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Minireview

Treatment of High-Risk Non-Muscle Invasive Bladder Cancer with Immuno BGC Moreau RJ. The ENCORE-01 Trial

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Abstract

Up to now, intravesical bacillus of Calmette-Guerin (BCG) remains the only truly effective intravesical therapy for non–muscle invasive bladder cancer (NMIBC), with proven effects reducing recurrence and prolonging survival. BCG restrictions have had an obvious clinical impact on bladder cancer treatment. Because of this situation, NMIBC patients might have received fewer doses of BCG than those recommended, might have received instillations of different BCG substrains depending on the BCG availability in each region, might have received a reduced length of standard maintenance therapy, and so forth. Moreover, there was an increased number of patients who had to be treated by cystectomy. At this moment, neither the reduction of the doses, nor the number of doses, nor the combination with intravesical chemotherapy nor the new immunotherapy with checkpoint inhibitors, seems to be as effective as BCG treatment in high and intermediate risk NMIBC. A recent study comparing the effectiveness of intravesical BCG-Tice and BCG-Moreau RJ in patients with NMIBC has shown no differences between the two strains. Due to BCG Moreau do not have PDIM (phthiocerol dimycocerosates) and (phenolic glycolipids) PGL, which have been related to virulence of mycobacteria, less adverse events have been reported. Prospective trials are required to confirm these findings in light of the BCG shortage. The Spanish Foundation for Research in Urology (FIU) and BIOFABRI SLU have proposed a prospective trial using intravesical BCG Moreau RJ in patients with high risk NMIBC with the aim of having an additional and effective BCG to reduce the impact of potential new BCG restrictions in bladder cancer.

Introduction

Non–muscle invasive bladder cancer (NMIBC) represents approximately 75% of all newly diagnosed cases of bladder cancer, and high-risk NMIBC accounts for approximately one third of the disease burden [1]. Generally, high-risk NMIBC comprises any of the following: a) T1 tumour, b) G3 high grade tumour, carcinoma in situ (CIS), and, c) multiple, recurrent (i.e. refractory to initial intravesical mitomycin), and large (>3cm) TaG1 / G2 low grade tumours with all three features being present. After initial transurethral bladder resection (TUR) and intravesical chemotherapy (mitomycin, epirubicin, gemcitabine), intravesical BCG is recommended for the treatment of intermediate and high-risk NMIBC to reduce tumour recurrence [2].

Bacillus Calmette-Guérin (BCG) is a live attenuated form of Mycobacterium bovis. In 1976, the first use of intravesical BCG in the treatment of non-muscle invasive bladder cancer was reported [7], based on the 6-weekly instillation of 120 mg of BCG (Pasteur strain) schedule proposed by Morales [3]. Nowadays, the precise mechanism of action by which BCG exerts its therapeutic effects remains poorly understood. Probably acts by stimulating both an inflammatory tumour response and a primary innate immune response. Recently, Sapre et al reported that BCG induces release of several cytokines (including interferon

and interleukins) and finally, promotes the killing of cancer cells through a T-mediated cytotoxic reaction [4].

The closure of BCG production plants, reduction of production, and the withdrawal of the BCG Connaught strain manufactured by Sanofi Pasteur has led to a sustained worldwide shortage of BCG. Given the methodological complexity and high demands of BCG production, future shortages are to be expected [5]. Therefore, we need to get new strains of BCG to treat high and intermediate risk patients with NMIBC. Currently, we are conducting a clinical trial using the Moreau RJ strain, which causes the same immunological reaction as TICE, with fewer side effects. Shortly the recruitment will be finished and the first results about the efficacy of this strain in non–muscle invasive bladder cancer will be analysed.

