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Paper Alert

BCG in Immunocompromised Patients: Is it effective? Is it safe?

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Intravesical instillation of Bacillus Calmette-Guerin (BCG) is the most effective "non-radical" therapy for high-risk non-muscle invasive bladder cancer (NMIBC) [1, 2]. It is reported to have rates of progression-free survival of around 60–80% [3–5]. While it's mechanisms of action are not completely understood, it is thought to initiate inflammation and cellular immune activity resulting in an anti-tumor response [6]. Moreover, being a live Mycobacterium, the possibility of it escaping the bladder after intravesical instillation causing a systemic infection ("BCGemia") has been well described [7, 8]. Thus, there is understandable concern that in patients who are immunologically compromised, either iatrogenically and/or because of underlying diseases, intravesical instillations of BCG will not be effective and potentially can be unsafe. While several small, single-institution historical series confirm its safety and efficacy in treating bladder cancer patients who are immunocompromised [7, 9–16], no large-scale assessment has been made, and in large prospective randomized studies testing BCG's efficacy, immunosuppressed patients and/or those receiving corticosteroids chronically have intentionally been excluded from participation (e.g., SWOG S1602 [PRIME]).

To try to better address this question Durant and colleagues looked at all NMIBC patients age ≥ 66 years identified in the Surveillance, Epidemiology and End Results (SEER)—Medicare database from 1975–2013 who had completed "adequate" treatment with BCG (at least 5 of 6 induction instillations and 2 of 3 in the first round of maintenance instillations within 12 months of the index transurethral resection of bladder tumor [TURBT]) [17], for outcome and toxicity [18]. Patients were classified as being "immunocompromised" if they had at least one inpatient admission or outpatient claim for autoimmune conditions (e.g., Crohn's disease, ulcerative colitis, psoriasis, rheumatoid arthritis, sarcoidosis, systematic scleroderma, Sjogren syndrome, systematic lupus erythematosus) and/or human immunodeficiency virus (HIV) infections, and/or receiving a solid organ transplant before they received their first dose of BCG. Patients without such conditions were considered "immunocompetent". Patients with pre-existing or subsequent (to the index NMIBC diagnosis) malignancies and those who received systemic chemotherapy before or after BCG administration were excluded. Of the 4277 NMIBC patients who received adequate BCG, 606 (14.2%) were immunocompromised; of those, over 97% had autoimmune diseases, with the rest being solid organ transplant recipients and/or having HIV. These patients' outcomes were compared with those of the remainder of the patients ($N = 3671$) who were deemed immunocompetent. The immunocompromised group was older (median age = 78 vs 75 years, $p < 0.001$), more were females (29.2% vs 22.4%, $p < 0.001$), and had

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higher instances of chronic obstructive pulmonary disease (COPD), diabetes, and moderate to severe renal disease—each of which (and/or their treatments) can adversely affect immune defenses.

Despite this, there were similar rates of disease progression, to receiving systemic chemotherapy, of undergoing partial or total cystectomy, of developing metastases and of dying (from bladder cancer or other causes) over the next 5 years in the two groups. Moreover, there were similar rates of disseminated Mycobacterial infections (<1.8% in immunocompromised and <0.7% in immunocompetent patients).

The authors concluded that BCG instillations can be offered to immunocompromised NMIBC patients with the same expected efficacy and safety/morbidity as in immunocompetent ones.

However, before proceeding with administering BCG to immunocompromised NMIBC patients without concern—several points about methodology and conclusions should be raised. Perhaps the most glaring is the selection going into this analysis; by requiring all patients to have received BCG "5 + 2", those who either could not tolerate it (including with systemic infections) or in whom it was rapidly ineffective (e.g., high grade stage $\geq T_1$ cancer following the induction course) were not included. Similarly, while the most concerning consequences of BCG's inefficacy—disease progression or death—were studied, the most common result of BCG failure, disease recurrence without progression, was not. Although the median number of TURBTs after the index TURBT were similar in both groups, this information is not an adequate replacement for knowing recurrence rates since repeat TURBT is often used as a means of achieving accurate staging rather than treating reoccurring cancer.

Moreover, as the authors point out, less serious toxicities were not ascertainable. Importantly, these may have affected accurate counts of how many patients who started BCG treatment had it discontinued because of non-septic toxicities and never received "5 + 2" instillations, so were never included in the data analyzed. Perhaps most important were the details of the immunosuppressed group in terms of how "immunosuppressed" those with autoimmune diseases really were, including whether they were receiving immunosuppressant medications. Similarly, common diseases (and their treatments) not considered autoimmune ones, such as COPD (16.4% of immunocompetent patients and 23.9% of immunosuppressed ones) and diabetes (24.5% in immunocompetent and 28.7% in immunosuppressed) can greatly affect the immune system.

Of course, these and many other limitations are inherent in "big data" studies. These limitations notwithstanding, with care and trepidation, hopefully some immunocompromised patients with NMIBC and be offered BCG therapy without resorting to (often) less effective intravesical therapies or radical cystectomy.

CONFLICTS OF INTEREST

The author has no conflicts of interest to report.

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