

Economic impacts of the Bacillus Calmette-Guérin (BCG) therapy shortage and the proposed solutions for patients with non-muscle invasive bladder Cancer in Aseer Province, Saudi Arabia

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ABSTRACT

Objective: To report the magnitude, the financial and the economic impact of Bacillus Calmette-Guérin (BCG) shortage in our institute and transfer of non-muscle invasive bladder cancer (NMIBC) patients to higher centers to receive the treatment. **Methods:** This is a retrospective study, between January 2015 and December 2017, the cases of NMIBC diagnosed at Aseer Central Hospital, Abha, Saudi Arabia were studied. Demographic features, clinical presentations, histopathological features, and the BCG therapy shortage and its economic impact were addressed. **Results:** Over a three years study review of 62 urothelial bladder cancer, NMIBC was diagnosed in 55 (89%) patients. Forty-three (78%) patients were males and 12 (22%) patients were females. The mean age \pm standard deviation (SD) (range) in this cohort was 59 ± 12 years (38-87). Gross hematuria was the main presentation in 51 (92%) patients of this cohort. Dysuria and other lower urinary tract symptoms were the presentations in 18 (32%) patients. Smoking history was positive in 33 (60%) patients and the rest 22 (40%) patients denied any form of tobacco consumptions. The BCG eligible were 46 (84%) patients of all NMIBC patients in this study. Twenty-seven (59%) patients of them received BCG in our institute. The rest 19 (41%) patients were opted to be transferred to a higher medical center to receive the BCG because of the BCG shortage in our center. The financial cost of traveling to receive the six-weeks induction BCG therapy was on average of 7200 Saudi riyals (1.745 €) for every patient. **Conclusions:** The BCG shortage in our institute is almost approaching half of eligible BCG cases. This has had an economic impact on the health budget. Such health catastrophe could be mitigated with proper health plans of a provision of the BCG to all tertiary care centers. Alternative therapies for such cases should be considered in cases of global BCG shortage.

Keywords: Bacillus Calmette-Guerin, cost-effectiveness, intravesical, non-muscle-invasive bladder carcinoma

Introduction

Bladder cancer is the 7th most common cancer in men and the 17th most common cancer in women worldwide with an age-standardized incidence of 17 and 6/100,000,

respectively.^[1] More than 70% of all bladder cancers are non-muscle invasive bladder cancer (NMIBC). Mortality of bladder cancer has decreased reflecting an advancing development of new therapeutic approaches.^[2,3]

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Transurethral resection of the bladder tumor (TURBT) followed by an adjuvant intravesical instillation with Bacillus Calmette-Guérin (BCG) is the most effective conservative therapy for the treatment of high-risk NMIBC.^[4-6] It can

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significantly reduce the probability of both disease recurrence and progression, thereby potentially improving survival.^[7,8]

In July 2012, Sanofi Pasteur (Lyon, France) announced that it was halting the production of ImmuCyst, the Connaught strain of BCG, after inspectors found mold in the sterile manufacturing area of Toronto, Canada, following a flood.^[9] The Toronto facility was the only one in the world manufacturing ImmuCyst, the market leader in many countries including the United Kingdom and the United States. This halt led to a severe worldwide shortage of BCG as other manufacturers struggled to keep up with demand.

Adding to the worldwide BCG shortage, there is considerable cost variation across countries. This was perhaps related to differences in practices such as inpatient or outpatient care, duration of hospitalization, methods of calculating costs and billing, cancer incidence, and the type and intensity of treatment and testing. Another source of variation in the cost of care is the method of estimating economic efficiency. In some European countries, BCG 6-week induction course varies from 528- 975 €. ^[10]

This worldwide BCG shortage was clearly manifested in Saudi Arabia. It was more predominant in peripheral Saudi provinces. For such reasons, patients were referred to higher national centers to receive BCG therapy.

The objective of this study is to measure the incidence of NMIBC patients treated in our institute over three years. Second to estimate the financial cost and the economic impact of receiving BCG in higher centers. This is the first study from Saudi Arabia to address and enlighten on this financial concern.

Materials and Methods

This research was approved on March 16, 2017 by the Research Ethics Committee (REC# 2017-2-8) of the College of Medicine, King Khalid University, Abha, Saudi Arabia. We scrutinized the cases of urothelial bladder cancers diagnosed at Aseer Central Hospital, Abha, Saudi Arabia between January 2015 and December 2017. The NMIBC incidence, demographic, clinical presentations, and pathological features were evaluated.

