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The journey from the pioneering work of Albert Calmette and Camille Guerrin in the discovery of BCG vaccine for tuberculosis to development of BCG in the management of carcinoma *in situ* and high grade non-muscle invasive (NMI) bladder cancer is over 100 years old.[1,2] The story is not only exhilarating but also full of exciting endeavours from Coleys toxin and Zbars' rule to the development of immune checkpoint inhibitors. The concept and development of BCG as an immune booster in the defence against infectious diseases to a potent anti-cancer drug, owes to the "magic bullet" concept of Paul Ehrlich.[3]

BCG has become one of the most potent immunotherapeutic agents in the management of high-risk bladder cancer. It is the treatment of choice for Ta/T1 high-grade (HG) cancer, Ta low grade (>3cm) as well as for *carcinoma in situ (CIS)*. It is the standard of care for these types of NMI urothelial carcinoma (UC) as a first occurrence and for recurrent BCG naïve cancers. It is also treatment of choice in cases of recurrent cancer with prior BCG treatment, not yet a case for radical cystectomy.[4] Two major concerns in NMI urothelial cancer are recurrence and progression of the disease. BCG is highly efficacious in the prevention of both complications. In five meta-analyses, it has been shown that BCG is superior to transurethral resection of bladder tumor (TURBT) / TURBT + chemotherapy for the prevention of recurrence.[5] Two high quality meta-analyses have provided level 1a evidence in support of BCG in significantly lowering the progression rate.[6] BCG is most effective when administered in 5-6 cycles of induction with follow-up of maintenance treatment upto three years. The maintenance treatment is 3-weekly instillations at 3, 6, 12, 18, 24, 30 and 36 months.

BCG, however, is not an infallible remedy. It is not only associated with significant side effects, but there is also significant proportion of patients who fail BCG therapy. The terminology to describe BCG failure is standardised.

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BCG refractory tumors are high-grade or *CIS* NMI cancer presenting at 3-month or following re-induction or one-cycle of maintenance and/or if a high-grade tumor appears during maintenance. BCG unresponsive includes T1Ta/HG recurrence within six months of completion of adequate BCG exposure or if a patient develops CIS within 12 months of completion of adequate BCG exposure. BCG relapsing is a high-grade recurrence after complete response on completion of maintenance therapy. BCG intolerance is the term used for discontinuation of therapy mandated by significant side effects.[7]

BCG refractory/unresponsive cancers are considered as an aggressive variant with significant potential for metastases.[8] The standard of care in these patients is radical cystectomy (RC). RC is not only oncologically safe, but it also provides better cancer-free survival than any other bladder sparing modality. It may, at times, be an over treatment; albeit in a small proportion of cases. There is overwhelming evidence that delay in performing cystectomy for BCG refractory cancer can adversely affect the survival.

Many bladder-sparing regimens are available for patients unwilling or unfit for cystectomy. These include cytotoxic treatment with newer cytotoxic agents, chemotherapy combinations, new drug delivery systems, device instillations, vaccine, recombinant proteins, photodynamic therapy, oncolytic adenovirus, gene therapy (nadofaragenefirodenovac), and immune checkpoint inhibitors. The last two are of particular interest; and have received recent FDA approval. However, they should be considered experimental until wider clinical experience is reported.

Cancers express various proteins that make them appear foreign. This results in T cell mediated immune response. In order to avoid this cascade, tumors often express programme death ligand (PD L1). This adaptive tumor response turns the immune system off. In order to reactivate the immune system, PD and PDL1 need to be blocked. In a recent phase II trial, pembrolizumab efficacy was assessed in a study called Keynote 057. Patients with high-grade papillary UC were divided into two groups, *i.e.* with or without concomitant C*IS*. Complete response of UC with *CIS* was the primary end-point; whereas, CR of any disease, duration of response and safety and tolerability were the secondary end-points. The CR was just over 40%, mean duration of response was 16.2 months.[9]

