

Editorial

Bacille Calmette-Guérin Supply Disruption Emphasizes the Importance of Stewardship

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Since the original trial published by Morales et al in 1976, intravesical Bacille Calmette–Guérin (BCG) has been a centerpiece in non-muscle invasive bladder cancer (NMIBC) treatment, with a rigorous induction and maintenance regimen shown to decrease cancer recurrence and progression.^{1,2} More than 50% of the 81,000 new cases of bladder cancer that are diagnosed each year in the United States (US) (550,000 in the world) are NMIBCs, and it is clear that effective and timely treatments like BCG are essential and must be readily available.^{3,4}

A combination of increased bladder cancer incidence, early diagnosis of bladder cancer, drug properties, and manufacturing setbacks have contributed to recurrent BCG shortages.⁵ In addition, shortages are influenced by the unusual nature of BCG, a live microorganism that requires a sterile environment and between 1 to 3 months for a batch to grow.⁶ Furthermore, the quantity required for BCG instillation is much higher than for tuberculosis vaccination, the other primary use of BCG. It has been estimated that the quantity required for one induction course would be enough to vaccinate between 10,000 and 100,000 people.⁷ The shortages impact patient care. Khanna et al demonstrated a decrease of BCG utilization ranging from 0.62% increase per year in the period from 2004 to 2012 to 0.29% increase per year in the period between 2013 and 2015, highlighting the negative impact of supply disruptions.⁵

Other factors, such as production challenges and restricted supply, have contributed to BCG disruptions. Only two BCG manufacturers had been approved for use in the US; Sanofi (Connaught strain) and Merck (TICE strain). In 2011, Sanofi's Connaught strain production was suspended by the Food and Drug Administration (FDA) after mold contamination was detected in the production plant. Sanofi stopped manufacturing BCG for North America in 2017, further endangering the supply of the drug at a time of rising demand and leaving Merck as the sole supplier of BCG in the

US. Merck has also had production challenges. In 2014, a strain contamination halted the production of Merck's TICE, thus causing shortages in North and South America. Recently, Merck announced renewed supply constraints during the first quarter of 2019.⁸

In this new era of BCG shortage, proper disease stratification, correct medication selection, and patient preparation with optimal transurethral resection of bladder tumors are essential. For low-risk NMIBCs, BCG is not recommended, and, instead, patients should receive a single perioperative instillation of intravesical chemotherapy such as Gemcitabine, which has shown effectiveness, a better safety profile and lower cost compared to mitomycin, and is now the preferred agent for low-risk disease in 2019 National Comprehensive Cancer Network (NCCN) guidelines.^{9,10} For intermediate-risk NMIBC with low grade recurrent/multifocal disease, intravesical chemotherapy with gemcitabine, docetaxel or mitomycin, instead of BCG, are reasonable options. For high-risk NMIBC, all efforts should be made to treat with full-dose BCG, which has been proven superior to chemotherapy.¹¹ In the setting of supply disruption, alternative treatment strategies should be employed to maximize the impact of the limited resource. One of the alternatives to be considered is reducing the dose to 1/3 or a reduction of maintenance therapy from 3 years to 1 year for intermediate or high-risk patients without carcinoma in situ (CIS). In a study by Oddens et al, reducing the maintenance therapy from 3 years to 1 year was not inferior in intermediate-risk patients. For high-risk patients, there was an increase in cancer recurrence but no differences in mortality or progression.¹² Other alternatives include induction BCG alone, reserving BCG maintenance therapy for patients with the highest risk disease. When BCG is not available, intravesical chemotherapy with mitomycin, gemcitabine, doxorubicin, docetaxel or sequential combination therapies might be offered.¹³ Finally, in patients with the highest risk of

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progression (e.g., T1 with CIS), a timely cystectomy should be considered.¹⁴

Moving forward, it is essential to identify new agents and improve our shared intravesical therapy supply chain. Trials that could improve reliability in treatment should be supported. The Southwest Oncology Group (SWOG) is conducting the SWOG 1602 trial, which is currently enrolling and randomizes patients with high-risk NMIBC to induction and maintenance with TICE strain vs. Tokyo strain vs. priming plus Tokyo strain.¹⁵ The trial not only reduces the current demand for the TICE strain, but it may add another BCG strain to our armamentarium, if favorable.

Supply disruptions are not unique to bladder cancer or BCG. In recent years, shortages of drugs and devices have resulted from natural disasters, manufacturing problems, market forces, and unintended consequences of regulatory intervention.^{16,17} These disruptions bring in to stark relief the essential work that must take place to ensure a more robust supply chain—including prioritization of a flexible supply base and avoidance of sole source suppliers, when feasible, along with proper incentives for manufacturers to improve reliability.¹⁸

Conflict of Interest

The authors declare that there is no conflict of interest.

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