short review

memo (2019) 12:319–323
https://doi.org/10.1007/s12254-019-00527-6

memo
magazine of european medical oncology

Nonmuscle invasive urothelial cancer— Bacillus Calmette–Guérin instillation or checkpoint inhibitor immunotherapy?

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Received: 31 July 2019 / Accepted: 7 September 2019 / Published online: 27 September 2019

Summary To date, intravesical instillation of Bacillus Calmette–Guérin (BCG) is the standard adjuvant treatment for most intermediate- and all high-risk bladder nonmuscle invasive urothelial carcinomas (NMIBC) after complete transurethral resection. Although BCG immunotherapy successfully reduces both recurrence and progression rates in affected patients, there are certain limitations associated with its application. Major issues are the relatively high failure rate in up to 40% of patients, the adverse effects of the instillations, and the shortage in BCG supply, requiring concerted alternative strategies. Furthermore, radical cystectomy, the currently suggested salvage treatment for patients failing BCG therapy, is often an overtreatment for a significant proportion of patients. Checkpoint inhibitor (CKI) immunotherapy has proven to be highly effective in a subset of advanced bladder cancer patients and is currently tested in various clinical scenarios alone and in combination with BCG in the adjuvant setting. CKIs' mechanism is to a large part similar to that reported for BCG—that is, activation of the immune system and elimination of cancer cells in the bladder. Furthermore, CKIs could synergistically enhance the effect of the immune system attracted by BCG and are generally associated with acceptable rates of adverse reactions. Thus, they may represent an ideal alternative to or partner for BCG immunotherapy in NMIBC. In case the recent encouraging results of currently ongoing trials translate into tangible improved outcomes, the combination of CKI and BCG immunotherapy can be expected to represent a valid treatment strategy for well-selected nonmuscle invasive bladder cancer patients in the future.

Keywords High-risk bladder cancer · BCG therapy · BCG failure · BCG phase III trial · Salvage treatment

Take home message

- Bacillus Calmette–Guérin (BCG) instillation immunotherapy is the standard adjuvant treatment for most intermediate and all high-risk nonmuscle invasive urothelial carcinomas (NMIBC) after transurethral resection of the bladder (TUR/B)
- Intravesical BCG with maintenance therapy has proven effective in reducing recurrence as well as progression rates, but up to 40% of patients eventually become BCG unresponsive
- Radical cystectomy is the standard treatment for BCG unresponsive and intolerant patients, but is associated with significant morbidity rates often representing overtreatment in a subset of patients
- Checkpoint inhibition (CKI) immunotherapy has become an effective standard therapy for metastatic bladder cancer and could represent a promising alternative therapy in high-risk and BCG unresponsive bladder cancer alone or in combination with BCG

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- Interim results of the KEYNOTE-057 phase II trial evaluating pembrolizumab in high-risk bladder cancer patients unresponsive to BCG reported complete response rates of 40% at 3 months
- Further immunotherapy phase II and phase III trials testing CKI alone or in combination with BCG in the BCG unresponsive or naïve setting are currently ongoing and will determine which patients benefit most from CKI therapy in the adjuvant setting

BCG therapy and definition of BCG unresponsiveness

Adjuvant BCG therapy with maintenance for nonmuscle invasive high-grade bladder cancer (NIMBC) by BCG instillation therapy has been shown to reduce recurrence and progression to muscle-invasive disease [1]. Intravesical instillation of BCG is performed after complete transurethral resection of the tumor using a 6-weekly induction schedule and followed by maintenance therapy with the SWOG schedule being the most recognized [2]. Patients failing BCG can be categorized into three groups: BCG refractory, early and late BCG relapsing and BCG intolerant patients. BCG refractory patients present with persistent high-grade disease at 6 months after the start of induction therapy or show progression by grade or stage 3 months after the start of induction therapy. Early relapse is defined by tumor recurrence within 6 months of last BCG therapy. Both BCG refractory and early relapsing patients are termed "BCG unresponsive". Late BCG relapse is seen as recurrence after a disease-free state of at least 6 months or later after last BCG exposure and these patients have a better prognosis than BCG unresponsive patients [3, 4]. Currently ongoing CKI trials mainly focus on BCG naïve or unresponsive patients aiming at providing an alternative or enhancement through synergy to BCG therapy or an alternative to salvage radical cystectomy in the case of BCG unresponsiveness.

In this review, we want to discuss the effects of BCG and CKI therapy on the immune system for NMIBC therapy and highlight the most important clinical trials involving CKIs in the setting of NMIBC.