In another interesting phase III study, a novel drug delivery

system, nadofaragenefiradenovac, for human IFNα2b gene, was studied. In a non-replicating adenovirus, gene of interest is inserted, the virus infects the cell and releases DNA that has significant anti-tumor activity. The anti-tumor activity is anti-proliferative, TRAIL (tumor necrosis factor apoptosis inducing ligand) mediated cytotoxicity and anti-angiogenic activity. The investigators concluded that intravesical nadofaragenefiraden-ovec was efficacious. Risk assessment indicates a favourable benefit: risk ratio, in patients with BCG-unresponsive NMI UC.[10]

The current European Association of Urology (EAU) guidelines indicate that standard of care for patients with BCG unresponsive disease is radical cystectomy (strong recommendation); whereas, evidence-favouring bladder preserving technique is weak. Close monitoring and early recognition of BCG unresponsiveness is important, as this shows aggressive cancer with significant potential for metastases.

REFERENCES

1. Calmette A. Preventive vaccination against tuberculosis with BCG. *Proc R Soc Med* 1931; **24(11)**: 1481-90.
2. Morales A, Eidinger D, Bruce AW. Intracavitary bacillus calmette-guerin in the treatment of superficial bladder tumors. *J Urol* 1976; **116(2)**:180-3. doi: 10.1016/s0022-5347(17)58737-6.
3. Ehrlich, P. Die Wertbemessungddes diphterieheilserums and derentheoretischgrundlagen. *KlinJahrb* 1897; **6**:299-326.
4. Witjes JA, Bruins HM, Cathomas R, Compérat EM, Cowan NC, Gakis G, *et al*. European association of urology guidelines on muscle-invasive and metastatic bladder cancer: Summary of the 2020 guidelines. *Eur Urol* 2021; **79(1)**:82-104. doi: 10.1016/j.eururo.2020.03.055.
5. Malmstrom, PU, Sylvester RJ, Crawford DE, Friedrich M, Krege S, Rintala E, *et al*. An individual patient data meta-analysis of the long-term outcome of randomised studies comparing intravesicalmitomycin C *versus* bacillus Calmette-Guerin for nonmuscle-invasive bladder cancer. *Eur Urol* 2009; **56(2)**: 247-56. doi: 10.1016/j.eururo.2009.04.038.
6. Sylvester RJ, van der Meijden APM, LammDL. Intravesical bacillus Calmette-guerin reduces the risk of progression in patients with superficial bladder cancer: A meta-analysis of the published results of randomised clinical trials. *J Urol* 2002; **168(5)**:1964-70. doi: 10.1097/01.ju.0000034450.80198.1c.
7. Kamat AM, Sylvester RJ, Böhle A, Palou J, Lamm DL, Brausi M, Soloway M, *et al*. Definitions, end points, and clinical trial designs for non-muscle-invasive bladder cancer: Recommendations from the international bladder cancer group. *J ClinOncol* 2016; **34(16)**:1935-44. doi: 10.1200/JCO.2015.64.4070.
8. Klaassen Z, Kamat AM, Kassouf W, Gontero P, Villavicencio H, Bellmunt J, *et al*. Treatment strategy for newly diagnosed T1 high-grade bladder urothelial carcinoma: New insights and updated recommendations. *Eur Urol* 2018; **74(5)**: 597-608. doi: 10.1016/j.eururo.2018.06.024.
9. Balar AV, Kamat AM, Kulkarni GS, Uchio EM, Boormans JL, Roumiguié M, *et al*. Pembrolizumabmonotherapy for the treatment of high-risk non-muscle-invasive bladder cancer unresponsive to BCG (KEYNOTE-057): An open-label, single-arm, multicentre, phase 2 study. *Lancet Oncol* 2021; **22(7)**:919-30. doi: 10.1016/S1470-2045(21)00147-9.
10. Boorjian SA, Alemozaffar M, Konety BR, Shore ND, Gomella LG, Kamat AM, *et al*. Intravesicalnadofaragenefiradenovec gene therapy for BCG-unresponsive non-muscle-invasive bladder cancer: A single-arm, open-label, repeat-dose clinical trial. *Lancet Oncol* 2021; **22(1)**:107-117. doi: 10.1016/S1470-2045(20)30540-4.