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Bacillus Calmette-Guérin (BCG) Refractory Non-Muscle-Invasive Bladder Cancer (NMIBC): Current Guidance and Experience from Clinical Practice

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Abstract: BCG is the standard of care for non-muscle invasive high-risk bladder cancer. Notwithstanding the high rate of cure, cancer may recur. A non-muscle invasive high-risk recurrence may be defined as BCG refractory or naïve. BCG refractory patients have been further divided into BCG unresponsive and BCG exposed. A recurrent high-risk bladder cancer within 1 year after BCG induction plus maintenance or two courses of BCG induction defines an unresponsive disease. Any recurrence after 24 months since induction and maintenance should be considered as BCG naïve. The remaining cases are BCG exposed. The standard of care for BCG exposed and naïve patients is another cycle of BCG in the first place, while radical cystectomy should be discussed as alternative with the patient. The preferred therapy for BCG unresponsive patients is radical cystectomy according to AUA or EAU guidelines. However, systemic immunotherapy with pembrolizumab or gene therapy with intravesical nadofaragene firadenovec may be administered for patients unfit or unwilling to undergo radical cystectomy with outcomes superior to intravesical docetaxel, gemcitabine or valrubicin. Our narrative review tries to elucidate BCG refractory definition and treatment specifically regarding alternative therapies to radical cystectomy yet approved or under investigation. The last years have been exciting regarding new developments in this field after a long period of stagnation. Unfortunately, data available on some alternative therapies are mainly limited mainly to Phase I or II studies with a lack of robust evidence, but a clear trend in future treatments has just been drawn.

Keywords: non-muscle invasive bladder neoplasms, BCG vaccine, intravesical drug administration, local neoplasm recurrences, clinical progression

Introduction

History of medicine has been plenty of serendipities. Bacillus of Calmette Guerin (BCG) has been one of them and eventually a success history. Simply put, it is the Mycobacterium bovis attenuated through several years of culture to mitigate its virulence. It is the vaccine against tuberculosis since it was first adopted in 1921. Random observation about neoplasms incidence in subjects recovered from tuberculosis lead to the empirical use of the vaccine to treat cancer. Since 1976 it was recognized as intravesical treatment for bladder cancer.[1] In 1991, the first clinical trial showed the superiority of BCG with respect to intravesical chemotherapy after transurethral resection of bladder tumors (TURBT).[2] Since then, many other trials have been published and eventually meta-analysis confirming the favorable impact on recurrence[3] and progression.[4] Nowadays, it is the standard treatment for non-invasive bladder cancer (NMIBC) at high risk of recurrence and progression after TURBT.[2] BCG is reserved to treat intermediate to high-risk NMIBC.[5–7] A high-risk relapse during or after BCG therapy may have many different outcomes.[5–7] Current guidelines incorporate BCG induction and maintenance schedule and identify different categories of high-risk bladder cancer recurrence during or after BCG immunotherapy, namely BCG refractory and BCG naïve tumors. BCG refractory tumors have been recently further

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divided into unresponsive[8] and exposed.[9] Since BCG has been an established therapy for bladder cancer, BCG refractory patients have been treated by means of radical cystectomy, according to guidelines, whenever possible. However, recently, ongoing or completed trials have demonstrated a significant impact on those patients from alternative therapies. We performed a narrative review to assess the definition of BCG refractory disease and to assess available treatments and recent advancements.

Materials and Methods

European and American guidelines were thoroughly reviewed trying to synthetize the common points and resolve discrepancies through clinical experience[6–8] A preliminary literature search was manually performed based on guidelines definition and treatment suggestions. Moreover, a systematic search of recent literature has been conducted to outline the current directions in the treatment of BCG refractory patients. On 28 August 2024, the subsequent keywords were used in PUBMED: "BCG refractory" or "BCG unresponsive". The search was limited to the last 10 years, clinical trials, randomized controlled trials, meta-analysis, reviews and systematic reviews. Overall, 129 papers were found and 14 were selected.[10–23]

Results and Discussion

What is a BCG Refractory Disease?

