30- and 60-minute dwelling times. He demonstrated that recurrence was significantly lower in the 60-minute treatment group. No recurrences were found in patients with low grade tumours when the 60-minute dwelling time was used. These results were supported by numerous studies conducted by Barlogie et al, Slee et al, Ozawa et al and Perry et al. Based on this data, Badalament’s suggestion for optimisation of the efficacy of intravesical chemotherapy included holding the dosing solution as long as possible (“Have the patient hold the intravesical therapy in his bladder as long as possible”) and dehydration of patient for reducing urine production (“Dehydrate patients prior to intravesical therapy”).

Prolongation of intravesical treatment dwell time is imperative for enhancing the anti-tumour effect of the instilled chemotherapy.

PROLONGING DWELL TIME

The novel ICDR system addresses these current treatment drawbacks. The system employs a novel hydrogel with unique thermo-sensitive properties which enable it to convert from a liquid state when cold into a gel at body temperature. In its liquid state, ICDR can easily be mixed with a specific drug for convenient catheter delivery into the bladder (as performed in the standard intravesical chemotherapy). Once inside the bladder, it solidifies, adheres to the mucosal layer and forms a drug reservoir. Upon contact with urine the gel reservoir dissolves and gel micelles entrapping the drug adhere to the mucosal layer of the bladder.

The drug is slowly released, keeping higher and effective tissue drug concentration for a longer period of time (approximately 6-8 hours). During the release of the drug, the gel is slowly dissolved and no traces of the gel are present after the treatment period. Since the gel dissolution is gradual, the gel delays the voiding of the drug from the bladder once the first urination occurs (in contrast to the standard intravesical chemotherapy) as well as decreases drug dilution by the ongoing produced urine which continuously enters the bladder (Figure 1).

PROLONGATION OF INTRAVESICAL TREATMENT DWELL TIME IS IMPERATIVE FOR ENHANCING THE ANTI-TUMOUR EFFECT OF THE INSTILLED CHEMOTHERAPY

ICDR CHARACTERISTICS

ICDR is a thermo-sensitive hydrogel with reverse thermal gelation (RTG) properties: it has high viscosity at body temperature and very low viscosity (fluid like) at 5°C. This temper-
Retention capabilities of the TheraCoat system.

The hydrogel is formulated solely with well-known ingredients, approved by the US FDA as inactive ingredients and widely used as excipients in numerous commercial formulations. The hydrogel is 100% biocompatible.

Following mixing with a drug, the gel is capable of storing the drug without changing the drug structure and activity. It is considered inert with no expected chemically modifying interaction within the gel and between the gel and its loaded drug. The gel formulation can be easily adjusted and tailored for retention of various drugs and delivery rates ranging from 3-24 hours.

The amphiphilic nature of ICDR facilitates incorporation of both hydrophilic and hydrophobic drugs.

It is water soluble, insensitive to pH, and also muco-adhesive and flexible, complying with the natural volume and shape changes of the internal cavity under treatment.

**PRECLINICAL & CLINICAL STUDIES**

ICDR was shown to cause no damage to the bladder, ureter or urethral tissues (preclinical results) and had no significant effect on instillation safety (preclinical and clinical results).

Studies in large animals (pigs) testing intravesical instillation of MMC in ICDR demonstrated a lower systematic exposure to MMC in comparison with standard treatment. MMC plasma levels were far below the blood toxic MMC levels. The lower systematic exposure of TheraCoat’s treatment suggest that TheraCoat’s treatment has the potential to lower adverse event rate and lower side effects leading to higher patient compliance. In addition, gel residues with MMC were detected in the pig bladder six hours following instillation, supporting the retention capabilities of the TheraCoat system.

Thus, the preclinical results demonstrate that ICDR increases the availability of MMC to the tissue and prolong its exposure duration (Figure 2a) while decreasing MMC exposure to the systemic circulation (Figure 2b).

Clinical safety studies with patients following single or multiple instillations with ICDR with and without MMC showed:

- Smooth injection of gel through catheter
- Catheter removal five minutes post instillation
- No bladder contraction due to gel instillation
- Free urination and no obstructive symptoms
- No study-related adverse events.

Preliminary results from ongoing clinical studies show efficacy of the delivery system in tumour ablation in low-grade bladder cancer patients. Figure 3 demonstrates a complete response to treatment (tumours were completely removed) in a patient after six weekly instillations of MMC with TheraCoat’s ICDR.

**FUTURE DIRECTIONS**

Current treatments for bladder diseases, including bladder cancer, comprise local intra-vesical drug instillations, but these treatments have largely proven to be insufficient. Scientific literature strongly supports that the longer the tumour tissue is exposed to chemotherapy the more effective it is to kill cancer cells, but once a drug is delivered into the bladder, it is quickly diluted and excreted due to continuous urine creation and voiding. Thereby, a clear unmet need exists for means to prolong drug retention and tissue exposure in order to improve efficacy.

TheraCoat effectively overcomes current treatment drawbacks and has developed a new proprietary drug delivery system for local treatment of bladder diseases. The novel hydrogel-based system enables controlled and longer exposure of bladder tissue to therapeutic agents as compared with standard intravesical instillations.

In addition to bladder cancer, TheraCoat is currently developing improved delivery modes for a number of bladder diseases including upper tract urothelial carcinoma, interstitial cystitis and overactive bladder.

**REFERENCES**


Novel drug delivery solutions for the optimal treatment of bladder diseases

- Sustained release of drugs within internal cavities
- Novel Reverse-Thermal Gelation technology
- Increased tissue exposure to drugs
- Reduced systemic toxicity

Products & clinical programs for Non Muscle Invasive Bladder Cancer (NMIBC), Upper Tract Urothelial Carcinoma (UTUC), Interstitial Cystitis (IC), and Overactive bladder (OAB)

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Redefining Entropy

Entropy - 'en-tra-p˜' Natural property of disorder in a system with increasing temperature