Body

Instillation therapy with bacillus Calmette-Guérin (BCG) subsequent to transurethral resection (TUR) still represents the gold standard treatment for high-risk non-muscle-invasive bladder cancer (NMIBC) [6]. The guidelines of the European Association of Urology (EAU) suggest 6-weekly instillations during an induction phase [2], followed by a maintenance schedule for optimal efficacy [7, 8]. The Southwest Oncology Group (SWOG) found highly significant benefits regarding recurrence-free survival for a standard induction followed by a maintenance phase of BCG once weekly for 3 weeks and at 3, 6, 12, 18, 24, 30, and 36 months after BCG induction, as compared with BCG induction alone [9]. Bacillus Calmette-Guérin (BCG) has proven highly effective in non-muscle-invasive bladder cancer (NMIBC), but it can cause severe local and systemic side effects. Side effects requiring stoppage of treatment are seen more frequently in the first year, so not all patients are able to receive the 1-3 year of treatment recommended in current guidelines [10].

Between 2013 and 2016, the urological community faced the suspension of BCG Connaught strain production [11]. The reason was a yeast contamination following flooding at the production site. In response to this unprecedented crisis, drug agencies had to take restrictive measures for the use of BCG for bladder cancer. The production of BCG Connaught has now resumed, supported by an increased production of other strains (RVM and Tice), ending a period of unprecedented shortage. However, although the pharmaceutical industry seems to be responding to the demand by increasing production, there is no guarantee that this production will be maintained in the future. The BCG production process is old, difficult, and poorly valued. Therefore, it is not surprising that pharmaceutical companies halt production by economic choice, which was the case for BCG Connaught [12]. Recently, Ourfali et al have detected an increase in costs that have impacted in health services due to the decrease in BCG production, estimated at approximately 783 € per patient with a new diagnosis of NMIBC during the period of restricted supply [12]. In this time, the prices of chemotherapies used for bladder cancer intravesical therapy spiked dramatically during a 2014 BCG shortage [13, 14].

Second-line treatment options for use during BCG shortages have been suggested, though reliability of these alternatives is limited [15]: shortening of maintenance duration, reduction of doses, less number of doses, intravesical chemotherapy (or combination with BCG), novel methods to enhance MMC delivery… Although in certain situations doses can be reduced to reduce toxicity, the group CUETO showed that the minimum effective dose was one third [16, 17]. According to recent data from the EORTC trial that compares dose and duration of maintenance, the use of full doses is generally recommended for at least 1 year in medium-risk tumours, which can last up to 3 years in high-risk tumours [18]. Reducing number of BCG doses is other option in case of restriction. However, in the NIMBUS trial, a non-inferiority trial published by the European Organisation for Research and Treatment of Cancer (EORTC), the reduced frequency schedule was inferior to the standard schedule regarding the time to first recurrence and, therefore, recruitment was stopped to avoid harm in the reduced frequency BCG arm [19].

A limited number of studies have evaluated combination of intravesical chemotherapy and BCG. The association of chemotherapy with BCG seems to increase its efficacy, but only to reduce the probability of recurrence, with no effect on progression, associating greater toxicity, so it is only recommended in patients with tumours with a high recurrence rate [20]. Electromotive drug administration (EMDA) of MMC represents an alternative for BCG in patients with high-risk NMIBC refractory to BCG [21]. However, further studies are needed to demonstrate its effectiveness in both BCG-refractory bladder cancer and as first-line therapy for high-risk NMIBC [12]. On the other hand, checkpoint inhibitors may represent an alternative to BCG for NMIBC, which have shown efficacy in metastatic bladder cancer. At present, there is a phase III trial (KEYNOTE-676), currently recruiting, which aims to randomise over 500 patients by 2022 with persistent or recurrent high-risk NMIBC after BCG induction therapy. This will compare either continuation of BCG therapy alone (for up to three years) and treatment with BCG plus systemic pembrolizumab, for up to two years [22]. Studies of combination treatment with immunotherapy may also be utilised in the future, with newer molecules, in both the BCG-naïve and the BCG-unresponsive setting. These include antibody-drug conjugates such as enfortumab vedotin and sacituzumab govitecan, as well as vaccines, immunomodulatory drugs, and oncolytic viruses (23). There is a wealth of new opportunities on the horizon that hopefully will make NMIBC a more treatable condition, with the opportunity to offer patients bladder preservation with more confidence than we currently have [24]. Nevertheless, its efficacy has not yet been demonstrated in NMIBC using this expensive approach (the NHS indicative price for pembrolizumab -Keytruda®- is currently £2360 per 100mg) [25]. In conclusion, to date no recommendation can be made to use other therapy than intravesical BCG with maintenance as the first-line treatment of high-risk NMIBC patients [12].

