Utilization of Bacillus Calmette-Guerin for Nonmuscle Invasive Bladder Cancer in an Era of Bacillus Calmette-Guerin Supply Shortages

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OBJECTIVES To study trends in Bacillus Calmette-Guerin (BCG) utilization for nonmuscle invasive bladder cancer (NMIBC) before and during national BCG shortages.

METHODS The National Cancer Database was used to identify patients with localized NMIBC. Multivariate logistic regression was used to assess factors associated with BCG use. Temporal trends in BCG use were studied using segmented regression analysis.

RESULTS We identified 238,279 patients with NMIBC from 2004 to 2015. Overall, 33,660 (14.1%) patients with NMIBC received intravesical BCG during the study period. Segmented regression revealed a slower rate of rise of BCG utilization following major supply interruptions in 2011 and 2012 (2004-2012: +0.62% increase per year [$P < .0001$]; 2013-2015: +0.29% increase per year [$P = .084$]). This trend was most pronounced in Ta-low grade patients and least pronounced in T1-high grade patients.

CONCLUSIONS BCG utilization for NMIBC increased significantly over the study period, possibly representing increased adoption of national guidelines for BCG in NMIBC. In the years following interruptions in BCG supply, BCG use appears to have been rationed based on clinical risk, with the steepest declines in BCG use occurring in the lowest risk patients. UROLOGY 124: 120−126, 2019.

The AUA, NCCN, and EAU clinical practice guidelines all offer strong recommendations in support of Bacillus Calmette-Guerin (BCG) use for high-risk nonmuscle invasive bladder cancer (NMIBC).[1-3] Compared to other intravesical therapies, BCG has demonstrated superior efficacy in reducing disease recurrence and progression among high-risk NMIBC patients.[4-6] There is little debate regarding the clinical utility of BCG in the treatment of NMIBC.

Despite this, Sanofi Pasteur, the largest supplier of the Connaught strain of BCG, announced in November 2016 that it would indefinitely cease BCG production in mid-2017.[7] The manufacturer estimated that existing supplies of Connaught BCG would be depleted by the end of 2018. Given that TICE BCG is the only other strain commercially marketed in the United States, the cessation of Connaught BCG production has prompted fears of BCG supply shortages.

Prior BCG supply interruptions have had considerable impacts on the management of patients with NMIBC. In 2011, Connaught BCG manufacturing was temporarily shut down by the FDA for regulatory noncompliance. This was followed shortly thereafter by a TICE BCG production halt in 2012 due to batch contamination.[8] These 2 successive interruptions in BCG supply led to real-world drug shortages lasting several months or longer. In the absence of available BCG, several anecdotal reports emerged of nonstandard treatment algorithms for NMIBC. Providers were forced to offer inferior intravesical therapies, use reduced BCG doses split across several patients, deviate from traditional BCG induction and maintenance schedules, forego intravesical therapy altogether, and even offer early radical cystectomy for NMIBC.[9-13]

Although anecdotal reports suggested deviations from standards of care during prior BCG shortages, the real-world utilization of BCG during supply interruptions has not been empirically studied. This study aimed to assess trends in BCG utilization during prior BCG supply shortages in 2011-2012 using the National Cancer Database.

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MATERIALS AND METHODS

The National Cancer Database (NCDB) was used to identify patients diagnosed with urothelial carcinoma of the bladder from 2004 to 2015. Patients with clinically localized nonmuscle invasive disease (cT1, cTa, cTIS; N0; M0) with pathologic confirmation of disease were included. WHO/ISUP grading for urothelial bladder cancer was not used due to unavailability of this variable before 2010. Instead, tumor grade was determined using a generic 4-level "grade" variable that is available for all tumors in NCDB. Patients with "well differentiated" or "moderately differentiated" tumors were categorized as "low grade", while patients with "poorly differentiated" or "undifferentiated" tumors were categorized as "high grade." For patients diagnosed after 2010, this grading scheme was compared to the WHO/ISUP grade and demonstrated appropriate concordance (98.9% and 95.3% concordant for WHO/ISUP low grade and high grade, respectively). Patients were then further characterized into clinical stage categories based on T-stage and tumor grade. These categories included Ta-low grade (TaLG), Ta-high grade (TaHG), T1-low grade (T1LG), T1-high grade (T1HG), and carcinoma in situ (CIS).