The definition of BCG resistance should be based on a proper management of bladder cancer that should be implemented in the first place. The outcome of BCG therapy and patient survival may be hampered by under staging or persistence of disease. This is the reason why a newly high-grade T1 cancer diagnosis always needs a second TUR to be performed before BCG induction because the rates of under staging or of persistent disease are significantly high.[24] The same goes for newly bulky Ta low- or high-grade disease especially if during the TUR it is not possible to identify healthy tissue at the tumor base.[24] Given the likelihood of loco regional spread or of involvement of the high urinary tract, a contrast scan (CT or MR) should be performed.[25] After a correct and complete assessment of the disease, BCG should be administered according to guidelines.[5–7] Follow-up should follow a strict schedule based on cystoscopy, urinary cytology, and contrast scan of the high urinary tract and of the whole abdomen.[26] Thereafter, different clinical scenarios may happen. The disease may not recur. It may recur at higher TNM stage, or a non-muscle invasive recurrence may occur. During follow-up, a urinary cytology positive for high-grade cancer, according to the Paris system, should be considered a high-grade non-invasive recurrence as it might be the unique expression of an undetected Cis after mired endoscopic (and random biopsies including prostatic urethra) and systemic examinations.[27] Radical cystectomy, radiotherapy, systemic therapies should be tailored according to the type of recurrence in the second case. Regarding the third case, there are two possibilities, a low-grade or a high-grade recurrence. Usually, low-grade non-muscle invasive recurrence has no significant impact regarding the quoad vitam prognosis in this setting. It may be treated with office fulguration preceded by cold biopsies or standard trans-urethral resection alone. BCG schedule should not be interrupted and follow up continued. However, multiple, greater than 3 cm, low-grade recurrence in patients aged 70 or more have a great likelihood of harboring an undetected part of high-grade cancer[28] and may be considered at high-risk as well as any high-grade recurrence according to EAU guidelines.[5]

A high-risk recurrence encompasses BCG unresponsive, exposed and naïve patients according to histology, BCG schedule and timing of the event. Regarding BCG schedule, it should be considered "adequate" induction (5/6 doses) and 2 doses of maintenance or a second induction in recurrent high-grade Ta/CIS or induction in recurrent T1 tumors. A recurrent T1 high-grade bladder cancer after BCG induction within 3 months from the first dose BCG, a recurrent TaT1 high-grade bladder cancer after adequate BCG within 6 months from the last dose of BCG and a recurrent Cis cancer after adequate BCG within 12 months from the last dose of BCG are BCG unresponsive cases. A recurrent Ta high grade or Cis after BCG induction only within 3 months from the first dose of BCG or any high-risk recurrence after adequate BCG after 12 months and 24 months before the last dose of BCG or any high-risk recurrence after inadequate BCG before 24 months from the last dose of BCG are BCG exposed cases. Any recurrence after 24 months from the last dose of BCG should be considered BCG naïve.[5–9]

What About BCG Therapy in BCG Naïve, Exposed, and Unresponsive Patients?

The trade-offs between risk of disease progression and side effects should always be at the ground of every clinical decision side by side with patients' perspectives.

BCG Naïve and BCG Exposed

If the benefit of another cycle of BCG in BCG naïve patients is clear,[3,4] the same cannot be told about BCG exposed which represents a category introduced by The International Bladder Cancer Group to ensure the correct allocation of patients in a grey zone[9] belonging to the BCG refractory group. Retrospective analysis of a large series shows that those patients were mostly treated with another cycle of BCG[29] or with chemotherapeutic agents, namely gemcitabine or mitomycin C.[30] A retrospective analysis of a large series, comprising 116 patients, assessing a second course of BCG induction in cases which now we would define "BCG exposed" showed a durable complete response rate of about 90% at 3-month and 66% at 3-year.[31] Recently, a trial with a genetically modified strain of BCG (in order to enhance immune response to BCG) showed a 50% complete response rate after 1 year.[32] Notwithstanding the limited evidence available, according to previous treatment habits,[29–31] a second BCG cycle may be a reasonable choice at the end. However, there is a lack of published prospective Phase III trials regarding BCG exposed to establish the best treatment choice.[33] Indeed, this is an area of huge future developments given the consistent number of ongoing trials centered on immune checkpoint inhibitors in combination with BCG, namely durvalumab (intravenous or intravesical) (NCT04106115, NCT03759496) nivolumab (intravenous) (NCT04149574), pembrolizumab (intravesical) (NCT03711032).[34] Moreover, intravesical gemcitabine in combination with BCG (NCT04179162) and erdafinitib, an FGFR inhibitor, is under evaluation in subjects carrying FGFR mutation (NCT04172675[35]).

