Ann Surg Oncol (2018) 25:2498–2499
https://doi.org/10.1245/s10434-018-6610-7

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

EDITORIAL – UROLOGIC ONCOLOGY

Cancer Immune Therapy: Prognostic Significance and Implications for Therapy of PD-1 in BCG-Relapsing Bladder Cancer

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Bacillus Calmette–Guérin (BCG) immune therapy is used for (1) preventing bladder cancer relapse following complete tumor excision of Ta and T1 papillary tumors, and (2) eradication of carcinoma in situ (CIS), which is not usually completely removed due to its diffuse and often multifocal involvement of the bladder. Tumors that relapse despite adequate BCG are often aggressive and life-threatening if not managed appropriately. Thus, radical cystectomy is the gold standard for BCG failures. Alternatives to cystectomy include intravesical valrubicin, which is US FDA-approved for BCG-unresponsive CIS and off-label approaches, including repeat instillation of BCG with or without interferon-α, or intravesical instillation of other immune or chemotherapeutic agents. Currently, a major obstacle in this field is the lack of understanding of immune regulatory pathways driving BCG responsiveness, making it difficult to understand why many patients do not respond to therapy.

The work by Kikuchi and colleagues is significant because it seeks to elucidate the characteristics of BCG-unresponsive tumors and their prognostic significance. Using a cohort of patients deemed BCG unresponsive, the authors found that tumor PD-1 staining was significantly increased in BCG-unresponsive tumors compared with pretreatment tumors from the same patient, and that increased programmed death 1 (PD-1, or CD279) staining in post-BCG-treated tumors was associated with a worse outcome.

PD-1 was discovered in 1992 as the gene responsible for programmed cell death[1]; however, its potential role in regulating immune tolerance did not emerge until many years later when phenotypes of mice deficient in PD-1 were characterized.[2] Prior elucidation of the potential of cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) blockade in treating cancer[3] facilitated identification of PD-1 ligands and the role of PD-1 in cancer. Because PD-1 is structurally similar to CTLA-4, the ligand to PD-1 was identified by identifying ligands that were similar to CTLA-4's binding ligands B7-1 and B7-2.[4,5] We now know that expression of PD-1 on naive T cells is induced by T cell receptor (TCR) activation and is one of the earliest markers of T-cell activation.[6] However, constitutive PD-1 expression resulting from chronic stimulation results in an exhausted T-cell phenotype, thereby putting the brakes on T-cell activation to limit autoimmune tissue damage. Binding of PD-1 by its ligand, programmed death-ligand 1 (PD-L1), induces apoptosis in T cells,[7] and, by expressing PD-L1, tumors exploit this phenomenon to favor their growth and progression.[8–10] Thus, an increase in the frequency of PD-1-expressing cells in the tumor microenvironment might be expected after the failure of therapy. Indeed, others have shown increased PD-1-expressing tissue following failed therapy in leukemia[11] and lymphoma.[12]

Several shortcomings to this work are notable. Given the importance of PD-1's ligand binding, the lack of PD-L1 staining in this study is unfortunate. Inman and colleagues have previously shown that tumor PD-L1 was a key determinant of stage progression among a cohort of

First Received: 11 June 2018;
Published Online: 3 July 2018

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patients treated with BCG.[13] Furthermore, most patients with CIS who did not respond to BCG immunotherapy showed 15- to 20-fold higher PD-L1 expression, especially within BCG granulomas. In addition, the level of PD-L1 was relatively low in CIS tumors before BCG treatment but increased after therapy, showing that PD-L1 expression is not a static property but a dynamic feature that changes in response to therapy. In addition, PD-1 could be engaged by PD-L2, which is also detectable on tumors cells[14] but was not analyzed in this cohort. Finally, since PD-1 is expressed both on tumor cells and immune cells[15], distinguishing tumor from immune cell PD-1 staining is important.[16]

Are there other limitations of the study design that could bias the results or limit its generalizability? One issue is that the pretreatment tumor blocks are older than post-treatment blocks. Antigen decay in paraffin-embedded tissue sections for immunohistochemistry is a common occurrence[17] that may have affected PD-1 staining in this study. It is possible that there is loss of PD-1 expression over time and this would systemically favor increased PD-1 expression in newer (BCG unresponsive) tissue samples. Second, the importance of BCG maintenance has been proven in randomized controlled trials and is recommended in bladder cancer guidelines. Nevertheless, in this study, BCG maintenance therapy was not administered. This is becoming more of an issue as trials in the BCG-unresponsive setting are emerging. Patients are not eligible for BCG-unresponsive clinical trials unless they have received an adequate amount of BCG, which includes at least five of six induction instillations and at least two of three maintenance instillations.[18] In this population, no patients received maintenance BCG, as the standard approach in Japan is to administer 6–8 weeks of induction only. Thus, it is difficult to generalize these findings towards what urologists in the US consider as BCG-unresponsive phenotypes.

In conclusion, this study has important prognostic relevance and validates earlier findings by Inman and colleagues[13] supporting a role for PD-1/PD-L1 axis signaling in BCG-unresponsive tumors. Although the conclusions drawn are subject to certain limitations, it moves the field forward by working to characterize BCG-unresponsive tumors and suggests that PD-1/PD-L1 blockade could be a therapeutic strategy in BCG-unresponsive patients.

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