While intensively studied, it is not clear yet by which mechanisms BCG immunotherapy mediates tumour immunity [26]. Based on recent evidence, BCG-induced specific tumour immunity seems likely because animals re-challenged with tumour cells following tumour challenge and BCG therapy mount an adaptive response and effectively eliminate these tumour cells [27, 28]. One of the main characteristics of mycobacteria is their cell wall, which contains long chains of mycolic acids, such as

phthiocerol dimycocerosates (PDIM) or phenolic glycolipids (PGL), that have been related to the interaction with host cells, are not equally present on the surface of the different BCG substrains.

Despite originating all strains of BCG from subcultures of the same Mycobacterium, passaging and subculturing through different distributors over the past decades, have selected mycobacteria with differential biological activity profiles, virulence, and reactogenicity. The genetic comparison of the different BCG substrains has demonstrated the deletion of some regions of their genomes, the inclusion of single-nucleotide polymorphisms or insertion sequences, or the appearance of tandem duplications. The first elimination of the Region of Differentiation (RD) 1 and point mutations in the original M. bovis strain generated the earliest BCG substrains, formed by the parent BCG and the first daughter strains: BCG Russia, Moreau, Japan, Sweden and Birkhaug. Later, the deletion of RD2 led to the late group of strains, which included BCG Prague, Glaxo, Danish, Tice, Frappier, Connaught, Phipps and Pasteur [14].

Owing to heterogeneity of retrospective series, lack of power and failure to administer maintenance cycles in prospective trials, there is a lack of robust evidence regarding superiority of one strain over the other. Therefore, current guidelines do not make any recommendation regarding the use of a specific strain [29]. As said before, identification of a more efficient strain and assessing its optimal administration schedule may improve oncologic outcomes in NMIBC, specifically because of the worldwide shortage in BCG availability [30]. Moreover, changes in the genetic background led in some cases to different mycobacterial phenotypes. For instance, BCG Moreau and Japan do not have PDIM and PGL, and both lipids have been related to the virulence and reactogenicity of mycobacteria [31].

M. bovis BCG Moreau RJ, the strain used for vaccine production in Brazil from 1927, is closely related to other more primitive strains, such as BCG Russia and Japan, believed to be similar to the original BCG [32]. But even with the long, continuous usage of this strain for vaccination of Brazilian children, little is known about BCG Moreau RJ physiology, when compared to BCG Pasteur [33]. In Brazil, there is extensive experience in treatment of NMIBC with BCG Moreau RJ, which appears to develop an immunological reaction similar to those produced with the TICE strain, but with less adverse events. Thus, BCG Moreau RJ treatment could be used more time than TICE for maintenance with the same doses, keeping immunologic status and better prophylaxis of recurrence or progression results for the patient. In this way, D´Andrea et al have compared retrospectively the efficacy of 2 bacillus Calmette-Guérin (BCG) strains, BCG-Tice and BCG-Moreau RJ, in the treatment of non–muscle-invasive bladder cancer (NMIBC). No differences in recurrence free survival (RFS) and progression free survival (PFS) were demonstrated for patients treated with BCG-Tice and BCG-Moreau RJ strains in patients with intermediate-and high-risk NMIBC. From their analysis, the authors concluded that prospective designed trials are required to confirm these findings in light of the BCG shortage [29].

From this point of view, the Spanish Foundation for Research in Urology (FIU) has proposed a prospective trial (NCT03982797; ENCORE-01), using BCG Moreau RJ (BIOFABRI SLU) in patients with high risk non-muscle invasive bladder tumour de novo or relapsed (with or without associated carcinoma in situ) or isolated carcinoma in situ and a risk of recurrence or progression greater or equal than 10 points according to CUETO tool, which was specifically designed to predict recurrence and progression in BCG-treated patients [34].

