Hyperthermia and Intravesical Therapy: Emerging One-Two Punch for Bladder Cancer?

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Bladder cancer is the fourth most common cancer (excluding skin cancer) in the United States and ranks eighth as a cause of death from cancer among men; there will be an estimated 70,530 new cases and 14,680 cancer-related deaths in the United States in 2010.[1] Of new cases, 70% to 80% present with non–muscle-invasive bladder cancer (NMIBC). Despite endoscopic and intravesical treatments with curative intent, 50% to 70% of these cancers recur, usually within 5 years, and 10% to 30% progress to muscle-invasive disease, in the majority of cases as high-grade lesions.[2,3]

Bladder cancer poses a significant economic burden due to the cost of the lifetime need for surveillance, the need to treat recurrent tumors, and the cost of complications associated with treatment. Medicare estimates have ranked bladder cancer treatment the seventh costliest among cancers, with a 5-year net cost of approximately one billion dollars.[4]

Because of the tremendous detriment to patients’ quality of life and the cost to society, minimally invasive treatments that can delay or prevent progression of bladder cancer are particularly attractive. The identification of somewhat effective and safe intravesical therapies has begun to meet this challenge, but despite over 30 years of research and clinical experience, the mechanism, risks, benefits, optimal regimens and treatment algorithms for these therapies remain unclear. Currently, the gold standard treatment for NMIBC is instillation of bacillus Calmette-Gurin (BCG) into the bladder. Still, despite an initial adequate response of about 70%, in many patients BCG eventually fails, and by 5 years more than half of originally treated patients have relapsed.[5] We have yet to provide a durable organ-sparing treatment when BCG fails.

In their report, Rampersaud, Vujaskovic, and Inman review the biology of hyperthermic treatment in cancers generally and then focus on the application of hyperthermia to intravesical therapy of urothelial cancer. The authors note that hyperthermia has a direct effect on cancer cells, with the potential to cause cell death, as well as indirect effects—activating the acquired and innate immune systems and sensitizing cancer cells to radiation and chemotherapy through impairment of DNA repair mechanisms. In addition, studies by Paroni and colleagues[6] have shown that the thermal effect provides better drug penetration into the bladder wall, which may potentially improve the effect of drugs on residual cancer cells.

The endocavitary nature of bladder cancer makes it an ideal candidate for simultaneous minimally invasive delivery of hyperthermia and chemotherapy. Innovations that employed thermal dosimetry to reliably monitor bladder wall temperature led to the initial clinical application. Colombo and colleagues conducted a randomized controlled trial comparing hyperthermic chemotherapy and intravesical mitomycin C (MMC) to MMC alone in patients with intermediate- and high-risk NMIBC; treatments were administered over eight induction and four maintenance sessions following endoscopic resection.[7] Patients treated with thermo-chemotherapy had a recurrence rate of 17% after 2 years, compared with a rate of 58% in those treated with chemotherapy alone ($P=.0002$). The only significant difference between the two groups with respect to clinical side effects was increased pain in the hyperthermia group; however, no patient stopped treatment because of pain.
Although limited by their retrospective nature, subsequent studies have reported a disease-free survival rate of 56% to 59% with use of hyperthermic chemotherapy in patients in whom BCG had failed.[8,9] Progression requiring cystectomy was noted in 3% to 10% of patients. These studies demonstrated no difference when subgroups were analyzed by type of BCG failure; however, patients with BCG-refractory disease trended toward worse outcomes. Lack of maintenance therapy was significantly associated with recurrence. By way of comparison, valrubicin, the only FDA-approved intravesical therapy for patients with carcinoma in situ in whom BCG has failed, was shown to have an 8% complete response rate at 2 years.[10] Other studies that used a third BCG course,[11] MMC,[12] gemcitabine (Gemzar),[13] or BCG plus interferon[14] have shown disease-free rates at 2 years of 20% to 45%. Still other studies, which have looked at the use of novel device-assisted intravesical therapeutic agents (such as photodynamic therapy), have been limited by small sample sizes.[15]

Given the favorable tolerability rate and the currently available data from a randomized controlled trial, the combination of MMC and hyperthermia can be an effective option for NMIBC (level I evidence). In addition, several series have reported improved recurrence-free survival with low progression rates for MMC and hyperthermia for NMIBC in patients in whom intravesical BCG has failed, compared with the recurrence-free survival and progression rates seen with other available organ-sparing treatment modalities. The addition of maintenance treatments with MMC and hyperthermia has been associated with a significantly better outcome than induction treatment alone. Nonetheless, while initial reports have been quite favorable, additional studies are warranted to determine optimal temperature, sequence, duration, and combinations of therapies. In addition, whether hyperthermia and chemotherapy may lead to significantly greater decline in bladder function—as manifested by such symptoms as frequency, urgency, urge incontinence, dysuria, poor compliance with renal deterioration, and refractory hematuria—than is seen with intravesical therapy alone remains to be fully elucidated.

Both *in vitro* and *in vivo* studies of the effects of hyperthermia have shown the susceptibility of cancer cells to temperature, particularly in the presence of other cytotoxic agents. Preliminary laboratory research and clinical trials have uncovered a few first pairings that can effectively take advantage of this synergy. However, because the data indicating favorable outcomes have come exclusively from European centers, this technology has yet to undergo wide investigation or to receive approval in the United States. As more chemotherapeutic agents and better temperature delivery systems develop, future trials that further exploit this relationship are likely to yield combinations that provide better cancer control and improved quality of life for patients, while simultaneously increasing the cost-effectiveness of management of NMIBC.

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