Intravesical Therapy for Superficial Bladder Cancer

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The intravesical instillation of therapeutic agents for the treatment of localized bladder cancer began in 1903 when Herring[1] summarized his experience with silver nitrate. Since then, intravesical chemotherapy and immunotherapy have emerged as effective adjuncts to endoscopic resection for superficial transitional cell carcinoma of the bladder.

Although advances in the treatment of superficial disease have been a major success story of clinical research efforts in urologic oncology, additional improvements are clearly needed to increase the proportion of patients with superficial disease who are cured and to treat patients who do not respond to current intravesical regimens. Drs. Baselli and Greenberg present an informative overview of the established intravesical therapies and provide insights into newer agents and combinations currently under investigation for the therapy and prophylaxis of superficial transitional cell carcinoma of the bladder.

Prevention and Early Detection
In addition to future improvements in intravesical therapy for superficial disease, new opportunities to reduce bladder cancer mortality will derive from research on bladder cancer prevention and early detection. Control of tobacco use and dietary and chemopreventive strategies have the potential to significantly reduce risk.[2-4]

Over recent decades, improvements in diagnostic techniques and endoscopic technologies have led to the diagnosis of many bladder cancers at a much earlier stage, providing urologists with the opportunity to apply therapeutic interventions that are more effective than currently existing therapies for advanced disease. However, continued progress in developing cytologic- and molecular-based tests of urine samples will provide opportunities to initiate treatment at an even earlier stage in a greater proportion of bladder cancer patients.

Based on the results of two different screening studies of the general population,[5,6] it has been suggested that screening for bladder cancer with a combination of a hematuria home reagent-strip testing and one or more other tests may be a cost-effective strategy for large populations, particularly those at higher risk due to age and smoking history.[7]

Currently, a number of tests for the early diagnosis of bladder cancer are under investigation for sensitivity and specificity in various population groups. These include the: (1) bladder-tumor–associated antigen (BTA) test; (2) BTA stat test; (3) fibrin/fibrinogen degradation products test; (4) nuclear-matrix protein (NMP 22) assay; and (5) BTA TRAK test.

Research to Improve Intravesical Therapies
The majority of bladder cancer patients in economically developed nations present with superficial papillary transitional cell carcinomas (70% to 80%) of low or intermediate grade. The treatment of choice for Ta and T1 lesions remains endoscopic transurethral resection. However, in most cases, resection alone will not ensure a long-term cure. Recurrence of superficial bladder cancer is typical, with approximately 50% to 70% of patients with TUR developing recurrent disease during their lifetime.[2]

Moreover, in some studies, up to one-third of patients with superficial disease will ultimately experience muscle-invasive or metastatic disease, which carries a grave prognosis. The majority of patients with metastatic disease die of bladder cancer within 2 years despite the recent development of multimodality interventions and active combination chemotherapeutic regimens with improved response rates.[2] These features of bladder cancer have provided the stimulus for the development of more effective intravesical treatment strategies for superficial disease. Bacillus Calmette-Guérin (BCG), the most commonly employed immunotherapeutic agent for superficial bladder cancer, has been shown to be the superior therapy for carcinoma in situ of the
bladder, leading to its approval by the US Food and Drug Administration (FDA) for this indication.[8] Bacillus Calmette-Guérin decreases recurrence in patients with carcinoma in situ, reduces the risk of progression following transurethral resection, and reduces death rates from bladder cancer.[8] Scientific debate and clinical experimentation continue concerning the role of BCG in the treatment of superficial disease in the absence of carcinoma in situ.

Instillation of BCG is not without risk, however; occasional systemic infections and deaths have been reported. Ongoing investigations are focusing on further delineating which patients will clearly benefit from BCG. The optimal scheduling of BCG and the role of maintenance therapy are also active areas of investigation that will require randomized, prospective cooperative group studies to arrive at definitive answers.

Other immunotherapeutic and biological agents currently under investigation in clinical and laboratory studies include interferons, various interleukins, bropirimine, and keyhole limpet hemocyanin (KLH). Efforts are also ongoing to improve therapeutic outcomes and reduce toxicity by combining other immunoregulatory and biological agents with BCG.[9] Furthermore, photodynamic therapy and gene therapy may ultimately prove to be safe, effective options or adjuncts to current approaches for superficial disease.[10]

Although a number of chemotherapeutic agents have demonstrated efficacy in the treatment of superficial disease, optimal regimens have yet to be defined and remain an area of active research. For example, studies are focusing on the timing, duration of use, and dosage of the various intravesical chemotherapeutic agents used in the treatment of bladder cancer.[11] The application of modern pharmacodynamic principles to achieve the optimal dosing of intravesical chemotherapy offers the potential to improve therapeutic outcomes.[12,13]

**Critical Role of Transurethral Resection**

Readers should not forget the critical role of transurethral resection in the treatment of superficial disease. In 1967, Barnes et al[14] described 505 patients with early-stage bladder cancer, 410 of whom were treated only with transurethral resection of their tumor. These authors reported 5-year survival rates of 65% in patients with grades 1 and 2 tumors and 19% in those with grades 3 and 4 tumors. The 5-year survival rate for all 505 patients, regardless of stage and grade, was 53%. More recently, Jakse and coworkers[15] showed 10-year survival rates of 78% in patients with stage T1, grade 2 tumors and 50% in those with stage T1, grade 3 tumors managed by transurethral resection alone.

These studies illustrate that although many patients with superficial disease are cured by transurethral resection alone, the risk of progression and death from recurrent bladder cancer is unacceptable. Additional efforts, perhaps using cellular and molecular markers to identify those at the greatest risk of progression, will help us define which patients may benefit from additional intravesical therapy and which are best managed by careful surveillance.

**Conclusions**

The authors remind us to consider the cost, efficacy, morbidity, and mortality associated with each treatment modality as we assess the development of new intravesical treatment approaches for superficial bladder cancer. In effect, the data that they present encourages us to critically analyze our current approach to the control of superficial bladder cancer with intravesical therapy. In doing so, we must repeatedly answer the question: “How can we improve the therapeutic index as we continue to perfect the treatment algorithm for this disease?” In the interim, our goals should be: (1) early detection; (2) decreased rates of recurrence; (3) prophylaxis against the progression of superficial transitional cell carcinoma to muscle-invasive and metastatic disease; (4) reduced rates of radical cystectomy; and, ultimately, (5) improved patient survival.

**References:**


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