Utilization of BCG was defined as either "Bacillus Calmette-Guerin or other immunotherapy" in the surgical treatment variable or a confirmation of immunotherapy administration in the immunotherapy variable. Baseline clinical and socioeconomic characteristics of patients receiving BCG were compared to those who did not receive BCG using the chi-square test. Multivariate logistic regression was used to identify patient and provider factors associated with BCG utilization. Hospital volume and distance from patient's residential zip code to hospital facility were converted into tertile ranks to facilitate analyses (distance from hospital: 33.3 percentile = 4.8 miles; 66.7 percentile = 12.8 miles). In order to detect changes in BCG utilization following BCG supply interruptions in 2011 and 2012, segmented regression was performed. Segmented regression compares the slope of a least squares regression line before and after a specific intervention or time-point.[14] Here, segmented regression was used to compare the rate of increase in BCG utilization before (2004-2012) and after (2013-2015) interruptions in BCG supply. Longitudinal trends in cystectomy utilization for patients with NMIBC were also assessed using segmented regression. Statistical significance was predetermined at $P < .05$.

The NCDB is a hospital-based all-payer cancer registry encompassing all geographic regions in the United States. The NCDB captures over 70% of all incident cancer cases, and includes more than 34 million patients. The current study was granted Exempt status by the Cleveland Clinic Institutional Review Board. All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

RESULTS

A total of 238,279 patients diagnosed with NMIBC from 2004 to 2015 were identified using the National Cancer Database. Overall, 14.1% of all patients with NMIBC received intravesical BCG during the study period. Baseline clinical and socioeconomic characteristics of the study cohort are outlined in Supplementary Table 1. Patients who received BCG treatment differed from those who did not receive BCG across all baseline variables except Charlson comorbidity index. The BCG cohort was comprised of more males, fewer racial and ethnic minority patients, and more patients with T1 or CIS disease.

Table 1. Multivariate logistic regression to identify factors associated with BCG use

Variable	Odds Ratio (95% Confidence Interval)	*P* value
Age		<.0001
>85	Referent	
75-85	1.7 (1.63-1.79)	
65-75	2.01 (1.92-2.11)	
55-65	1.96 (1.85-2.07)	
<55	1.96 (1.84-2.1)	
Race		<.0001
White	Referent	
Black	0.84 (0.79-0.9)	
Other	0.87 (0.81-0.94)	
Ethnicity		<.0001
Hispanic	Referent	
Non-Hispanic	1.29 (1.18-1.41)	
Sex		.0002
Male	Referent	
Female	0.94 (0.91-0.97)	
Median income quartile		.0079
4th (lowest)	Referent	
3rd	0.96 (0.9-1.01)	
2nd	0.95 (0.9-1.01)	
1st (highest)	0.91 (0.85-0.96)	
Education quartile		<.0001
4th (lowest)	Referent	
3rd	1.27 (1.2-1.33)	
2nd	1.45 (1.37-1.53)	
1st (highest)	1.53 (1.44-1.62)	
Insurance coverage		<.0001
Uninsured	Referent	
Private insurance	1.25 (1.12-1.39)	
Public insurance	1.12 (1-1.24)	
Charlson comorbidity index		.0018
2	Referent	
1	1.05 (1-1.12)	
0	1.09 (1.03-1.14)	
Metropolitan area		<.0001
Suburban	Referent	
Metropolitan	0.84 (0.81-0.88)	
Rural	1.1 (1.01-1.21)	
Facility type		<.0001
Community	Referent	
Academic	1.2 (1.14-1.26)	
Comprehensive community	0.87 (0.83-0.91)	
Integrated cancer center	1 (0.95-1.06)	
Distance to hospital		<.0001
Near	Referent	
Far	1.18 (1.14-1.22)	
Intermediate	1.09 (1.05-1.12)	
Facility volume		<.0001
Low	Referent	
High	1.22 (1.16-1.28)	
Intermediate	1.04 (0.99-1.1)	
Clinical tumor stage		<.0001
TaLG	Referent	
CIS	5.64 (5.32-5.99)	
T1HG	7.81 (7.54-8.09)	
T1LG	3.71 (3.52-3.92)	
TaHG	5.52 (5.31-5.74)	

