Recirculant Hyperthermic IntraVESical Chemotherapy (HIVEC™) in intermediate–high-risk non-muscle-invasive bladder cancer.

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Abstract:

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 (NMIBC).

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.
Combined effects of hyperthermia

Clinical hyperthermia is defined as the therapeutic use of temperature between 41°C to 44°C. The introduction of thermal energy at these temperatures into cancer tumors 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 tumor mass. At 43°C the cytotoxicity 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 effects 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).

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.

Chemo-hyperthermia multifactorial modes of action create a strong combination effect, ensuring cancer tumors 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.

### Mitomycin C remains stable at higher temperatures

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<th>Temp.</th>
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*0 hr : immediately after reconstitution.