Transurethral resection remains the standard for first-line treatment of transitional cell carcinoma of the bladder. This technique clearly defines the pathologic grade and is essential in determining the clinical stage of the patient's disease. The article by Drs. Baselli and Greenberg is a concise review of recent information supporting the use of maintenance therapy for patients with superficial bladder cancer. The decision to initiate intravesical therapy in patients with superficial disease is determined by the risk assessment of each patient's particular disease. Tumor characteristics obtained at the time of endoscopic resection, as detailed by Baselli and Greenberg, are critical in determining the risk of progressive disease and the need for adjuvant therapy.

**Differentiating Heterogeneous Lesions**

Historically, the classification of superficial bladder cancer has included lesions with vastly different biological characteristics and clinical behavior. Carcinoma in situ of the bladder and papillary lesions of all grades (whether confined to the mucosa or invasive into the lamina propria) have been included in the category of superficial disease. As described by the authors, low-grade lesions confined to the epithelial layer (Ta) demonstrate minimal potential to progress or metastasize, thereby posing little risk to the patient's life. In contrast, high-grade lesions that are invasive into the lamina propria (T1) or carcinoma in situ carry a greater than 50% risk of progressing to muscle-invasive disease and should be considered potentially life threatening.

Differences between low-grade Ta and higher-risk superficial lesions are further emphasized by their genetic differences that include differential defects in cell-cycle regulation, cell-adhesive properties, and angiogenesis. Limitations of the current staging system for superficial bladder cancer are potentially misleading, and the vast differences between these heterogeneous lesions must be recognized by the clinician in order to properly assign treatment.

**Is There a Substitute for Transurethral Resection?**

As stated in the article, the mainstay of treatment for non-muscle-invasive disease has been, and remains, transurethral resection. Removal of the primary lesion(s) via resection or fulguration provides the best results in terms of controlling local disease and enhancing the effects of subsequent intravesical treatments. Even under the best circumstances, intravesical therapy should not be considered equivalent to, or a substitute for, definitive transurethral resection.

While effective at managing macroscopic disease within the bladder, the limitations of transurethral resection to control subsequent recurrences are quite obvious. This factor led to the development of adjuvant intravesical treatments designed to decrease the incidence of tumor recurrences and potentially lower the risk of subsequent progression to muscle-invasive disease. Several chemotherapeutic or immunostimulatory agents have been studied extensively for this purpose.[1]

Combined analysis of the larger prospective trials using a variety of intravesical chemotherapeutic agents, including thiotepa (Thioplex), mitomycin (Mutamycin), and doxorubicin (Adriamycin), have demonstrated the ability to decrease the short-term recurrence risk after transurethral resection; however, these benefits are not durable.[2] Similarly, the risk of progression to muscle-invasive disease following transurethral resection remains unchanged despite exposure to a variety of regimens using these cytotoxic agents.

**Lingering Questions Over BCG**
In contrast, bacillus Calmette-Guérin (BCG) has emerged as the most effective agent in the treatment and prophylaxis of superficial bladder cancer. The effect of BCG in lowering the risk of recurrence appears more durable than that demonstrated by the cytotoxic agents. This agent has also been reported to decrease the risk of progression in patients with high-risk disease[3]; however, this finding has been inconsistent in other studies.

As alluded to in the Baselli and Greenberg article, several inherent difficulties are involved in establishing the beneficial effect on progression rates in patients with superficial bladder cancer. Many series contain large percentages of low-risk patients combined with a higher-risk population. The addition of these low-risk patients requires that enormous numbers of patients be included to identify a statistically significant benefit to treatment. Thus, many negative studies are actually underpowered to identify differences in progression, further emphasizing the need to focus future evaluations on specific subgroups of superficial bladder cancer patients who are at highest risk of experiencing adverse outcomes.

Early studies using intravesical BCG initiated treatment with an empiric dose that included six weekly instillations.[4] Following the initial success of BCG therapy, additional doses in the form of a maintenance regimen were studied to further enhance its long-term effects. Until recently, data have been lacking to support the routine use of maintenance regimens.

As clearly described in the Baselli and Greenberg article, the Southwest Oncology Group (SWOG) reported on a well-designed, long-term study that demonstrated improved outcomes following maintenance BCG therapy. Of note, however, is that while a significant decrease in the recurrence pattern was observed in the maintenance arm, no benefit in overall survival was identified. Furthermore, despite the apparent benefits of maintenance therapy, the toxicity of long-term BCG administration was not insignificant and should not be overlooked. Most patients experience local symptoms following BCG exposure, which may simply represent a manifestation of the desired immunologic reaction within the bladder. These symptoms typically increase with the number of instillations, as highlighted in the SWOG study, in which only 16% of patients in the maintenance arm received all scheduled doses.

While many patients with high-risk superficial disease will benefit from initial management with BCG, they remain at lifelong risk of experiencing progressive disease. Long-term studies have documented that patients with high-grade Ta and T1 disease have a 60% and 40% disease-specific survival at 15 years despite having received intravesical treatment.[5] These patients must remain under lifelong close surveillance of the bladder and upper urinary tract, which may also develop disease.

Ongoing studies are underway to identify second-line agents that are capable of salvaging BCG failures. The future treatment of high-risk lesions will undoubtedly be guided by molecular markers that better characterize tumors likely to progress to invasive disease as well as the development of more effective systemic therapies to salvage patients that do progress while receiving more conservative intravesical treatment. In the meantime, radical cystectomy with lower urinary tract reconstruction will offer an excellent long-term disease-free survival in these patients.[6] Cystectomy should be considered in patients who fail to have their disease eradicated following a reasonable course of intravesical treatment or at the first sign of tumor progression.

References:


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