Results from the multivariate logistic regression to identify factors associated with BCG use are shown in Table 1. The variable most strongly associated with BCG use was tumor stage, with higher likelihood of use in those with high-grade histology

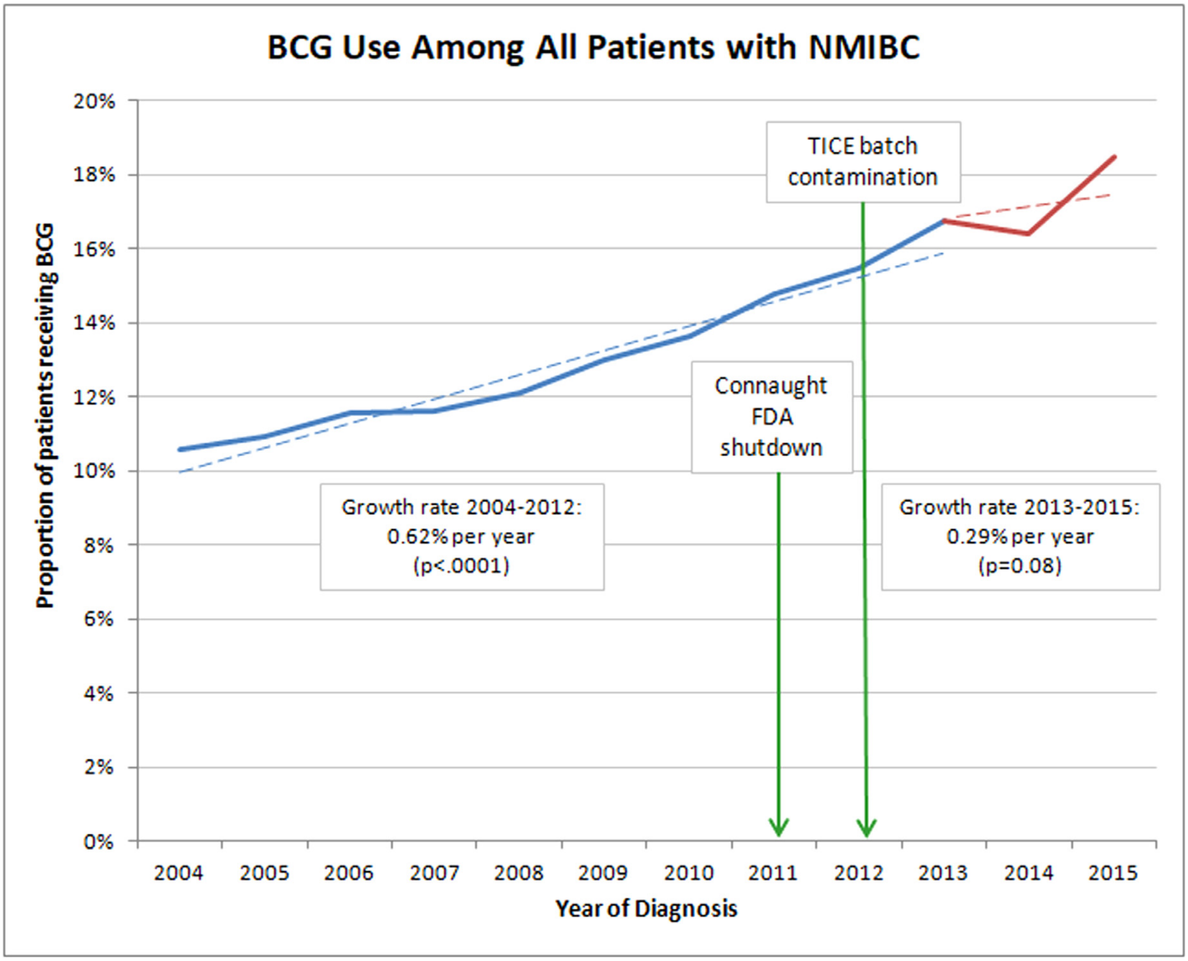

Figure 1. Trends in BCG utilization before and after BCG supply shortages. (Color version available online.)

