Review Article

Defining Progression in Nonmuscle Invasive Bladder Cancer: It is Time for a New, Standard Definition

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Abbreviations and Acronyms

BCG = bacillus Calmette-Guérin

CIS = carcinoma in situ

MMC = mitomycin C

NMIBC = nonmuscle invasive bladder cancer

TURBT = transurethral resection of the bladder tumor

Accepted for publication July 22, 2013.

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† Financial interest and/or other relationship with Sanofi Pasteur.

‡ Nothing to disclose.

§ Financial interest and/or other relationship with Ipsen, Sanofi Pasteur, Allergan, Telormedix, Photocure, GE Healthcare, MEL Amsterdam and TheraCoat.

|| Financial interest and/or other relationship with Archimedes Inc., FKD, Photocure, Sanofi, Cubist and Allergan.

¶ Financial interest and/or other relationship with GE Medical, Sanofi Pasteur, Dendreon and Astellas.

For another article on a related topic see page 261.

Editor's Note: This article is the first of 5 published in this issue for which category 1 CME credits can be earned. Instructions for obtaining credits are given with the questions on pages 276 and 277.

Purpose: Despite being one of the most important clinical outcomes in nonmuscle invasive bladder cancer, there is currently no standard definition of disease progression. Major clinical trials and meta-analyses have used varying definitions or have failed to define this end point altogether. A standard definition of nonmuscle invasive bladder cancer progression as determined by reproducible and reliable procedures is needed. We examine current definitions of nonmuscle invasive bladder cancer progression, and propose a new definition that will be more clinically useful in determining patient prognosis and comparing treatment options.

Materials and Methods: The IBCG (International Bladder Cancer Group) analyzed published clinical trials and meta-analyses that examined nonmuscle invasive bladder cancer progression as of December 2012. The limitations of the definitions of progression used in these trials were considered, as were additional parameters associated with the advancement of nonmuscle invasive bladder cancer.

Results: The most commonly used definition of nonmuscle invasive bladder cancer progression is an increase in stage from nonmuscle invasive to muscle invasive disease. Although this definition is clinically important, it fails to include other important parameters of advancing disease such as progression to lamina propria invasion and increase in grade.

Conclusions: The IBCG proposes the definition of nonmuscle invasive bladder cancer progression as an increase in T stage from CIS or Ta to T1 (lamina propria invasion), development of T2 or greater or lymph node (N+) disease or distant metastasis (M1), or an increase in grade from low to high. Investigators should consider the use of this new definition to help standardize protocols and improve the reporting of progression.

Key Words: urinary bladder neoplasms; disease progression; BCG vaccine; drug therapy; administration, intravesical

Disease progression is recognized as one of the most relevant clinical outcomes in patients with NMIBC (Ta/T1/CIS) and the prevention of progression is a key goal in the treatment of these patients. Despite

0022-5347/14/1911-0020/0
THE JOURNAL OF UROLOGY®

http://dx.doi.org/10.1016/j.juro.2013.07.102
Vol. 191, 20-27, January 2014
Printed in U.S.A.

the universally recognized importance of disease progression, there is currently no standard definition of this outcome in NMIBC. Major clinical trials, systematic reviews and meta-analyses have used varying definitions (Appendix 1)[1–13] or have failed to define this important end point altogether. For example, Cochrane investigators recently performed a comprehensive review of gemcitabine trials (including marker studies) and concluded that progression in NMIBC ranges from 0% to 38%.[14] However, the investigators failed to define what qualified as disease progression in this analysis. Similarly a randomized, placebo controlled study on the diagnostic efficacy of 5-aminolevulinic acid cystoscopy for tumor recurrence in NMIBC (370) reported progression outcomes but also failed to define this end point.[15]

Lack of a standard definition of progression makes it difficult to determine whether an intervention indeed prevents the advancement of NMIBC, and may also lead to incongruous and perhaps even inaccurate management recommendations. Therefore, we examine some of the most commonly used definitions of NMIBC progression, discuss the limitations of these definitions, and propose a standard definition of bladder cancer progression that will be more relevant and clinically useful in determining patient prognosis, selecting appropriate interventions and assessing treatment response.

MATERIALS AND METHODS

A comprehensive MEDLINE® search was conducted to identify published clinical trials, systematic reviews and meta-analyses on progression in NMIBC as of December 2012. Key words included bladder cancer, nonmuscle invasive, disease progression, BCG, intravesical chemotherapy and TURBT. Reference lists of meta-analyses and original papers were also reviewed to identify additional applicable literature.

The members of the IBCG (the authors) met on 2 occasions (June 23, 2012 and April 6, 2013) to critically review the identified literature and form consensus on a new, standard definition of disease progression in NMIBC that would improve the consistency and precision of reports of therapeutic trials, potentially improve our ability to compare and select treatments, and better estimate the prognosis of patients with NMIBC. Recommendations provided are based on group consensus.

RESULTS

Current Definitions of Progression

Lay dictionaries define progression as the action or process of advancing, and medical dictionaries define this term as increasing in extent or severity, or an advancing or moving forward (Appendix 2).[16–19] Unfortunately these definitions are too vague to be useful as trial end points or prognostic indicators of progression in NMIBC. Even the National Cancer Institute definition of progression (ie "the course of a disease…as it becomes worse or spreads in the body") is of little use in defining bladder cancer progression.

One of the most commonly (yet inconsistently) used definitions of progression in NMIBC is an increase in stage from nonmuscle invasive disease (ie stage Ta, T1 or CIS) to muscle invasive disease (ie stage T2 or greater [stage T3, T4, lymph node positive (N+) or metastatic (M+)]) (Appendix 1). This definition of stage progression is accepted because of the major difference in prognosis and treatment between nonmuscle invasive and muscle invasive disease. Once a urothelial cancer invades the muscle or enters vascular spaces, the likelihood of metastasis increases dramatically and the chances of curing the cancer are significantly reduced. While defining progression as advancing from nonmuscle invasive to muscle invasive (or higher) disease has clear clinical importance, should the term progression be limited to this definition? Are there other criteria of advancing disease that would provide important prognostic information or improve the measurement of success in therapeutic clinical trials?

Limitations of Current Definitions

The commonly used definition of progression as local progression from Ta, T1 or CIS to muscle invasion is likely inadequate. Clearly, death from metastasis in a case of high grade T1 disease is evidence of advancing disease, as is an increase in stage from Ta noninvasive disease to T1, lamina propria invasion. The ability of a cancer to invade the basement membrane signals the capability to enter small vessels and, thus, metastasize. Metastatic urothelial cancer has a low cure rate despite the use of systemic chemotherapy.

Lack of a proper definition of progression makes it difficult to compare the antitumor efficacy of therapeutic interventions, and may also lead to inconsistent recommendations and conclusions. For example, the landmark EORTC (European Organization for the Research and Treatment of Cancer) trial 30911 comparing 3-week, 3-year maintenance BCG with 3-week, 3-year maintenance epirubicin limited the definition of progression to the development of muscle invasive disease (ie metastases and cancer specific mortality were excluded from this definition).[12] Although a significant reduction in metastases and death from bladder cancer was noted with maintenance BCG, the progression end point, as defined by the authors, did not reach statistical significance. This has led some experts to conclude that BCG maintenance therapy does not