



Editorial

The Implications of BCG Shortage for the Management of Patients with Non-Muscle-Invasive Bladder Cancers

Usama Nihad Rifat*

Emeritus Professor of Urology, Iraqi Board for Medical Specializations.

***Corresponding author:** Usama Nihad Rifat, Emeritus Professor of Urology, Iraqi Board for Medical Specializations, POB : 954410, Amman, Jordan

Citation: Rifat UN (2022) The Implications of BCG Shortage for the Management of Patients with Non-Muscle-Invasive Bladder Cancers. J Urol Ren Dis 7: 1245. DOI: 10.29011/2575-7903.001245.

Received Date: 05 February, 2022; **Accepted Date:** 08 February, 2022; **Published Date:** 11 February 2022

Bladder cancer is a global disease. It is the ninth commonest cause of cancer death in the UK, accounting for more than 5000 deaths per year. Around 80% of new cases are Non-Muscle-Invasive Bladder Cancers (NMIBC) of which approximately 20% carry a high risk of recurrence or progression to muscle-invasive disease (MIBC) [1]. The closure of BCG production factories, reduction of production, and the withdrawal of the BCG Connaught strain has led to a worldwide shortage of BCG [2]. As BCG is a live attenuated vaccine, there can never be a guarantee on its availability. Licensing other strains may provide an immediate solution [3]. Alternative therapies should be considered in cases of global BCG shortage [4].

Dispensing from adjuvant intravesical BCG treatment is associated with increased mortality in patients with T1 high-grade transitional cell carcinoma of bladder [5]. Research efforts are needed in future studies towards the development of effective BCG replacement vaccines [6]. BCG_{SD}, EPI and MMC exhibited established efficacy for preventing tumor recurrence in postoperative bladder cancer patients [7]. As an alternative is intra arterial, chemotherapy combined with intravesical chemotherapy [8] After resumption of normal production of BCG following the recent global shortage, Medicare Benefits Schedule (MBS) data suggests; prescription patterns for CIS are deficient. Such prescription patterns for CIS are conflicting with international guidelines reporting management strategies for NMIBC. There is a critical need for improved management of CIS in the current state of BCG availability [9].

Providing a second induction course of BCG may not be appropriate. Valrubicin, the only other FDA-approved intravesical therapy in previously defined BCG-refractory disease, has a poor complete response rate. Radical Cystectomy (RC) is the 'gold standard' for BCG-unresponsive disease, however, the high

morbidly associated with it excludes many patients from agreeing to undergo RC [10]. The persistent worldwide shortage of BCG began in 2012 with suspension of production of Connaught BCG in Canada due to a risk of fungal contamination. A new facility was constructed to supply BCG. Strict regulatory obstacles, recurrent shortages of production supplies, increased acceptance and use of BCG for bladder cancer. Furthermore, the limited profit in the production of BCG has led to long term, world-wide recurrent shortages. The shortage of BCG has resulted in the removal of bladders that could have been saved and increased tumor recurrence, morbidity, mortality and expense of bladder cancer.

The disastrous shortage of BCG for childhood vaccination is worsened by the increased recognition of the highest benefit and cost effectiveness of intravesical immunotherapy in bladder cancer. A single BCG instillation for bladder cancer requires potentially enough BCG to vaccinate as many as 1000 infants.

As a cancer treatment, BCG has long been criticized as a nonspecific immune stimulant whose mechanism is unclear. Recognition that this non-specificity is associated with protection from unrelated bacterial and viral pathogens, particularly respiratory virus infections possibly including COVID-19 could increase the demand for BCG and risk further reductions in the supply. The low profit of manufacturing BCG using current techniques provide no hope that the shortage will be relieved unless a new, more expensive and reliably-manufactured product such as recombinant BCG is approved.

Immunotherapy is an old treatment for cancer that was nearly discarded following the advent of chemotherapy in the early 20th Century, but recognition of the important role of the immune system in cancer control produced interest in the immune stimulation induced by BCG. In superficial high-risk bladder cancer, was BCG to become the clear treatment of choice.

Randomized clinical trials and real-world population studies have proved current BCG immunotherapy is superior to chemotherapy, and prevention of recurrence is long term in many patients [11]. It has been observed that OncoTICE is associated with a lower recurrence rate [12].

