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Short Communication

Clarification of Bladder Cancer Disease States Following Treatment of Patients with Intravesical BCG

At the most recent Genitourinary Cancers Symposium in Orlando February 2015, a task force was organized to discuss issues in trial design in non-muscle invasive bladder cancer. Our aim was to provide further clarification regarding disease states following treatment of patients with intravesical BCG and to determine what events constitute progression following any treatment for non-muscle invasive bladder cancer (NMIBC). The panelists were asked to address a number of specific Tasks, enumerated below.

Task #1: Define a population that will not benefit from further BCG therapy. This has been called BCG-refractory and BCG-resistant or any other term but choose a term to describe this population and the amount, timing, and frequency of prior intravesical BCG therapy that defines them. Please keep in mind what is practical and reasonable in a trial design with meaningful collection of previous therapy details.

Panel: The definition "BCG Unresponsive" identifies those patients with high grade (HG) NMIBC who have been treated with adequate BCG (see below) and are unlikely to benefit from and should not receive further intravesical BCG. The term "BCG Unresponsive" includes patients who did not respond to BCG treatment and have a new (if previously treated for a low-grade NMIBC) or persistent high-grade (HG) recurrence at or around 6 months after BCG was initiated, and those who despite an initial complete response to BCG, relapse with HG NMIBC within 6 months of their last intravesical treatment with BCG. The following criteria further refine this patient population:

1. Have received at least 2 courses of intravesical BCG – defined as at least 5 of 6 induction instillations of BCG and at least 2 of 3 instillations of maintenance BCG.
    a. Exception: those who have T1HG disease at first evaluation following induction BCG alone (at least 5 of 6 doses) would qualify.
2. Patients should be within 6 months of last exposure to BCG at the time of tumor recurrence – this applies especially to those on maintenance BCG. Note: for trial enrollment, they can be within 9 months (i.e. 3 months lead time for referral/enrollment is allowed).
3. No maximum limit to the amount of BCG administered, but maintenance BCG should be administered on a schedule similar to the SWOG 8507 regimen [1]. Single intravesical instillations do not stimulate an adequate immune response are not considered adequate maintenance therapy.
4. Have Ta/T1 HG with or without concomitant Carcinoma in Situ (CIS); CIS of the bladder and/or CIS of the prostatic urethra at study entry. Patients with CIS of the prostatic urethra require staging TURP in order to open the bladder neck for subsequent intravesical therapy and to rule out prostatic stroma involvement (T4) which would require proceeding to radical cystectomy. Patients with ductal/acinar CIS only would meet the entry criteria.
5. Note: prior to study entry, all visible papillary tumors must be resected and if there is persistent T1HG disease on re-TUR, radical cystectomy is generally recommended. These patients should not be enrolled without a re-resection prior to study entry demonstrating less than T1 disease.
6. A patient who recurs with Ta low grade tumor may continue on therapy at the discretion of the

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investigator and will not be deemed to reach the recurrence endpoint in trials that require HG disease at study entry.

Task #2: Determine what events should be classified as progression in a trial of NMIBC. For instance, should it be the old criteria of stage progression to muscle-invasive or metastases versus a more recent suggestion of progression in grade without change of stage and/or progression of stage from Ta to T1.

Panel: After induction BCG, a patient with non-muscle invasive bladder cancer would be defined as having progression whenever there is:

1. Increase in T stage from CIS or Ta to high grade T1 (lamina propria (LP) invasion),
2. Development of T2 or greater or lymph node (N+) disease or distant metastasis (M1),
3. T1 (LP invasion) or T4 (stroma invasion) of the prostate.
4. Increase in grade from low to high (for patients initiating therapy with low grade NMIBC).
5. Investigators should consider the use of this new definition to help standardize protocols and improve the reporting of progression.
6. This is harmonized with the International BCG group definition [2].

Consideration should be given to the inclusion of upper tract urothelial carcinoma in the primary endpoint for patients receiving systemic therapy as part of the trial and not for those receiving intravesical therapy except as a sensitivity analysis.

Prostatic urethral recurrence should be an event. We also recommend including CIS of the prostatic urethra within the definition of BCG unresponsive and would not exclude those patients from a trial if patients refused cystectomy. Please note requirement for re-TURP in Task#1 (1) above.

Task #3: The FDA has already made a determination that "BCG-intolerant" patients should not be included in this group, but we may want to come up with a strict definition for this population in case a drug product is being developed to treat just them.

Panel: We agree and it is very hard to determine with precision criteria for "intolerant". We elected not to come up with a definition.

Task #4: The revised European Association of Urology Guidelines includes multifocal, frequently recurrent, large volume (>3cm) TaG1,G2 disease in the high risk category for progression.

Panel: The American Urological Association does not provide a risk stratification scheme.

There was consensus that these patients have approximately half the progression compared to TaHG and thus should remain in EAU intermediate risk category.

Respectfully submitted by:
Seth P. Lerner (Baylor College of Medicine) – Co-chair Panel
Colin Dinney (University of Texas MD Anderson Cancer Center) – Co-chair Panel
Ashish Kamat (University of Texas MD Anderson Cancer Center)
Trinity J. Bivalacqua (Johns Hopkins)
Matthew Nielsen (University of North Carolina at Chapel Hill)
Michael O'Donnell (University of Iowa)
Mark P. Schoenberg (Montefiore, New York)
Gary Steinberg (University of Chicago)

REFERENCES

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[2] Lamm D, et al. Defining progression in nonmuscle invasive bladder cancer: It is time for a new, standard definition. J Urol 2014; 191(1):20-7.