Based on the BCG therapy indication, we divided NMIBC patients into either BCG eligible or BCG non-eligible patients. BCG eligible are patients with high-risk NMIBC (high-grade Ta, or any grade T1 or carcinoma *in situ* (CIS). Patients with low-risk NMIBC (i.e. those that are small, solitary and presenting for the first time) are not eligible for BCG therapy. Intravesical BCG therapy was given as induction therapy two weeks after transurethral resection of bladder tumor (TURBT) on weekly intravesical therapy for six weeks. Then, maintenance intravesical therapy monthly for six months. Regular check cystoscopy for local recurrence or progression of the bladder cancer is done every three months in the first two years.

We defined BCG shortage if a patient was diagnosed with NMIBC and was a BCG eligible, but BCG was not commenced 4 weeks after TURBT due to the non-availability.

The financial cost of transfer to higher centers was estimated using a designed model including the flight cost, housing accommodation cost, and the daily budget for transportation and meals. This cost was just estimated for the BCG induction therapy only. The BCG shortage solutions were concisely reviewed.

Statistical analysis

The incidence of NMIBC cases in our institute was measured. The economic impact and the financial cost of transferring patients to a higher center to receive the BCG therapy were estimated. Statistical Package for Social Sciences (SPSS) software was used for the analysis.

Results

Over three years review, 62 cases of urothelial cancers were diagnosed at our health center. NMIBC was in 55 (89%) patients. Forty-three (78%) patients were males and 12 (22%) patients were females. The mean age \pm SD (range) in this cohort was 59 ± 12 years (38–87). Gross hematuria was the main presentation in 51 (92%) patients. Dysuria and other lower urinary tract symptoms were observed in 18 (32%) patients of the study cohort. Smoking history was positive in 33 (60%) patients. A chronic indwelling catheter was used in 15 (27%) patients. Eight (14%) patients showed a history of urinary bilharziasis [Table 1].

The histologic grading of the NMIBC specimens was as the following. Most of our study series were predominantly T1 in 34 (62%) patients. Ta, however, was in 9 (16%) patients. Tis in 12 (22%) patients of this study [Table 1].

The BCG eligible were 46 (84%) patients of all NMIBC patients in this study. Twenty-seven (59%) patients received BCG in our institute. The rest 19 (41%) patients were opted to be transferred to a higher medical center to receive the BCG because of the BCG shortage in our center [Table 1].

The financial cost of traveling to receive the six weeks induction BCG therapy was in 7200 Saudi riyals (1.745 €) on an average for every single patient [Table 2].

Discussion

BCG immunotherapy is a live-attenuated strain of *Mycobacterium bovis* that is indicated in intermediate and high-risk T1, high grade or carcinoma *in situ* (CIS) of NMIBC after transurethral resection (TUR).^[4] High-risk NMIBC represents a challenging disease state with up to 80% and 45% of patients experiencing disease recurrence and progression at 5 years, respectively.^[11]

In our series, 89% of the urothelial bladder cancer cases were NMIBC. This slightly elevated the rate than those reported in

Table 1: Clinical and demographic features

Item	Number (%)
55 patients (89%)	Male 43 (78%) Female 12 (22%) Mean age±SD (range) 59±12 years (38-87)
Symptoms	Hematuria 51 (92%) Dysuria and other lower urinary symptoms 18 (32%)
History	Smoking 33 (60%) urinary bilharziasis 8 (14%)
Histology	
Ta	9 (16%)
T1	34 (62%)
Tis	12 (22%)
BCG eligible	46 (84%) Received BCG 27 (59%) BCG shortage 19 (41%)

BCG: Bacillus Calmette-Guérin; SD: standard deviation

Table 2: Economic impact of BCG shortage on every patient

Item	Cost
Abha-Riyadh round trip (one person)	600 Saudi riyals
One-night hotel stay	300 Saudi riyals
One day budget (food and transportation)	300 Saudi riyals
Total cost for six visits (x6)	1200 × 6=7200 Saudi riyals

BCG: Bacillus Calmette-Guérin

the literature^[1,2] is perhaps related to the early presentation of our patients because of the free and quick access to the health facilities.

