Baselli and Greenberg have presented a comprehensive overview of intravesical strategies for the management of superficial urothelial malignancies of the bladder, both past and present. A number of points made in the article deserve further emphasis. I will also address some future directions in this area, which has seen relatively little change of consequence over the past decade.

The importance of transurethral resection as the cornerstone of the management of superficial bladder cancer warrants reemphasis. This procedure has the potential for eradicating existing visible lesions and allowing for accurate staging and grading. Over 70% of bladder tumors are noninvasive at presentation, and their risk of progression is low, ie, 5% to 10%. Conversely, in most patients diagnosed with a high-grade or invasive lesion, this is their first tumor event. Identification of patients who are most likely to benefit from intravesical therapies, therefore, requires accurate endoscopic observation and staging.

I concur with the authors' goals for intravesical therapy; namely, destruction of all tumor, prophylaxis against recurrence, and prevention of progression. These goals, however, should be pursued while maintaining the caveat of preserving a functional bladder in patients with low-grade papillary disease, in whom intravesical chemotherapy or immunotherapy coupled with repetitive transurethral resection may lead to bladder contraction.

Potential indications for intravesical therapy in superficial disease, therefore, include the following:

1. Eradication of existing disease that cannot be controlled endoscopically—either extensive papillary disease or carcinoma in situ (CIS)
2. Prevention of recurrence in the presence of high-risk factors, including tumor multiplicity, bulky tumor volume, concomitant CIS, and short intervals between recurrences.
3. Decreasing the risk of progression to muscle invasion or metastasis in the presence of high-grade tumors, lamina propria invasion, and associated CIS (eg, a progression rate of 4% for Ta, G1 tumors vs a progression rate of 29% for T1 tumors).

**High-Risk or Refractory Superficial Bladder Cancer**

* Bacillus Calmette-Guérin (BCG) remains the most effective single agent for CIS of the bladder, yielding complete response rates of approximately 70%. The ability of BCG to lessen recurrence and progression in patients with T1 lesions has been demonstrated; however, the durability of these responses is open to question.

* Mitomycin (Mutamycin) has been the chemotherapeutic agent most often selected as an alternative to BCG. Studies comparing these agents have been controversial: Mitomycin has proved equivalent or superior to BCG in decreasing recurrences in patients with papillary disease in some series, and has shown efficacy in treating CIS and higher-grade lesions in others.[1] European studies demonstrated an improvement in responses of CIS to the combination of BCG and mitomycin, as compared with mitomycin alone.[2] However, these studies did not compare the two agents combined to BCG alone. Furthermore, the combination offered no advantage over mitomycin alone with respect to prophylaxis against rapidly recurring Ta/T1 tumors.

* Valrubacin (Valstar) currently is the only agent approved by the Food and Drug Administration (FDA) for the management of refractory CIS. This novel anthracycline is currently undergoing a phase II clinical trial in patients with refractory papillary transitional carcinoma and/or CIS, coordinated by the Eastern Cooperative Oncology Group (ECOG). Also, a large-scale, prospective, randomized study of
single-dose valrubicin as neoadjuvant intraesical therapy immediately following transurethral resection is actively accruing patients.

The ability of valrubicin to eradicate residual papillary disease was demonstrated in a European marker lesion study. Moreover, the observation of bladder wall absorption in a depth of penetration study suggests the efficacy of valrubicin in tumors at high risk for superficial invasion.[3,4] Given these findings, coupled with the relatively low toxicity profile of this agent, particularly with regard to systemic effects, it would seem appropriate to consider a phase III trial of valrubicin as first-line therapy.

Although mitomycin and interferon-alfa (Intron A, Roferon-A) have shown initial results similar to those of valrubicin in BCG-refractory urothelial disease,[5] the impact of these agents on duration of response and delay of progression requires substantiation.

Newer Agents and Strategies

As Baselli and Greenberg state, complacency regarding current protocols and agents is not an acceptable stance, given the imperfect results to date. Newer treatment approaches may include combinations of current agents, but a search for innovative strategies, such as novel immunoregulatory factors or cytoreductive gene therapy, is more important.

The recognition that intravesical BCG and other immunoactive agents can induce cytokine expression has led to the use of biological response modifiers both in clinical trials and preclinical animal models. Interferon-alfa has shown single-agent activity, although response rates are inferior to those achieved with BCG.

Interferons have a more promising role in patients whose disease is refractory to BCG or other agents, however, and may show the greatest promise in combination with BCG, with which they are compatible. Synergy between interferons and BCG has been demonstrated in vitro; consequently, the dose of BCG can be lowered when the two agents are used in combination, potentially decreasing BCG-related toxicity. To date, two studies, although small, have confirmed the safety and relative efficacy of this combination.[6,7] Further phase III trials are warranted.

Future concepts currently in evolution include the use of interleukin-12 (IL-12), a promising cytokine active at several stages of the immune response; its effects include activation of cytotoxic natural killer (NK) and lymphokine-activated killer (LAK) cells. Preclinical trials have examined combinations of IL-12 with chemotherapy, radiation therapy, or BCG, and will likely lead to clinical trials with intravesical applications.[8]

Based on observations that p53 overexpression represents a powerful marker of disease progression following BCG therapy, Peralta and colleagues recently demonstrated that human bladder cancer xenografts established in immunodeficient mice could be favorably modulated by the administration of cytotoxic T cells that were altered to recognize overexpressed p53.[9] This model suggests the selective targeting of sites, such as p53, as a tantalizing strategy with potential intravesical application.

Other focused immunomodulatory attacks on bladder tumors await effective gene therapies. The most daunting aspect of these strategies has been gene delivery. Given its accessibility, the urinary bladder represents an attractive target for intravesical gene therapies, utilizing either viral (eg, adenoviral) or nonviral vectors suitable for transduction of therapeutic genes to neoplastic bladder cells.

Summary

Drs. Baselli and Greenberg are to be commended for their thorough review of intravesical therapies for urothelial malignancy. Immunoactive and chemotherapeutic agents in the adjunctive management of superficial transitional carcinoma can decrease the rate of recurrence and prolong the disease-free interval.

At present, BCG appears to be the best available prophylactic agent for patients with superficial transitional tumors and the best therapeutic agent for those with CIS, although chemotherapy may provide similar results in selected patients. Further understanding of the risk factors for and distinctive molecular alterations in superficial and invasive disease will lead to better identification of patients most suitable for intravesical therapies.

References:


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