In a recent issue of ONCOLOGY (15:85-88, 2001), Drs. Edgar C. Baselli and Richard E. Greenberg presented a brief overview of maintenance intravesical chemotherapy for superficial bladder cancer.[1] Along with two accompanying reviews,[2,3] this article highlights the continuing controversy surrounding the management of this disease. While numerous drugs have been and continue to be used in the treatment of superficial bladder cancer, the true impact of such treatment on recurrence, progression, and survival remains unclear. Some investigators (eg, Lamm et al[4]) suggest that intravesical chemotherapy has only a minor effect on tumor recurrence rates and question the advisability of its routine use (as opposed to immunotherapy with bacillus Calmette-Guérin, or BCG). In fact, Lamm et al reported that the addition of chemotherapy produced only a 14% decrease in the recurrence rate at 1 to 3 years post-transurethral resection of the bladder (TURB).

**Literature Limitations**

The literature related to this topic suffers from multiple limitations, making interpretation problematic. For instance, the summary published by Lamm et al[4] combined studies in patients with primary and recurrent bladder tumors, without stratifying this parameter. Biological differences may exist between primary and recurrent disease, which may be reflected in the response to chemotherapy. Thus, stratification of this parameter would be informative. Second, this analysis failed to calculate recurrence rates at specific end points (eg, 1 or 2 years post-TURB). Third, and most importantly, the analysis was not performed via standard statistical methods designed specifically for combining data from multiple randomized clinical trials (ie, meta-analyses).[5]

**More Recent Analyses**

In an attempt to clarify the ambiguities in the existing published database, our group performed two meta-analyses using 1-, 2-, and 3-year recurrence rates as end points.[6,7] The relevant clinical trials were pooled using accepted meta-analytic techniques.[5] Combined data from 11 trials enrolling over 3,703 patients with primary superficial bladder cancer showed a 30% to 80% reduction in the incidence of recurrence at 1 to 3 years following TURB plus intravesical chemotherapy vs TURB alone.[6] Of all the chemotherapeutic agents used, mitomycin-C (Mutamycin) appeared to be the most effective. Also, long-term treatment protocols (ie, 2 years) were more effective than short-term or single-instillation schedules.

Among patients treated for recurrent bladder tumors, intravesical chemotherapy reduced recurrence by 38% at 1 year compared with TURB alone, while 2- and 3-year recurrence rates were decreased by 54% and 65%, respectively. Doxorubicin was shown to be significantly less effective than all other drugs studied.

Heterogeneity across the available studies, in terms of tumor stage, grade, treatment schedule, chemotherapeutics employed, clinical end points, and treatment durations, makes the translation of existing information into clinical practice guidelines difficult. In order to distill clinically useful information from such data, appropriate statistical techniques must be employed.[5] These techniques not only allow calculation of a summary estimate of effect but also enable evaluation of statistical heterogeneity. Such analyses can provide important insight into potential biases in study design or elucidate confounders that may produce spurious results.

We feel that intravesical chemotherapy probably has a greater impact on tumor recurrence in this setting than previously suggested and that prior estimates of its biological impact are questionable. We are currently designing further analyses of chemotherapy and immunotherapy in superficial bladder cancer and agree that, in the future, molecular markers of aggressive biological behavior may eventually be integrated into clinical decision-making.
References:


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