The 6-week induction schedule of BCG is still administered as described originally by Morales *et al.*^[12] In our institute, we are following these recommendations. However, the ideal maintenance schedule is less clear.^[13] The most commonly utilized maintenance schedule is 3-weekly instillations at months 3, 6, and 12, and beyond up to 3 years.^[5]

A total of 41% of our BCG eligible patients were referred to higher health services because of the BCG shortage in our institute. For the induction BCG therapy only, the approximate financial cost was 7200 Saudi riyals (1.745 €) on average per patient. This obviously has an economic impact on the health budget. The social and psychological impact of sending patients to higher centers for the BCG need to be addressed by future studies.

The BCG shortage has various clinical implications at different levels. First, the shortage of the vaccine may force physicians to lower the administered BCG dose or shift to less efficacious treatment options with potential implications on disease outcomes. Second, BCG shortage may lead to a reduction in maintenance courses resulting in, a possible, suboptimal treatment.^[14] It is not currently known whether such a reduction, for example, four instead of six instillations during induction and two instead of four during maintenance, is sufficient. Moreover,

the increased price of the only other available therapeutic options such as intravesical chemotherapy will increase the burden on patients as well as on health-care systems.^[15]

In the absence of sufficient BCG supply, mitomycin c (MMC) represents an appealing alternative to BCG when considering progression as the most important endpoint because results from individual patient data meta-analysis did not find a statistically significant difference between BCG and MMC in term of progression, cancer-specific or overall survival.^[5] After MMC induction, a maintenance course should be administered. The optimal maintenance is not clear yet. Nevertheless, the maintenance schedule for more than 1 year is generally not recommended.^[16] It should be stressed that intravesical MMC has a higher risk of recurrence but a lower risk of side-effects.

Device-assisted intravesical chemotherapy instillations such as microwave-induced hyperthermia and electromotive drug administration hold the promise to improve patient outcomes. The utilization of hyperthermia with local chemotherapeutics is reported to provide a synergistic effect for decreasing the proliferation of urothelial carcinoma.^[17] Data on patients treated with intravesical thermo-chemotherapy (hyperthermia and MMC) especially using Synergo radiofrequency-induced hyperthermia (Amstelveen, The Netherlands) showed low rates of recurrence and higher bladder preservation in comparison with MMC alone.^[17-19]

Intravesical gemcitabine, an antimetabolite could also be a reasonable alternative when BCG is not available.^[20,21] In fact, gemcitabine showed similar efficacy to BCG in intermediate-risk NMIBC and higher efficacy in BCG-refractory patients with a lower toxicity profile.^[22,23] Similarly, gemcitabine demonstrated higher efficacy and lower toxicity in comparison with MMC in patients with recurrent NMIBC as well as refractory NMIBC.^[24] Unfortunately, it was less effective than BCG in patients with high-risk NMIBC.^[25]

High-risk NMIBC (e.g. pT1HG/G3 ± CIS) represents a very challenging disease state. Despite adequate treatment with TUR and BCG, about 20% of patients experience disease progression to muscle-invasive bladder cancer. Radical cystectomy provides excellent oncological outcomes. However, up to 50% of patients will be overtreated if all high-risk patients undergo radical cystectomy.^[26] The proper selection of the optimal candidate for immediate radical cystectomy without overtreating patients likely to respond to BCG is the real dilemma.

The current status of BCG shortage should trigger an alarm to evaluate every possible therapeutic pathway to provide sufficient patient care. Responsible medical authorities should be encouraged to support domestic BCG production to provide optimal care for patients with NMIBC. The potential reduction in competition among manufacturers could result in more frequent and long-term drug shortages and an increase in the price of products. Accordingly, establishing nonprofit manufacturers

could improve competition and address generic drug market failure and supply market demand steadily.^[27]

It is the first study from Saudi Arabia to address this BCG shortage of economic impact on patients. Since it was a retrospective review and a quite short number of cases, this, however, debilitates its power. Large prospective comparative studies are warranted. Furthermore, the social and psychological impacts of BCG shortages on patients need to be deeply evaluated.

Conclusion

The BCG shortage in our institute has had an economic impact on the health budget. Such health catastrophe could be mitigated with proper health plans on the provision of the BCG to all tertiary care centers. Alternative therapies for such cases should be considered in cases of global BCG shortage. Domestic BCG manufacturing should be the optimal goal of health policy planners to encounter the BCG shortage and its health and economic consequences. Until the problem of BCG shortage is addressed, more efforts should be undertaken to identify predictive biomarkers to select the potential patients who are likely to respond to BCG immunotherapy.

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Conflicts of interest

There are no conflicts of interest.

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