BCG Unresponsive

The benefit of radical cystectomy for unresponsive BCG tumors is undebatable It is the first treatment of choice in guidelines.[6–8] 5-year cancer specific survival reaches 80% in patients with non-muscle invasive disease submitted to radical cystectomy before progression occurs.[6–8] However, patients may not be willing to undergo this procedure, which requires urinary deviation and is associated with a significant morbidity and mortality[36] and may affect greatly quality of life.[37] Moreover, fragile and complex comorbid patients may not be suitable for the procedure. Following a long period of stagnation, the last 10 years have been exciting in the research for alternative treatments and some of them[10–14] have been yet incorporated in non-European guidelines for selected patients[7,8] (Table 1). Those therapies may be divided in chemotherapeutic drugs, adenoviral vector-based gene therapy, immunostimulants, and immune checkpoint inhibitors. Overall chemotherapies have not shown enthusiastic results so far. Sequential intravesical instillation of gemcitabine and docetaxel has shown a 51% 2-year recurrence free rate for BCG unresponsive cases in a meta-analysis, being the best treatment in this category.[10] Intravesical valrubicin, another drug deemed to be a concrete alternative and FDA approved for the purpose, showed a 18% complete response rate for BCG unresponsive Cis after 6-month follow up.[11] Keynote 057 is Phase II study designed to assess the activity of intravenous pembrolizumab monotherapy in BCG unresponsive patients who were ineligible or did not want to undergo radical cystectomy. Pembrolizumab is an in immune check point inhibitor. It is a monoclonal antibody designed to inhibit the PD – 1 protein. Arm A included Cis with or without papillary tumor unresponsive to BCG and Arm B Ta T1 high risk without Cis unresponsive to BCG. Pembrolizumab was administered intravenously at the 200 mg dose every 3 weeks up to 2 years. The main endpoint was recurrence and progression free survival at 1 year. 38% of arm A and 43% of arm B were disease free at 1 year demonstrating a significant activity against unresponsive patients.[12] A phase III study with Pembrolizumab is ongoing comprising BCG exposed and unresponsive cases[34] and will be able to clear the role of the drug in the future. Nadofaragene is a non-replicating viral vector base gene therapy studied specifically for unresponsive BCG cancer. Data are yet mature. After 5-year follow up in a phase III trial enrolling 157 patients, 49% were cystectomy free, 43% in the Cis arm and 59% in TaT1 arm, complete response was maintained in 13% and 33% of the Cis and TaT1 arm respectively and overall survival was 80%.[13] More data are needed for definitive conclusions. However, survival is similar to radical cystectomy as first line therapy (with only half of the cases submitted to the procedure). Nogapendekin alfa inbakicept is an interleukin-15 receptor agonist given in combination with BCG. The QUILT-3.032 is ongoing study (NCT03022825) comparing

