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Commentary On Hyperthermia as a treatment for bladder cancer

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The review by Rampersaud et al. [1] provides an excellent summary of the scientific rationales for using hyperthermia to treat cancer and the current status of combinations of hyperthermia with chemotherapy or radiotherapy. In view of the demonstrated efficacy of the combination of intravescial hyperthermia and mitomycin C (MMC) therapy in preventing the progression and recurrence of nonmuscle-invading bladder cancer in several clinical trials, Rampersaud et al. advocate additional studies to further optimize the delivery of hyperthermia and to delineate its clinical utility in this disease.

The concept of using hyperthermia to treat cancer was introduced several decades ago. Initially, there was concern that hyperthermia might enhance metastasis (e.g., [2]). This concern has since been ruled out and combinations of hyperthermia with chemotherapy or radiotherapy have been in multiple clinical trials in sarcoma, melanoma, and cancers of the head and neck, brain, lung, esophagus, breast, genitourinary tract, and organs in the peritoneal cavity. For example, in hyperthermic intraoperative intraperitoneal chemotherapy, a solution of drugs such as cisplatin or mitomycin C is heated to 41–43 °C, instilled into the peritoneal cavity and maintained for 30 min to 2 hr. In transurethral microwave hyperthermia of the prostate, a higher temperature of 45°C is employed to manage symptoms derived from benign prostatic hypertrophy.

This commentary addresses the potential benefits and limitations of combination intravesical hyperthermia and chemotherapy, from the perspectives of drug delivery to tumor sites, potential efficacy and usage.

Hyperthermia can enhance drug delivery to tumors in several ways. In the order of quantitative importance, the most significant effect is the transient and reversible damage to epithelium; a study in sheep shows that intravesical hyperthermia causes macroscopic and microscopic changes, including foci of hemorrhage on the serosal tissue and partial, superficial sloughing of urothelium [3]. The urothelium is a major barrier to drug penetration; we have shown that in patients, only about 3% of an intravesical MMC dose can penetrate an intact urothelium whereas a compromised urothelium, e.g., due to the presence of tumors or surgical wounds, permits drastically increased absorption (about 10-fold). Similarly, Paroni et al. showed that hyperthermia significantly enhances the MMC absorption into the systemic blood (by ~5-fold), with even greater increases for patients with unresected tumors [4]. Second, diffusion, a major transport mechanism in tissue interstitium, is enhanced at elevated temperature. For example, the diffusion coefficient of solute in water, according to the Stokes-Einstein equation, will increase by about 14% when the temperature is increased from 37°C to 43°C. Similarly, the hydraulic conductivity, the primary determinant of convective transport, is also increased by about 12% due to the

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enhanced permeability in tissue interstitium and reduced fluid viscosity at the higher temperature.

On the other hand, some effects of hyperthermia reduce drug delivery to tumors. In the order of quantitative importance, the most significant effect is the transient edema, which was observed in sheep bladder tissues [3] and reflected in the doubling of urine production in patients treated with hyperthermia relative to the normothermic patients (81 mL vs 38 mL). Compared to the dosing volume of 50 mL, this newly produced urine would result in a 86% greater dilution of the drug concentration in the urine (162% vs 76%) and thereby reduces the drug delivery to a similar magnitude. Other, less important effects of hyperthermia are increases of blood flow and vessel permeability. The microvascular permeability of a large molecule dextran (150,000 Da) is increased by 30–50% when the temperature is increased from 37°C to 43°C [5]. Applying hyperthermia at 43EC for 1–2 hr increases the blood flow to the skin and muscle of a rat by 3.5- to 6-fold [6]. Although these changes will enhance the drainage/removal of drug from the blood-perfused muscularis tissues into the circulation, they are not likely to affect the drug levels in the urothelium, which is the locations of Ta and Tis and is not blood-perfused. The drug levels in the lamina propria where T1 tumors reside would depend on the net results of the various and opposing effects of hyperthermia.

With respect to the higher stage tumors, such as T2-T4 tumors residing in the deeper muscularis layers, we posit that hyperthermia is not likely to enhance the MMC delivery to the extent that will improve the treatment efficacy. This hypothesis is based on our previous observations on MMC pharmacokinetics in human bladder tissues and MMC pharmacodynamics in T2-T4 tumors, which show that meaningful antitumor activity would require about 100-times higher drug delivery. This cannot be achieved even if hyperthermia completely ablates the absorption barrier function of the urothelium and enhances the MMC absorption from about 3% to the maximal value of 100% (33-fold increase). In addition, as discussed above, the hyperthermia-induced increases in blood flow and vessel permeability will reduce the drug levels in the deeper tissues.

Based on the above considerations, hyperthermia is expected to improve the delivery of MMC to Ta and Tis tumors such that significant benefits can be expected. It is noted, however, hyperthermia may enhance the tumor cell sensitivity to MMC, in which case the combination may yield synergy in the deeper tumors as well.

Bladder cancer, the fourth most common cancer, is one of the least lethal cancers and there are ~540,000 survivors in the US. Nonmuscle-invading tumors account for about 70–80% of cases. These tumors have a high recurrence rate of 40–80%, and can progress to muscle-invading and metastatic disease. Due to the long-term survival and the frequent recurrences, the cost per patient of bladder cancer from diagnosis to death is the highest of all cancers (up to over $US 187,000 in 2001 values) in the US. These staggering costs add to the attractiveness of exploring promising modalities such as combination intravesical hyperthermia and chemotherapy. However, in view of the well-known problem of the under-utilization of intravesical therapy (e.g., only 42% of high risk patients receive therapy in spite of the American Urological Association recommendation as standard of care [7;8]), efforts should be directed to ascertain that the added complexity due to the hyperthermia procedures would not further deter the usage of intravesical therapy.

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