Each patient will be instilled via transurethral each time with 80 mg of IMMUNO BCG Moreau RJ. There are 15 instillations during the clinical trial, 6 instillations on induction phase (once per week during first six weeks after inclusion), and 3 instillations (one per week) on month three, another three on moth six and last three on month twelve, during maintenance phase. All patients must have undergone a second transurethral bladder resection as re-staging procedure (re-TUR). For NMIBCs, residual tumour rates may vary between 33 and 76% for all cases, including 27-72% and 33-78% for Ta and T1 tumours respectively [35]. Also, 7-30% of these patients are understaged after initial TURBT, increasing up to 45% when resection does not include detrusor muscle [36]. As a result, intravesical therapy do not appear to reliably compensate for inadequate resection and are not recommended to replace secondary resection, especially for high-risk NMIBC [37].

The primary objective of our trial is to assess the progression-free survival of patients diagnosed with high-risk NMIBC treated with IMMUNO BCG Moreau RJ adjuvant. The secondary objectives are to analyse the disease-free survival (DFS), the quality of life (using the Functional Assessment of Cancer Therapy-Bladder, FACT-BL 4th version), adverse reactions and the dropout rate due to toxicity. As an exploratory objective, the immune response will be measured by cytokine analysis in urine prior to instillation on induction visits 1, 2, 5 and 6. The cytokines to be studied in each and every one of the analysed are: CXCL10 (IP10), CXLCL9 (MIG), IL4, IL10, TRAIL, IL8 and IFNγ. To achieve these objectives, a sample size of 306 patients has been estimated. Currently, 15 Spanish centres have started recruiting patients for the trial which is expected to be completed by 2022. An intermediate analysis of the study will be carried out next June.

Conclusion

Up to now, it is fair to say that BCG remains the only truly effective intravesical therapy for NMIBC, with proven effects reducing recurrence and prolonging survival (35). BCG shortage periods have had an obvious clinical impact on bladder cancer treatment. NMIBC patients might have received fewer doses of BCG than those recommended, might have received instillations of different BCG substrains, might have received a reduced length of standard maintenance therapy. Moreover, there was an increased number of patients who had to be treated by cystectomy [13]. Recently, no differences between the effectiveness of intravesical BCG-Tice and BCG-Moreau RJ in patients with NMIBC have been shown [26]. Furthermore, less adverse events have been reported using the BCG-Moreau RJ strain. The Spanish Foundation for Research in Urology (FIU) and BIOFABRI SLU have proposed a prospective trial using BCG Moreau RJ

in patients with high risk NMIBC that will end recruitment in 2022, and whose first results will be analysed shortly.

