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Predicting Response to Intravesical Bacillus Calmette-Guérin Immunotherapy: Are We There Yet? A Systematic Review

Ashish M. Kamat[a,*], *Roger Li*[a], *Michael A. O'Donnell*[b], *Peter C. Black*[c], *Morgan Roupret*[d], *James W. Catto*[e], *Eva Comperat*[f], *Molly A. Ingersoll*[g], *Wim P. Witjes*[h], *David J. McConkey*[i], *J. Alfred Witjes*[j]

[a] *Department of Urology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA;* [b] *Department of Urology, University of Iowa, Iowa City, IA, USA;* [c] *Department of Urologic Sciences, University of British Columbia, Vancouver, BC, Canada;* [d] *Department of Urology, Groupe Hospitalier Pitie-Salpetriere, Assistance Publique Hopitaux de Paris, Faculty of Medicine Pierre et Marie Curie, University Paris Sorbonne, Paris, France;* [e] *Royal Hallamshire Hospital and University of Sheffield, Sheffield, UK;* [f] *Department of Pathology, Tenon Hospital, AP-HP, University Pierre and Marie Curie, Paris, France;* [g] *Department of Immunology, Institut Pasteur and INSERM U1223, Paris, France;* [h] *EAU Research Foundation, EAU Central Office, Arnhem, The Netherlands;* [i] *The Greenberg Bladder Cancer Institute, Johns Hopkins School of Medicine, Baltimore, MD, USA;* [j] *Department of Urology, Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands*

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Abstract

Context: Bacillus Calmette-Guérin (BCG) is currently the most effective intravesical therapy for nonmuscle invasive bladder cancer, reducing not only recurrence rates but also preventing progression and reducing deaths. However, response rates to BCG vary widely and are dependent on a multitude of factors.
Objective: To review existing data on clinical, pathologic, immune, and molecular markers that allow prediction of BCG response.
Evidence acquisition: PubMed and MEDLINE search of English language literature was conducted from its inception to July 2017 using appropriate search terms. Following systematic literature review and analysis of data, consensus voting was used to generate the content of this review.
Evidence synthesis: As seen in the EORTC and CUETO risk nomograms, clinicopathologic features, especially tumor stage and grade, are the most effective predictors of BCG response. Data are less robust with regards to the association of response with age, female sex, recurrent tumors, multiplicity of tumors, and the presence of carcinoma in situ. Single biomarkers, such as tumor p53 and urinary interleukin-2 expression, have had limited success in predicting BCG response, possibly due to the multifaceted nature of the generated immune response. More comprehensive biomarker panels (eg, urinary cytokines), have a more robust correlation with response, as do patterns of urinary cytologic fluorescent in-situ hybridization examination. Gene expression data correlate with disease progression, but studies examining potential associations with BCG response are limited.
Conclusions: Currently, the best predictors of BCG response are clinicopathologic features such as tumor grade and stage. Panels of urinary cytokines, as well as fluorescent in-situ hybridization patterns of cytologic anomalies, appear to be promising biomarkers. The complexity of the immune response to BCG and the heterogeneity of bladder

* Corresponding author. Department of Urology, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Unit 1373, Houston, TX 77030, USA. Tel. +1 713 792 3250; Fax: +1 713 794 4824.
E-mail address: akamat@mdanderson.org (A.M. Kamat).

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cancer suggest that future studies should amalgamate measures reflecting innate immune response and tumor/stromal gene expression before these can be adopted for clinical use.

Patient summary: Bacillus Calmette-Guérin (BCG) immunotherapy is an effective treatment for many patients with nonmuscle invasive bladder cancer. An individual's response to BCG can be predicted by using various features of the cancer. In the future, predictive markers using molecular measures of the tumor type and the immune response to BCG may allow us to precisely know an individual's likely outcome after BCG treatment.

1. Introduction

For more than 4 decades, intravesical Bacillus Calmette-Guérin (BCG) has been the most effective intravesical therapy for nonmuscle invasive bladder cancer (NMIBC) [1]. Despite its success, recurrence rates range from 32.6% to 42.1% and progression rates from 9.5% to 13.4% [2,3]. Patients who develop disease progression often have compromised survival due to the delay in curative therapy (eg, radical cystectomy or trimodal therapy) [4]; even recurrent, nonprogressive disease imposes heavy financial burdens on health care systems and is associated with morbidity for patients. Thus, clinically applicable tools to predict disease recurrence and progression are much needed. In this review, we summarize the published evidence on markers of response to intravesical immunotherapy with BCG.

2. Evidence acquisition

PubMed and MEDLINE search of the English language literature was conducted from its inception to July 2017 using terms: "non-muscle invasive bladder cancer," "bladder cancer," "BCG," "immunotherapy," "cytokine," "interleukin," "immune response," "recurrence," "progression," "survival," "molecular marker," "prognosis," "single nucleotide polymorphism," "gene signature," and "immune signature." Reference lists in pertinent articles were reviewed to augment source material. Full texts of selected studies (eg, review articles) [5,6] relevant to this manuscript were reviewed. Evidence was collated and condensed by the first and second authors and a summary document circulated to all coauthors for consensus on "definitely useful" and "probably useful" in predicting response to BCG. Evidence not robust enough to be classified into the above categories was placed into the "emerging strategies" category (Table 1).

3. Evidence synthesis

3.1. *Definitely useful*

3.1.1. *Clinicopathologic features*

The first attempts to predict response to BCG centered on clinicopathologic features. Recognizing that a combination of factors would be most accurate, two comprehensive efforts were put forth by the European Organization for Research and Treatment of Cancer (EORTC) and Club Urologico Espano de Tratamiento Oncologico (CUETO) groups. In a pooled cohort of 1062 patients treated with BCG, the CUETO group identified female sex (hazard ratio [HR]: 1.71), recurrent tumors (HR: 1.9), tumor multiplicity (HR: 1.1–1.7), and presence of carcinoma in situ (CIS; HR: 1.54) to predict recurrence, and recurrent tumor (HR: 1.62), high-grade tumors (HR: 5.64), T1 tumors (HR: 2.15), and recurrence on 3-mo endoscopic examination (HR: 4.6) to predict progression to muscle invasive bladder cancer (MIBC) [3]. Based on the analysis, a scoring system was constructed categorizing patients into four risk groups each for recurrence (C-index: 0.64) and progression (C-index: 0.69–0.70) [7].

While useful, one weakness of the CUETO data was the group's nonstandard maintenance BCG protocol of six fortnightly treatments after induction wherein patients only received 5–6 mo of maintenance therapy. In contrast, a subsequent EORTC nomogram was formulated with data extracted from 1812 patients who received 1–3 yr of maintenance therapy in accordance with the widely used

Table 1 – Consensus classification of factors as "definitely useful" and "probably useful" in predicting response. Evidence not robust enough to be classified is listed as "Emerging strategies"

Definitely useful		Probably useful	Emerging strategies
Before treatment		**Before treatment**	**Before treatment**
Clinicopathologic features (level of evidence)		Tumor molecular biomarkers[a]	Molecular subtypes
Grade	(+++)	Host genomic signature[b]	
Stage	(+++)		
Recurrent tumors	(++)	**During treatment**	
Multiplicity	(++)	Clinical immune response measures	
CIS	(+)	Urinary cytokines (eg CyPRIT)	
Female sex	(+)	Cell-mediated immunity markers	
Age	(+)	Immunologic milieu (Th1 vs Th2)	
During and after treatment			
FISH pattern on cytologic examination			

CIS = carcinoma in situ; FISH = fluorescent in-situ hybridization; Th = T helper.
[a] See Table 2.
[b] See Table 3.