or more invasive tumors (T1HG vs TaLG: OR 7.8, 95% confidence interval 7.5-8.1). Patients treated by academic or high-volume facilities were also more likely to receive BCG. Additionally, nonwhite race, Hispanic ethnicity, female sex, and uninsured status were all associated with lower likelihood of BCG use, highlighting potential socioeconomic disparities in the utilization of BCG for NMIBC.

In order to ascertain the impact of BCG supply shortages on the utilization of BCG, segmented regression was performed. As shown in Figure 1, there was steady growth in BCG use for NMIBC patients prior to supply shortages in 2011-2012 (+0.62% per year for 2004-2012, $P < .0001$). However, following interruptions in BCG supply, the growth in BCG use stagnated (+0.29% per year for 2013-2015, $P = .084$).

To further explore the overall trend in BCG use after supply shortages, segmented regression was performed for each clinical tumor stage. Figure 2 depicts BCG usage trends by clinical stage. Table 2 outlines the results of segmented regression in each subgroup. BCG use increased from 2004 to 2012 for all clinical stages except TaLG. In 2013-2015, BCG use declined significantly for TaLG while continuing to increase for T1HG. BCG use among T1LG, TaHG, and CIS stagnated during this time period and did not increase nor decrease.

To test the hypothesis that BCG supply shortages led to increased use of radical cystectomy among NMIBC patients, an additional segmented regression was performed with radical cystectomy as the outcome. This segmented regression revealed no increase in cystectomy utilization following BCG supply shortages (Supplementary Fig. 1).

COMMENT

This study examines temporal trends in the utilization of BCG for NMIBC from 2004 to 2015 using data from the National Cancer Database. BCG use in NMIBC increased steadily over the study period. However, the rate of increase in BCG utilization for the overall cohort decreased significantly in 2013-2015. This coincides with 2 prominent BCG supply interruptions that occurred in 2011 and 2012, the combination of which led to significant drug shortages in subsequent months and years.

Overall, there was an increase in BCG utilization for NMIBC over the last decade. This trend is consistent with prior studies examining trends in BCG use. Pugliese et al demonstrated increased use of BCG for high risk NMIBC at their institution from 1997 to 2007, particularly following the publication of AUA guidelines.[15] Similarly, Lambert et al. found that BCG use in T1 patients doubled over time at their institution from 26% in 1990-1998 to 57% in 1998-2005.[16] Population-based studies