BCG and activation of the immune system

BCG is derived from a strain of attenuated *Mycobacterium bovis* and is thought to attach to bladder urothelium after instillation [5]. Attachment and uptake of the bacterium are a key step in innate immune system activation and cytokine expression, which subsequently attracts more innate immune cells to the bladder. The innate immune system then triggers a strong T helper 1 (T_H1) immune response involving the production of T_H1 cytokines. These T_H1 cytokines activate macrophages and CD8+ killer cells, which are able to eliminate infected cells [6–8]. A T_H2 helper cell response, however, has been correlated with BCG failure [9]. In order to enhance the effect of BCG, several trials have been testing the co-administration of the bacterium together with immunostimulating agents, such as interferon alpha (INFα), a cytokine that has been shown to induce bladder cancer apoptosis [10]. However, BCG plus INFα was not proven to be superior to BCG therapy alone, and agents that could boost the reaction of immune system towards BCG are currently a major area of research in BCG therapy optimization [11–13].

Checkpoint inhibitors and activation of the immune system

Activation of cytotoxic T-cell activity is, besides cytokine regulation, also modulated via specific receptors on T-cells or ligands binding to these receptors present on interacting cells [14]. PD-L1 is a ligand on malignant cells that can down-regulate T-cell activity by binding to PD-1 on T-cells [15, 16]. CTLA4 is a receptor on T-cells that transmits inhibitory signals when regulatory or antigen-presenting cells bind to it [17]. Monoclonal antibodies such as pembrolizumab, atezolizumab, or ipililumab targeting PD-1, PD-L1, or CTLA4 block transmission of inhibitory signals and are thus able to enhance T-cell activation [18]. In late-stage metastatic bladder cancer, CKIs have been shown to result in sustainable responses in approximately 20–30% of patients [19, 20]. Regarding side effects, CKIs are generally well tolerated with immune-related adverse events occurring in less than 17% of patients. Side effects are usually self-limiting, and only some patients need short-course immunosuppressive drugs or TNFα-receptor antagonists when glucocorticoids fail [21]. Response to CKIs depends on multiple factors involving molecular characteristics of the tumor and interaction with the immune system, but expression of PD-1/PD-L1, tumor mutational burden and tumor immune infiltration seem to play a role for adequate response [22]. In bladder cancer, NMIBC tumors have been reported to express lower levels of PD-1 than MIBC, but BCG infection can induce PD-L1 expression in regulatory T-cells [23]. Furthermore, PD-L1 is enhanced on tumor tissue after BCG treatment in BCG resistant patients, making combination or sequential CKI therapy a promising option [24]. Also, a subset of high-grade NMIBC harbor mutations in DNA damaged genes which are known to be associated with a higher mutational load potentially resulting in better response rates to CKIs [25].

Current trials for adjuvant NMIBC therapy

Due to the observed success rates in metastatic bladder cancer, CKI trials have recently also been initiated in the adjuvant setting for NMIBC. Table 1 gives an overview of currently ongoing, selected phase II and III trials. We especially want to highlight recent results for the single-arm KEYNOTE-57

Table 1 Current ongoing phase II and phase III trials evaluating CKI in high-risk NMIBC

Name	Phase	Treatment	Drug	Target	Population	No. Planned	Start date	End date	Study design	Primary endpoint
KEYNOTE-057 NCT02625961	II	Pembrolizumab, 200 mg, iv, every 3 weeks for up to 24 months	Pembrolizumab	PD1	BCG-unresponsive, ineligible for or refusal of RC	260	February 10, 2016	July 30, 2023	Single Group Assignment	CRR, DFS
KEYNOTE-676 NCT03711032	III	BCG + pembrolizumab iv every 3 weeks for 35 doses vs. BCG mono therapy	Pembrolizumab, BCG	PD1	HR NMIBC and treated with at least 1 course of BCG induction therapy	550	December 24, 2018	November 25, 2024	Randomized Parallel Assignment	% with CIS achieving CR
NCT03504163	II	Pembrolizumab after TUR as single agent, 3-week intervals for 9 doses	Pembrolizumab	PD1	HR T1 NMIBC	37	June 27, 2018	March 31, 2016	Single Group Assignment	% DFS
NCT02844816	II	Atezolizumab iv every 21 days for up to 17 cycles	Atezolizumab	PD-L1	Recurrent, NMIBC, unfit for RC, BCG-unresponsive	202	February 7, 2017	April 1, 2021	Single Group Assignment	CR at 25 weeks for CIS, event-free survival at 18 months in BCG-unresponsive
ALBAN NCT03799835	III	BCG + atezolizumab (every 3 weeks for 1 year) vs. BCG	Atezolizumab, BCG	PD-L1	HR NMIBC	614	January 17, 2019	February 1, 2028	Parallel Assignment	RFS
NCT02901548	II	Durvalumab iv every 4 weeks for 13 cycles over 12 months	Durvalumab	PD-L1	BCG unresponsive	34	February 16, 2017	December 31, 2021	Single Group Assignment	CR at 6 Months
NCT03759496	II	Durvalumab weekly intravesical for up to 6 weeks or until progression/toxicity	Durvalumab	PD-L1	HR NMIBC, refractory to BCG, intolerant to BCG	39	November 15, 2018	December 31, 2021	Single Group Assignment	Max tolerated dose, HGFR
POTOMAC NCT03528694	III	Durvalumab + BCG (IND + MAIN; IND only or BCG only)	Durvalumab	PD-L1	HR, BCG-naïve, previously BCG but stopped >3 years ago	975	May 14, 2018	November 25, 2024	Randomized Parallel Assignment	Efficacy of Durvalumab + BCG, DFS
CheckMate 9UT NCT03519256	II	Nivolumab vs. Nivolumab + BCG vs. Nivolumab + BMS-986205 vs. Nivolumab + BMS-986205 + BCG	Nivolumab, BCG	PD1	BCG-unresponsive	436	May 25, 2018	April 16, 2023	Randomized Parallel Assignment	CIS participants with CR, Duration CR, EFS
PREVERT NCT03950362	II	60–66 Gy in 30-33 Fractions to bladder; Avelumab before EBR, then 8 cycles Avelumab	Avelumab	PD-L1	BCG-unresponsive, HR, unfit for RC	67	June 15, 2020	June 15, 2024	Single Group Assignment	RFS at 1 year

