Combination Intravesical Hyperthermia and Chemotherapy for Bladder Cancer

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The review by Rampersaud and colleagues provides an excellent summary of the scientific rationale for using hyperthermia to treat cancer and of the current status of combinations of hyperthermia and chemotherapy or radiotherapy. In view of the demonstrated efficacy of the combination of intravesical hyperthermia and mitomycin C (MMC) therapy in preventing the progression and recurrence of non–muscle-invading bladder cancer (NMIBC) in several clinical trials, Rampersaud and colleagues 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.[1] This has since been shown not to be an issue, and combinations of hyperthermia and chemotherapy or radiotherapy have been studied 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. In one example of such a combination regimen—hyperthermic intraoperative intraperitoneal chemotherapy—a solution of an agent such as cisplatin or MMC is heated to 41° to 43°C and perfused into the peritoneal cavity, with a total perfusion time of 30 minutes to 2 hours.[2]

In this commentary, we address the potential benefits and limitations of combination intravesical hyperthermia and chemotherapy, from the perspectives of drug delivery to tumor sites, efficacy, and difficulty/ease of use.

Hyperthermia can enhance drug delivery to tumors in several ways. Its most significant effect is the transient and reversible damage it causes in the epithelium. A study in sheep has shown that intravesical hyperthermia causes macroscopic and microscopic changes, including hemorrhagic foci 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 humans, only about 3% of an intravesical MMC dose can penetrate an intact urothelium, whereas a urothelium that has been compromised as the result, for example, of tumors or surgical wounds, permits drastically increased absorption—about ten-fold. Similarly, Paroni and colleagues showed that hyperthermia significantly enhances the absorption of MMC into the systemic blood (by about five-fold), with even greater increases in patients with unresected tumors.[4]

Second, diffusion, a major transport mechanism in tissue interstitium, is enhanced at elevated temperatures. For example, the diffusion coefficient of solute in water, according to the Stokes-Einstein equation, increases 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% with this rise in temperature; the greater hydraulic conductivity is the result of the enhanced permeability in tissue interstitium and the reduced fluid viscosity at the higher temperature.

On the other hand, some effects of hyperthermia reduce drug delivery to tumors. The most significant such effect is transient edema, which was observed in sheep bladder tissues[4] and which was reflected in the doubling of urine production in patients treated with hyperthermia, as compared with production in normothermic patients (81 mL vs 38 mL). With a dosing volume of 50 mL of a drug-containing solution, the urine produced in patients treated with hyperthermia would exhibit an
86% greater dilution of the drug concentration than that seen in the urine of normothermic patients (162% vs 76%); drug delivery would thus be reduced by a similar magnitude.

Other, less important effects of hyperthermia associated with reduced drug delivery are increases in blood flow and vessel permeability. The microvascular permeability by a large-molecule dextran (150,000 Da) is increased by 30% to 50% when the temperature is increased from 37°C to 43°C.[5] Applying hyperthermia at 43°C for 1 to 2 hours increases the blood flow to the skin and muscle of a rat by 3.5- to 6-fold.[6] Although these changes enhance the drainage/removal of a drug from the blood-perfused muscularis tissues and its subsequent deposit into the circulation, they are not likely to affect drug levels in the urothelium, which is the location of Ta and Tis tumors and is not blood-perfused. The drug levels in the lamina propria, where T1 tumors are found, would depend on the net results of the various and opposing effects of hyperthermia.

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

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

Bladder cancer, although it is the fourth most common cancer in the United States, is one of the least lethal cancers, and there are about 540,000 US survivors.[7] Non–muscle-invading tumors account for about 70% to 80% of cases.[8] These tumors have a high recurrence rate (40% to 80%) and can progress to muscle-invading and metastatic disease. Because of the long-term survival and frequent recurrences, in the United States the cost per patient with bladder cancer from diagnosis to death is the highest of all cancers (for a total cost of $3.7 billion in 2001 values).[9] 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 (eg, only 42% of high-risk patients receive this therapy even though the American Urological Association has recommended it as standard of care[10,11]), efforts should be made to ascertain that the increased complexity that would result from the addition of hyperthermia procedures would not further deter oncologists from using intravesical therapy.

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