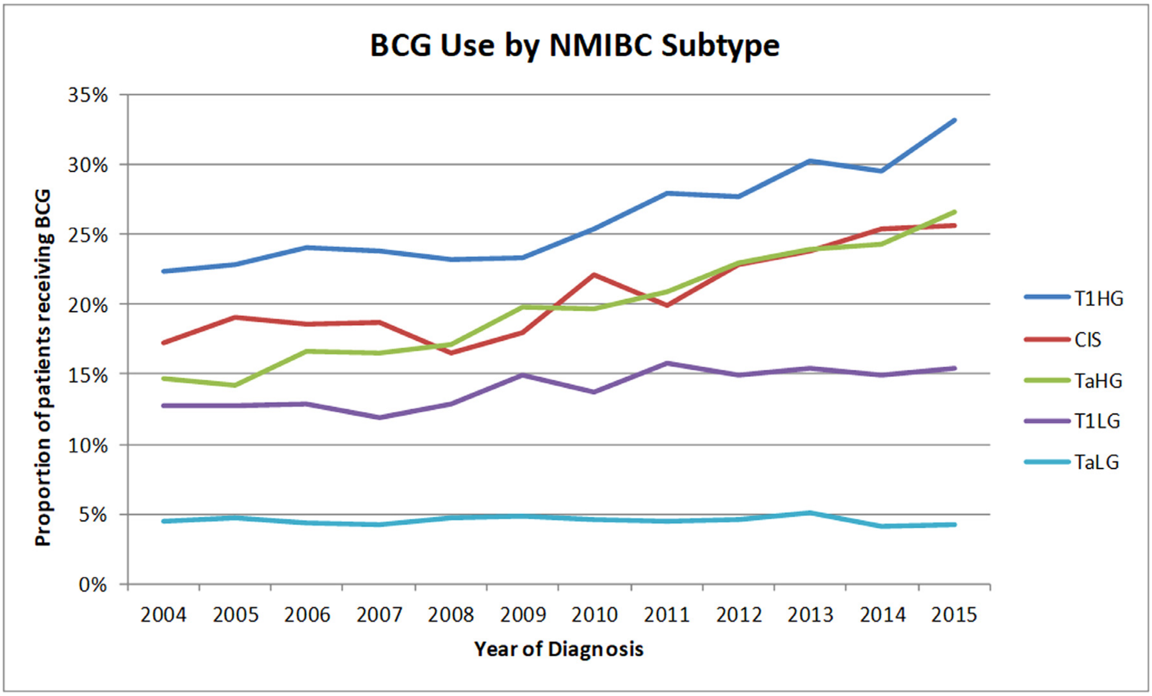

Figure 2. Trends in BCG use by tumor stage. (Color version available online.)

using SEER-Medicare data have also demonstrated increased BCG use over time for NMIBC patients.[17,18] The trend toward increased BCG use demonstrated in the current and prior studies is a welcome 1, as it represents increasing concordance between empirical evidence and real world practice.

Unfortunately, this growth in BCG utilization appeared to stagnate following 2 prominent interruptions in BCG supply in 2011 and 2012. In response to anecdotal reports of BCG shortages, several thought leaders suggested strategies to treat NMIBC in the absence of available BCG. Meeks et al proposed using reduced doses of BCG at one-third strength,[8] even though reduced BCG doses are known to be associated with higher recurrence rates.[19] Veeratterapillay et al suggested shortening BCG maintenance schedules down to 1 year or less.[9] Mostafid et al propose the use of intravesical chemotherapy agents or even thermotherapy.[10] All authors advised urologists to lower their threshold for early radical cystectomy for NMIBC patients in the absence of available BCG.

While several commentaries and editorials offered strategies to cope with BCG shortages, the current study is the first to empirically study real-world BCG use following supply interruptions. From 2004 to 2012, growth in overall BCG use was steady at 0.62% per year ($P < .0001$). However, from 2013 to 2015, in the setting of diminished BCG supply, the growth rate was not statistically significant ($P = .084$), suggesting that overall BCG use effectively flat-lined during this time period.

Interestingly, subanalyses by clinical tumor stage may suggest preferential rationing of BCG based on oncologic risk. In 2013-2015, BCG use decreased most significantly in the TaLG group. This is generally the lowest risk NMIBC subgroup, and the one for which clinical indications for BCG use are limited. Conversely, BCG use notably increased in 2013-2015 for the T1HG subgroup, despite ongoing BCG supply shortages. This is the highest risk subgroup for which clinical guidelines offer the strongest support of BCG use.[1-3] Taken together, these findings may suggest that when faced with limited supply of BCG, urologists preferentially offered it to those at highest risk, while limiting its use in those with least aggressive disease. Additionally, while early cystectomy was advocated by several experts during BCG shortages, empirical data from

Table 2. Growth rate in BCG use by clinical stage before and after BCG supply shortages