The increasing global demand for BCG led to worldwide shortage of Merck's TICE BCG [13]. The American Urological Association (AUA), American Association of Clinical Urologists (AACU), Bladder Cancer Advocacy Network (BCAN), Society of Urologic Oncology (SUO), the Large Urology Group Practice Association (LUGPA) and the Urology Care Foundation (UCF) remain extremely concerned about this ongoing shortage and its effects on the care of bladder cancer patients. Scott K. Swanson, President, American Urological Association, in his letter to members stated that there are efforts to engage the U.S. Food and Drug Administration to approve additional strains, supplies of BCG are continuing, Merck's stressed that their commitment to TICE BCG, while other companies have stopped production, is at the core of Merck's mission to save and improve lives. Their teams remain focused on maximizing the output and trying hard to provide additional supply of TICE BCG to patients. Although this will take years to be fully realized. BCG should not be used for patients with low-risk disease. Intravesical chemotherapy should be used as the first-line option for patients with intermediate-risk NMIBC. Patients with recurrent/multifocal low-grade Ta lesions who require intravesical therapy should receive intravesical chemotherapy such as mitomycin, gemcitabine, epirubicin, or docetaxel instead of BCG.

In conclusion, the global shortage of the BCG should be contained. Increased production and alternative therapies should be considered.

References

1. Nikhil Mayor, Christian Fankhauser, Vijay Sangar, Hugh Mostafid (2021) Management of NMIBC during BCG shortage and COVID-19. *Trends in Urology & Men's Health* 2021.
2. Brantley Thrasher (2020) TP-Bx: The answer to rising infectious complications?. *Urology Times Journal* 2020.
3. Vaibhav Modhil, Sophia Cashman (2016) The BCG shortage – what isn't the fuss about? *TRENDS IN UROLOGY & MEN'S HEALTH* 2016.
4. Mishari HM, Alamri A, Assiri AA (2020) 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, *Journal of Family Medicine and Primary Care* 9: 2758-2762.
5. Vladimir Novotny, Michael Froehner, Johanna Ollig, Rainer Koch, et al. (2016) Impact of Adjuvant Intravesical Bacillus Calmette-Guérin Treatment on Patients with High-Grade T1 Bladder Cancer, *Urol Int* 96: 136-141.
6. Patricia Mendez-Samperio (2019) Current challenges and opportunities for bacillus Calmette-Guérin replacement vaccine candidates. *Scand J Immunol* 2019: 12772.
7. Wu C, Zhou X, Miao C, Zhang J, Tang Q, et al. (2017) Assessing the Feasibility of Replacing Standard-Dose Bacillus Calmette-Guérin Immunotherapy with Other Intravesical Instillation Therapies in Bladder Cancer Patients: A Network Meta-Analysis, *Cell Physiol Biochem* 41: 1298-1312.
8. Bin Huang, Gaowei Huang, Wenji Li, Lingwu Chen (2021) Intra-arterial chemotherapy combined with intravesical chemotherapy compared with intravesical BCG immunotherapy retrospectively in high-risk non-muscle-invasive bladder cancer after transurethral resection of the bladder tumor. *Journal of Cancer Research and Clinical Oncology* 147: 1781-1788.
9. Marlon Perera, Nathan Papa, Daniel Christidis, Shannon McGrath (2018) The impact of the global bacille Calmette-Guérin shortage on treatment patterns: population-based data, *BJU Int* 121: 169-175.
10. Jacob Taylor, Ezequiel Becher, Gary D (2020) Steinberg, Update on the guideline of guidelines: nonmuscle-invasive bladder cancer, *BJU Int* 125: 197-205.
11. Lamma DL, Morales A (2021) A BCG success story: From prevention of tuberculosis to optimal bladder cancer treatment Vaccine 39: 7308-7318.
12. Matthew Hillen, Alex Rawlinson, Amy Slater, Caroline Coull, Ian Mitchell (2014) How the worldwide shortage of BCG (ImmuCyst) affected the management of high-risk, non-muscle invasive bladder cancer in a district general hospital. *International Journal of Surgery* 12: S13eS117.
13. AUA Members Communication October 2020 Announcement about BCG Production.