References

1. Thomas F, Noon AP, Rubin N, et al. Comparative outcomes of primary, recurrent, and progressive high-risk non-muscle-invasive bladder cancer. Eur Urol Suppl. 2013;63(1):145-54.
2. Babjuk M, Burger M, Comperat EM, et al. European Association of Urology Guidelines on Non-muscle-invasive Bladder Cancer (TaT1 and Carcinoma In Situ) - 2019 Update. Eur Urol. 2019;76(5):639-57.
3. Morales A, Eidinger D, Bruce AW. Intracavitary Bacillus Calmette-Guerin in the treatment of superficial bladder tumors. Urol J. 1976;116(2):180-3.
4. Sapre N, Corcoran NM. Modulating the immune response to Bacillus Calmette-Guerin (BCG): a novel way to increase the immunotherapeutic effect of BCG for treatment of bladder cancer? BJU internat. 2013;112(6):852-3.
5. Mayor N, Fankhauser C, Sangar V, et al. Management of NMIBC during BCG shortage and COVID-19. Trends Urol Men Health. 2021;12:7-11.
6. Sylvester RJ, Rodriguez O, Hernandez V, et al. European Association of Urology (EAU) Prognostic Factor Risk Groups for Non-muscle-invasive Bladder Cancer (NMIBC) Incorporating the WHO 2004/2016 and WHO 1973 Classification Systems for Grade: An Update from the EAU NMIBC Guidelines Panel. Eur Urol Suppl. 2021;79(4):480-8.
7. Bohle A, Bock PR. Intravesical bacille Calmette-Guerin versus mitomycin C in superficial bladder cancer: formal meta-analysis of comparative studies on tumor progression. Urol. 2004;63(4):682-6; discussion 6-7.
8. Bohle A, Jocham D, Bock PR. Intravesical bacillus Calmette-Guerin versus mitomycin C for superficial bladder cancer: a formal meta-analysis of comparative studies on recurrence and toxicity. J urol. 2003;169(1):90-5.
9. Lamm DL, Blumenstein BA, Crissman JD, et al. Maintenance bacillus Calmette-Guerin immunotherapy for recurrent TA, T1 and carcinoma in situ transitional cell carcinoma of the bladder: a randomized Southwest Oncology Group Study. J urol. 2000;163(4):1124-9.
10. Brausi M, Oddens J, Sylvester R, et al. Side effects of Bacillus Calmette-Guerin (BCG) in the treatment of intermediate- and high-risk Ta, T1 papillary carcinoma of the bladder: results of the EORTC genito-urinary cancers group randomised phase 3 study comparing one-third dose with full dose and 1 year with 3 years of maintenance BCG. Eur urol. 2014;65(1):69-76.
11. Dal Moro F. BCG shortage in Europe. Prev Med. 2013;57(2):146.
12. Ourfali S, Ohannessian R, Fassi-Fehri H, et al. Recurrence Rate and Cost Consequence of the Shortage of Bacillus Calmette-Guerin Connaught Strain for Bladder Cancer Patients. Eur Urol Focus. 2021;7(1):111-6.
13. Davies BJ, Hwang TJ, Kesselheim AS. Ensuring Access to Injectable Generic Drugs - The Case of Intravesical BCG for Bladder Cancer. NEJM 2017;376(15):1401-3.
14. Guallar-Garrido S, Julian E. Bacillus Calmette-Guerin (BCG) Therapy for Bladder Cancer: An Update. Immunotargets Ther. 2020;9:1-11.
15. Fernandez-Gomez JM, Carballido-Rodriguez J, Cozar-Olmo JM, et al. Treatment of non muscle invasive bladder tumor related to the problem of bacillus Calmette-Guerin availability. Consensus of a Spanish expert's panel. Spanish Association of Urology. Actas urologicas espanolas. 2013;37(7):387-94.
16. Portillo JA, Madero R, Solsona E, et al. Influence of the true number of Bacillus Calmette-Guerin instillations on the prognosis of non-muscle invasive bladder tumors. Actas urologicas espanolas. 2014;38(5):280-4.
17. Ojea A, Nogueira JL, Solsona E, et al. A multicentre, randomised prospective trial comparing three intravesical adjuvant therapies for intermediate-risk superficial bladder cancer: low-dose bacillus Calmette-Guerin (27 mg) versus very low-dose bacillus Calmette-Guerin (13.5 mg) versus mitomycin C. Eur urol. 2007;52(5):1398-406.
18. Oddens J, Brausi M, Sylvester R, et al. Final results of an EORTC-GU cancers group randomized study of maintenance bacillus Calmette-Guerin in intermediate- and high-risk Ta, T1 papillary carcinoma of the urinary bladder: one-third dose versus full dose and 1 year versus 3 years of maintenance. Eur urol. 2013;63(3):462-72.
19. Grimm MO, van der Heijden AG, Colombel M, et al. Treatment of High-grade Non-muscle-invasive Bladder Carcinoma by Standard Number and Dose of BCG Instillations Versus Reduced Number and Standard Dose of BCG Instillations: Results of the European Association of Urology Research Foundation Randomised Phase III Clinical Trial "NIMBUS". Eur urol. 2020;78(5):690-8.
20. Solsona E, Madero R, Chantada V, et al. Sequential combination of mitomycin C plus bacillus Calmette-Guerin (BCG) is more effective but more toxic than BCG alone in patients with non-muscle-invasive bladder cancer in intermediate- and high-risk patients: final outcome of CUETO 93009, a randomized prospective trial. Eur urol. 2015;67(3):508-16.
21. Di Stasi SM, Giannantoni A, Stephen RL, et al. Intravesical electromotive mitomycin C versus passive transport mitomycin C for high risk superficial bladder cancer: a prospective randomized study. J Eur. 2003;170(3):777-82.
22. Boormans JL, Zwarthoff EC, Black PC, et al. New horizons in bladder cancer research. Urol oncol. 2020;38(12):867-85.
23. Kamat AM, Lerner SP, O'Donnell M, et al. Evidence-based Assessment of Current and Emerging Bladder-sparing Therapies for Non-muscle-invasive Bladder Cancer After Bacillus Calmette-Guerin Therapy: A Systematic Review and Meta-analysis. Eur Urol Oncol. 2020;3(3):318-40.
24. Alvarez-Maestro M, Guerrero-Ramos F, Rodriguez-Faba O, et al. Current treatments for BCG failure in non-muscle invasive bladder cancer (NMIBC). Actas Urol Esp (Engl Ed). 2021;45(2):93-102.
25. Gill J, Prasad V. Pembrolizumab for Non-Muscle-Invasive Bladder Cancer-A Costly Therapy in Search of Evidence. JAMA Oncol. 2021;7(4):501-2.
26. Pettenati C, Ingersoll MA. Mechanisms of BCG immunotherapy and its outlook for bladder cancer. Nat Rev Urol. 2018;15(10):615-25.
27. Rentsch CA, Derre L, Dugas SG, et al. Building on a Solid Foundation: Enhancing Bacillus Calmette-Guerin Therapy. Eur Urol Focus. 2018;4(4):485-93.
28. Larsen ES, Joensen UN, Poulsen AM, et al. Bacillus Calmette-Guerin immunotherapy for bladder cancer: a review of