BCG Bacillus Calmette–Guérin, *CIS* Carcinoma in situ, *CR* Complete response, *CRR* Complete response rate, *DFS* Disease-free survival, *EBR* External Beam Radiation Therapy, *EFS* Event-free survival, *HGFR* Rate of high-grade relapse free, *HR NMIBC* High-risk nonmuscle-invasive bladder cancer, *IND* induction, *MAIN* maintenance, *PD-L1* Programmed cell death 1 ligand 1, *PD-1* Programmed cell death protein, *RC* Radical cystectomy, *RFS* Recurrence-free survival, *TUR* transurethral resection

phase II trial evaluating pembrolizumab for NMIBC patients unresponsive to BCG. The latest trial update reported a 3-month complete response rate (CRR) of 40%, and a 53% maintained complete response for more than 9 months. Importantly, no progression to MIBC or metastatic disease was observed [26]. A phase III trial (KEYNOTE-676, NCT03711032) for pembrolizumab + BCG vs BCG monotherapy in patients having received at least one course of BCG induction therapy has recently been started, and pembrolizumab as single adjuvant therapy for high risk T1 NMIBC tumors is also being tested (NCT03504163). For all other CKIs, no trial results have been reported yet, but phase II trials for atezolizumab (NCT02844816), durvalumab (NCT02901548, NCT03759496), nivolumab (CheckMate 9UT, NCT03519256) and avelumab (PREVERT, NCT03950362) in the BCG unresponsive setting are ongoing. Noteworthy, phase III trials evaluating atezolizumab (ALBAN, NCT03799835) and durvalumab (POTOMAC, NCT03528694) are already actively recruiting.

Conclusion and further directions

A multitude of clinical trials assessing CKI therapy in BCG unresponsive patients as well as first-line combination therapy with BCG are being conducted, and—depending on outcomes of these trials—addition of CKI to BCG may become a standard option in the future, thereby, reducing the need for radical cystectomy. However, it is still unclear which patients respond to CKIs and which do not. From mechanistic studies in patients receiving CKIs, we know that tumors with sufficient PD-L1 expression, high in mutational burden/neoantigen load, and inflamed tumors are the most likely to respond to CKIs [27]. Current trials will need to evaluate whether combination with BCG can synergistically enhance CKI efficacy and lead to stronger immune responses without increasing adverse events, or whether only a subset of patients with adequate molecular profiles will profit from CKIs as therapy for high-risk NMIBC. In conclusion, there is no doubt that we are discovering dimensions to the therapy of NMIBC never seen before, and identifying the best therapy for each tumor in each patient at the right time may finally usher in an age of tailored immunotherapy.

Funding Open access funding provided by Medical University of Vienna.

Conflict of interest S.F. Shariat: Honoraria for lectures or consulting/advisory boards for Astellas, Astra Zeneca, Bayer, BMS, Cepheid, Ferring, Ipsen, Janssen, Lilly, MSD, Olympus, Pfizer, Pierre Fabre, Richard Wolf, Roche, Sanochemia, Sanofi, Takeda, Urogen. S. Brönimann and M.R. Hassler declare that they have no competing interests.

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