Clinical Tumor Stage	Annual Growth Rate 2004-2012	*P* value*	Annual Growth Rate 2013-2015	*P* value*
TaLG	+0.02%	.56	-0.43%	.004
T1LG	+0.36%	.001	-0.34%	.63
TaHG	+1.1%	<.0001	+0.32%	.48
T1HG	+0.71%	<.0001	+0.86%	.03
CIS	+0.53%	.006	+0.34%	.75

*Any *P* value >.05 indicates lack of statistical significance. Null hypothesis is accepted in such cases, implying no growth in BCG use over that time period.

the NCDB did not reveal an increase in radical cystectomy use for NMIBC patients during this time. This may reflect a reluctance among urologists to proceed with life-altering and morbid surgery among NMIBC patients, who would otherwise not commonly be treated with up-front cystectomy.

In addition to rationing by clinical tumor stage, several socioeconomic factors were associated with BCG utilization. Multivariate logistic regression revealed that female patients and those of nonwhite race and Hispanic ethnicity were all less likely to receive BCG therapy. Conversely, patients with higher education or private insurance coverage were more likely to receive BCG. Future studies should attempt to understand whether these socioeconomic disparities are a result of disproportionate drug shortages among hospitals serving vulnerable populations, or if these observations reflect disparities in physician practice patterns.

Given the overall trend of increasing adoption of BCG into clinical practice and the demonstrated impacts of supply interruptions, addressing BCG supply shortages is more pressing than ever. At the time of this manuscript preparation, Connaught BCG production has been ceased and current supplies of the Connaught strain are expected to be exhausted in less than 1 year. If prior BCG supply shortages are any indication, a significant BCG shortage is imminent and can be expected to significantly alter real world clinical practice patterns. There are several potential strategies to mitigate the effects of this shortage, including the development and adoption of alternative BCG strains, the use of alternative intravesical therapies, and alternate funding sources for BCG.

Elimination of Connaught BCG from the marketplace is especially concerning in light of emerging evidence that the Connaught strain may have greater efficacy than the alternative TICE strain.[20] Nonetheless, alternative BCG strains should be explored to help boost BCG supply as manufacturing slows. The Moreau BCG strain was recently introduced in Europe, and demonstrated favorable 5-year recurrence and progression outcomes in a single institutional study.[21] Additionally, a phase III clinical trial is currently underway examining the efficacy of the Tokyo-172 BCG strain.[8,22] Exploration of different BCG strains should be encouraged as a potential mechanism to mitigate upcoming supply shortages. The development of alternative intravesical therapies altogether should also be fostered. Current research is underway to explore the utility of intravesical gemcitabine,[23,24] intravesical adenovirus derivatives,[25,26] and even nanotechnology utilizing gold nanorods in the treatment of NMIBC.[27] Indeed, a recent prospective randomized trial of intravesical gemcitabine for low-risk NMIBC demonstrated reduced cancer recurrence at 4 years compared to placebo (hazard ratio 0.66, $P < .001$). Finally, the use of public funds to incentivize stable BCG production should be considered. This has been proposed in the form of tax credits or lending to BCG manufacturers, increasing Medicare fees for coverage of BCG, or allowing importation of internationally produced BCG.[12]

The current study has notable limitations. First, cancer recurrence and progression outcomes are not captured by NCDB. Thus, we cannot determine the impact of variations in BCG use on subsequent oncologic outcomes. Second, the database lacks granularity in identifying intravesical chemotherapy use, precluding an analysis of trends in intravesical mitomycin use during BCG shortages. Third, doses of administered BCG cannot be determined. Thus, patients receiving rationed or reduced doses (eg, one-third dose) during BCG shortages were still counted as having received BCG. Similarly, duration of BCG induction and/or maintenance therapy cannot be determined, precluding an assessment of nonstandard regimens. This may have led to underestimation of the impact of supply shortages on BCG usage patterns. Fourth, the latest NCDB dataset includes data only through 2015. This precludes a more contemporary analysis of the impacts of Sanofi Pasteur's recent decision to halt production of Connaught BCG starting in 2017. Finally, administration of intravesical BCG cannot be accurately distinguished from the administration of systemic immunotherapy. However, the current cohort includes patients from 2004 to 2015, a time period when the use of systemic immunotherapy for NMIBC is not expected to have been substantial.