immunological aspects, clinical effects and BCG infections. APMIS. 2020;128(2):92-103.
29. D'Andrea D, Soria F, Abufaraj M, et al. Comparative Effectiveness of Intravesical BCG-Tice and BCG-Moreau in Patients With Non-muscle-invasive Bladder Cancer. Clin Genitourin Canc. 2020;18(1):20-5 e2.
30. Abufaraj M, Mostafid H, Shariat SF, et al. What to do during Bacillus Calmette–Guérin shortage? Valid strategies based on evidence. 2018;28(6):570-6.
31. Leung AS, Tran V, Wu Z, et al. Novel genome polymorphisms in BCG vaccine strains and impact on efficacy. BMC Genom. 2008;9:413.
32. Abdallah AM, Hill-Cawthorne GA, Otto TD, et al. Genomic expression catalogue of a global collection of BCG vaccine strains show evidence for highly diverged metabolic and cell-wall adaptations. Sci Rep. 2015;5:15443.
33. Behr MA. BCG--different strains, different vaccines? Lancet Infect Dis. 2002;2(2):86-92.
34. Fernandez-Gomez J, Madero R, Solsona E, et al. Predicting nonmuscle invasive bladder cancer recurrence and progression in patients treated with bacillus Calmette-Guerin: the CUETO scoring model. J urol. 2009;182(5):2195-203.
35. Cumberbatch MGK, Foerster B, Catto JWF, et al. Repeat Transurethral Resection in Non-muscle-invasive Bladder Cancer: A Systematic Review. Eur urol. 2018;73(6):925-33.
36. Shindo T, Masumori N, Kitamura H, et al. Clinical significance of definite muscle layer in TUR specimen for evaluating progression rate in T1G3 bladder cancer: multicenter retrospective study by the Sapporo Medical University Urologic Oncology Consortium (SUOC). World J urol. 2014;32(5):1281-5.
37. Del Giudice F, Busetto GM, Gross MS, et al. Efficacy of three BCG strains (Connaught, TICE and RIVM) with or without secondary resection (re-TUR) for intermediate/high-risk non-muscle-invasive bladder cancers: results from a retrospective single-institution cohort analysis. J canc res clin oncol. 2021.

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