

Paper Alert

Antibiotics and BCG

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Intravesical instillation of *Bacillus Calmette Guerin* (BCG) has long been a critical means to treat intermediate and particularly high risk, non-muscle invasive (NMI) urothelial cancer (UC) of the bladder [1]. These cancers recur frequently after transurethral resection (TURBT) and may progress to muscle invasive or more extensive UC. BCG instillations administered with induction plus maintenance regimens reduce recurrence and progression events and clearly lower the likelihood of patients “requiring” cystectomy (the recommended treatment for patients with high risk NMI UC who fail to reach or maintain a disease-free status with “adequate” BCG therapy [3]).

While having been used for over 45 years [1], the precise mechanisms of BCG’s activity are poorly understood, although they clearly involve the innate and adaptive immune responses, not only to BCG but also to UC [4–6].

In recent years it has become recognized that the microbial flora in the gastrointestinal (GI) tract can modify both immune responses and the development/behavior of certain cancers (both of GI and non-GI origin) [7–11]. Additionally, it is now clear that the urinary tract, traditionally thought of as being sterile, has its own microflora, which can be associated with both bladder health and symptomatic conditions [12–14]. Moreover, solid cancers in many

different sites have their own microbial flora [10]. These organisms require special methods of culturing and characterization, which are not routinely performed in a standard aerobic urine culture. Finally, many urologists prescribe antibiotics, not only to treat symptomatic, culture proven urinary infections (UTIs) but also as surgical and peri-procedural prophylaxis and as empirical therapy in patients with irritative voiding symptoms, the cause of which is not culture confirmed. Clearly, these treatments can affect the microbial flora in the GI and urinary tracts-and other locations (including tumors [10]).

With this background, it is interesting to note the findings recently published by Pak and colleagues from a cohort of 276 patients with primarily high risk NMI UC treated with induction (6 weekly instillations) and maintenance (3 weekly instillations at months 3, 6, and 12) BCG (strain and dose not given) between 2008 and 2017 at the National Cancer Center in Korea [14].

Besides looking at standard tumor and treatment (e.g. use of reTURBT) characteristics and demographic information, the authors reported the oncologic impact of the type and duration of antibiotic use in these patients prior to and/or concomitant with BCG therapy. The authors chose 30 days preceding induction BCG as the cutoff for how long before the start of BCG therapy antibiotic use was monitored because previous work indicated that the GI microflora were restored by that time [15], and because induction BCG was started around that time after the index TURBT. They also reported results of

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pre-BCG standard aerobic urine cultures which were “negative” in 94.7% of patients. All patients received a single dose of a quinolone or cephalosporin antibiotic as surgical prophylaxis at the index TURBT. Patients were divided into “no” antibiotics (really one dose because of surgical prophylaxis) (23.9%), “short course” (2–6 days) (41.3%) or “long course” (≥ 7 days) (34.8%) — — — most in the short course group received antibiotic treatment prior to BCG therapy, but most in the long course group received antibiotics prior to, and concurrent with BCG treatment. The groups did not differ significantly in age, gender, ECOG performance status or tumor characteristics (with over 80% being high grade, nearly 60% being stage T1, nearly 60% having multiple tumors, 25% having carcinoma in situ [CIS], and 5% having variant histology). Recurrences had to be pathologically confirmed, and progression was considered developing histological stage T2 or extravesical disease. Median follow-up was 55 months.

The authors found that patients treated with short course antibiotics experienced recurrence and progression slightly more frequently than those in the no antibiotics group (but differences were not significantly different). However, those treated with long-term antibiotics recurred and progressed significantly more frequently than patients in the other two groups (5-year recurrence free survival [RFS] 62.2% for the no antibiotics group vs 26.9% for the long-course group [$p < 0.001$]; 5-year progression free survival [PFS] 79.6% for the no antibiotics group vs 53.3% for the long-course group [$p < 0.0006$]).

While this is a single institution, retrospective study, it was conducted at a time when awareness of the effects of the GI microbiome on immunity were rudimentary, and those of the urinary tract and tumor microbiomes (or even their existence) were barely recognized. Moreover, the concept of antibiotic stewardship was (and to some degree, still is) more focused on preventing emergence of multiple drug resistant strains of bacteria that were being selected for, than on microbiome stability and restoration. This may explain why antibiotic courses were being administered to empirically treat cystitis-like symptoms, usually in the face of a negative ($>90\%$ of the time) or even no (data not given) culture. Given the irritable voiding that BCG often causes, it is actually surprising that nearly a quarter of the cohort received “no” antibiotics.

As the authors readily acknowledge, this study clearly has limitations, including: lack of demonstrating causality for the effect described; lack of

data on the composition of either the GI or urinary micro-biome before and after antibiotic administration; less than a clear understanding of how the gut and urinary microbiomes influence systemic or local immune responses; the possibility that the urinary microbiome can influence bladder cancer development and behavior beyond effects on the immune system (e.g. by carcinogen metabolism) [10]; failure to recognize that on some occasions, through its effect on microbial flora, antibiotic administration can occasionally cause tumor regression [10]; and of course lack of a detailed understanding of mechanisms of BCG’s immune and anti-tumor effects. However, it’s take-home message, that empirical and unguided use of antibiotics in patients receiving BCG can be harmful, is clear.

Indeed, over a decade ago Herr reported that not treating asymptomatic bacteriuria in patients receiving BCG was neither symptomatically nor oncologically harmful to his bladder cancer patients. We now may be beginning to understand why [16, 17].

CONFLICTS OF INTEREST

The author has no conflicts of interest to report.

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