CONCLUSIONS

BCG utilization for NMIBC increased significantly over the study period, possibly representing increased adoption of national guidelines for BCG in NMIBC. In the years following interruptions in BCG supply, BCG use appears to have been rationed based on clinical risk, with the steepest declines in BCG use occurring in the lowest risk patients. Efforts should be made to boost BCG supply to keep up with rising demand, especially in the setting of upcoming production disruptions.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.urology.2018.07.055.

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EDITORIAL COMMENT

We commend the authors on their recent publication on trends in BCG utilization during periods of temporary supply shortages. Notably, the study compares the periods 2004-2012 versus 2013-2015, which does not include the most recent announcement in 2016 by Sanofi to exit the market completely. This begs the question: if temporary shortages decrease utilization growth by half, then what will be the impact of a complete market exit?

BCG is uniquely vulnerable to manufacturing shortages.[1] First, since it is a vaccine derived from a living organism, it is regulated as a biologic. To account for inherent variability in batches, special measures must be taken to ensure homogeneous identity, strength, quality, purity, and potency. Second, unlike traditional vaccines, BCG is delivered intravesically and manufactured quantities must be relatively large. When combined with high frequency of treatments in induction/maintenance regimens and expanding indications in nonmuscle-invasive bladder cancer, the market is predisposed to shortages. Lastly, the fact that BCG was discovered over 100 years ago makes it difficult to escape generic pricing. Thus, it is easy to see why manufacturers have struggled to cover higher cost structures involved in producing it. Although the SWOG trial, S1602, was developed in response to the recent shortage and is performing necessary work in comparing BCG strain efficacy, it is unclear how introducing the Tokyo strain in North America would circumvent the issues outlined here and prevent a future exit.

Regulatory reform must necessarily be part of the solution. The Biologics Price Competition and Innovation Act of 2009 was intended to enable quick approval for generic biologics (so-called "biosimilars"), but the first drug was not approved until 2015. Recently, the FDA expanded this program with an emphasis on time-to-market. Additionally, a FDA Drug Shortages Task Force was established to explore manufacturing issues like this one; however, BCG is not on the official drug shortages list. It is a mystery why – the authors of this study have clearly demonstrated the impact of shortages on clinical practice, and it would behoove regulators to pay attention.

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AUTHOR REPLY

We appreciate the authors' insightful commentary on our recent study examining trends in BCG utilization during national supply shortages. We agree that the impact of even just temporary supply interruptions on BCG utilization is impressive. Certainly, exploring the impact of Sanofi's recent complete market exit is a worthwhile endeavor. However, due to a requisite time lag to allow maturation of data in the NCDB and other large administrative and population-based datasets, a more contemporary analysis is not yet feasible. Thus, while we anticipate that the recent cessation of BCG production by Sanofi may have profound effects on BCG treatment patterns, the necessary data to empirically study this question is not yet available. For this reason, we elected instead to explore the impacts of prior BCG supply interruptions, in hopes that prior trends might inform the current discourse about ongoing BCG supply shortages.

The authors also share valuable insight into the challenges faced by BCG manufacturers and the market forces that lead to supply shortages. We agree that even if scientifically validated, an additional strain of BCG (Tokyo) entering the marketplace may ultimately suffer from the same issues facing current BCG manufacturers, and would likely not be a panacea for this challenging drug shortage issue. Thus, in our manuscript we highlight the importance of exploring potential alternatives to BCG. However, none of these appears ripe for immediate widespread clinical use, and BCG is likely to continue as a mainstay of NMIBC treatment for the foreseeable future. Thus, addressing BCG supply remains a high priority for our bladder cancer patients.

We agree wholeheartedly that regulatory reform is a requisite and central component in addressing BCG shortages. We applaud the authors for their role in bringing BCG supply issues into the national spotlight.[1] Hopefully our current work can help frame these drug shortages into a real-world context that can ultimately be used to advocate for durable change.

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