Table 1 Available Alternative to Radical Cystectomy in BCG Unresponsive Patients

Agent	Reference	Mechanism	Clinical Target	Status
Sequential intravesical gemcitabine and docetaxel	[10]	Chemotherapy	BCG unresponsive	Approved for clinical use
Intravesical valrubicin	[11]	Chemotherapy	BCG unresponsive carcinoma in situ	Approved for clinical use
Systemic pembrolizumab	[12,34]	Immunotherapy	BCG unresponsive (preferably after failure of other options given systemic side effects)	Approved for clinical use
Intravesical nadofaragene plus BCG	[13,23]	Gene therapy (adenoviral vector-based)	BCG-unresponsive	Approved for clinical use
Intravesical nogapendekin alfa inbakicept in combination with BCG	[14]	Immunostimulant	BCG-unresponsive	Approved for clinical use
Intravesical oncofid-P-B	[15]	Chemotherapy	BCG- unresponsive carcinoma in situ with or without papillary tumor	Not approved for clinical use
Intravesical cretostimogene	[16]	Gene therapy (adenoviral vector-based)	BCG unresponsive CIS/ high-grade Ta	Not approved for clinical use
Intravesical OncoTherad	[17]	Immunostimulant	BCG-unresponsive	Not approved for clinical use
Systemic atezolizumab	[18]	Immunotherapy	BCG unresponsive carcinoma in situ	Not approved for clinical use
Systemic durvalumab	[19]	Immunotherapy	BCG unresponsive with carcinoma in situ	Not approved for clinical use
Systemic sunitinib	[20]	Tyrosine kinase receptor inhibitor	BCG unresponsive	Not approved for clinical use
Intravesical electroMotive drug administration of Mitomycin C	[21]	Chemotherapy	BCG unresponsive	Not approved for clinical use
Intravesical CG0070	[22]	Gene therapy (oncolytic adenovirus)	BCG- unresponsive	Not approved for clinical use
Radiotherapy	NCT06310369	Radiotherapy combined with a radiosensitizer (nadofaragene firadenovec or TAR-200)	BCG- unresponsive	Not approved for clinical use
Intravesical photodynamic therapy	NCT03945162	An intravesical instillation of the photosensitizer TLD 1433 followed by activation with a 520 nm intravesical laser under general anesthesia	BCG- unresponsive carcinoma in situ with or without papillary tumor	Not approved for clinical use
Intravesical detalimogene voraplasmid	NCT04752722	Non-viral based gene therapy	BCG- unresponsive carcinoma in situ with or without papillary tumor	Not approved for clinical use
Intravesical releasing system of gemcitabine	NCT04640623 (Sunrise study)	Intravesical release of gemcitabine with or without cetrelimab (Immunotherapy)	BCG- unresponsive	Not approved for clinical use

intravesical Nogapendekin alfa inbakicept (NAI) plus BCG or NAI alone in BCG unresponsive. Preliminary data are available. Arm A cases were Cis with or without papillary tumor and arm B cases papillary TaT1 tumors without Cis treated by means of NAI plus BCG. Arm C cases were Cis with or without papillary tumor but treated only by means of NAI.[14] Arm C was closed early because the NAI activity was insignificant; only 2 patients out of 10 experienced a complete 3-month response rate. The median disease-free survival was 26 months in arm A and 19.3 months in arm B. Cystectomy rate was 7% in both arms.[14] Preliminary data are available of other agents that are not yet been included in guidelines. Oncofid P-B is a paclitaxel-hyaluronan conjugate. After intravesical induction (once a week, 12

instillations) and maintenance (once a month, 12 instillation) complete response was respectively 70% and 45%.[15] Cretostimogene grenadenorepvec is an oncolytic adenovirus. Intravesical instillation of Cretostimogene plus systemic Premluzimab was administered in a phase II study. The 1-year and 2-year complete response rate was 57.1% and 51.4%.[16] OncoTherad is composed by phosphate and metal salts (CFI-1) linked to glycosidic proteins (P14 and P16 proteins). It activates immune response. The complete response rate after 24 was 72.7%, whereas mean response duration was 14.3 months in the complete response group.[17] ElectroMotive drug administration of mitomycin C[21] and intravesical administration of the CG0070 oncolytic vector[22] also showed promising results, while Atezolizumab,[18] Durvalumab[19] and Sutinitb[20] had not reached satisfying outcomes. Finally, ongoing trials are trying to elucidate the role of radiotherapy (NCT06310369), of intravesical photodynamic therapy (NCT03945162), non-viral-based gene therapy (NCT04752722) and intravesical placed device releasing gemcitabine with or without immunotherapy (NCT04640623) (Table 1).

Conclusion

BCG refractory disease is a heterogeneous group which encompasses cases yet amenable of another BCG cycle, namely BCG exposed, and cases in which radical cystectomy represents the standard of care, BCG unresponsive. For many years intravesical instillation of chemotherapy drugs, mainly gemcitabine, docetaxel, and valrubicin were the only alternative available and viable. Recently, there has been an explosion of studies looking for alternatives that are more effective. Gene therapy, oncolytic adenovirus and immune checkpoint inhibitors are being under evaluation. Interim analysis and phase I or II studies have been completed. Pembrolizumab or nadofaragene has already been incorporated into non-European guidelines for the treatment of BCG unresponsive patients unfit or unwilling to undergo radical cystectomy. However, taken together, available data are limited, and there is a lack of phase III trials showing superiority to radical cystectomy in terms of oncological safety for all the options discussed.

Disclosure

The authors report no conflicts of interest in this work.

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