BCG infections

Tae-Hyoung Kim[1]
[1]Urology, Chung-Ang University, Seoul, South Korea

Abstract

Bladder cancer is commonly presented as a highly recurring superficial form. Following endoscopic resection, current practice recommends repeated intravesical instillation of the attenuated Bacillus Calmette-Guerin (BCG). BCG instillations are generally safe, with irritative voiding symptoms and flu like symptoms indicating treatment effect. However, less than 5% have presented with complications both localized and systemic. Early complications are generally systemic in nature, with low yield of microbiological diagnosis, whereas later complications tend to show granulomatous lesions, appearing later than 1 year or more since instillation. These complications are generally successfully managed with RIF, INH, and EMB, following treatment guidelines for tuberculosis. However, miliary tuberculosis may occur, requiring corticosteroid use and intensive care. Localized sites, with granulomatous mass lesions obstructing the genitourinary tract may require surgical management. The overall outcome is positive, however, in cases of vascular involvement high mortality may ensue.

List of Abbreviations

BCG – Bacillus Calmette-Guérin
EMB – Ethambutol
GoR – Grade of Recommendation
INH – Isoniazid
LoE – Level of Evidence
PCR – Polymerase Chain Reaction
PZA – Pyrazinamid
RIF – Rifampicin
TUR – Transurethral Resection
UTI – Urinary Tract Infection

Summary of recommendations

1. Irritative voiding symptoms and flu-like symptoms within 24–48 hours following intravesical BCG instillation is an expected inflammatory reaction (GoR B). Following this period, patients presenting with genitourinary or systemic symptoms should be suspected of BCG infection after excluding alternative diagnoses (GoR B).
2. Microbiologic diagnosis and/or histologic confirmation is recommended, but accompanies a high false negative rate, and clinical judgement with high suspicion based on history of previous BCG instillation is necessary (GoR C).
3. Local or systemic complications are treated with INH, RIF, and EMB for 2 months, followed by INH and RIF for 4 months. PZA is not recommended (GoR C).
4. In case of extensive systemic involvement, such as miliary tuberculosis, consider corticosteroid adjuvant therapy (GoR C).
5. In the presence of abscess, and/or genitourinary mass lesions, consider surgical treatment (GoR C).

1 Introduction

Bladder cancer most commonly presents as a superficial type, amenable to endoscopic surgery. However, approximately 90% of these patients will develop tumor recurrence. Since Morales et al. first

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introduced intravesical instillation of Bacillus Calmette-Guerin (BCG) to treat superficial bladder cancer in 1976, it has shown wide success, eradicating residual tumors in more than 60% of patients with papillary carcinoma and 70% of patients with carcinoma in situ [1].

Intravesical instillation of BCG utilizes the live attenuated strain of *Mycobacterium bovis* and has since become a mainstay adjunctive therapy for superficial bladder cancer. The procedure involves repeated instillations of BCG following endoscopic resection. A T-cell-centric delayed host response occurs in the damaged bladder mucosa, ultimately conferring a tumor immunotherapeutic potential in the process [2].

While usually well tolerated, BCG instillation is, ultimately, an iatrogenic UTI, running the risk of, however low, both local and systemic complications with some cases reaching fatal results. Hence, the proper understanding of the various forms of presentation of BCG induced adverse events and their management is necessary when treating superficial bladder cancer patients with intravesical BCG instillation.

2 Methods

A systemic literature search was performed for the last 30 years in MEDLINE with the terms “Bacillus Calmette-Guerin”, “BCG”, “superficial bladder cancer”, “intravesical instillation”, and “complications” to identify literature pertaining to the subject since its introduction. Only peer reviewed articles written in the English language were included.

The studies were rated according to the level of evidence (LoE) and the grade of recommendation (GoR) using ICUD standards [3], [4].

3 Scope of clinical response and complications

3.1 Self-limiting response

The difficulty in properly collating evidence defining BCG related complications primarily lies in its nature as a form of UTI. Patients commonly experience self-limiting symptoms along the spectrum of irritative voiding to flu-like symptoms following instillation [5], [6]. Patients commonly complain of urgency, dysuria, frequency, and even hematuria, as well as low grade fever and malaise, limited, mostly within 24 to 48 hours following instillation. However, this is expected, as the therapeutic action of BCG itself involves release of a wide spectrum of inflammatory cytokines and local recruitment and infiltration of neutrophils, monocytes, and T-lymphocytes [7]. In fact, elevated levels of IL-2 have been suggested to correlate with a positive outcome, whereas low levels suggested a greater likelihood of tumor recurrence [8], [9], [10]. Hence, these symptoms are generally regarded as a sign of adequate treatment effect [11]. These presentations are similar to those following BCG vaccination and are expected to pass without further treatment [12], [13].

3.2 Systemic complications

The incidence of systemic BCG infection has been reported to present from 3 to 7% [13], [14], [15], [16]. The scope of these complications range from fever, malaise, chills, sweats, weight loss, shortness of breath, and arthralgia, and accounts for one third of cases involving BCG infection [13], [14], [15], [16]. However, less commonly complications such as hepatitis [17], [18], [19], [20], [21], [22], [23], polyarthritis [24], [25], [26], or prosthetic joint infection [27] have also been reported, suggesting high level of clinical suspicion is required addressing atypical infective symptoms following BCG instillation.

Most systemic presentations generally appear earlier, within 8 to 12 weeks following instillation and up to 1 year [13]. Several risk factors for developing BCG systemic infection have been suggested, such as, recent interval to procedures breaching urothelial mucosal integrity, and poor technique during administration [28], [29], [30]. However, the paucity of studies constituted only anecdotal evidence, further aggravated by the possibility a missed diagnosis where confirmation by culture or PCR assay might have provided false negative results. Two studies have failed to show correlation between time from recent TUR to BCG instillation [6], [16].

The importance of a high level of suspicion in diagnosing these patients is again stressed, as previous literature show that culture of biopsied tissue was less likely to yield positive results (31%) compared to

later forms of more localized presentations (64%) [13]. However, many cases might have missed diagnosis due to lack of utilizing newer PCR-based assays [16], [30], [31].

The most dangerous complication is systemic sepsis, characterized by chills, fever, hypotension, and progressive multiorgan failure. The incidence is reported to be 0.3–0.4% [6], [13], [32].

3.3 Localized complications

In contrast to systemic complications, localized complications generally occur later (>1 year in most literature), without generalized symptoms such as fever and chills. Biopsy of the affected tissue reveals non-caseating granulomas, and there is higher probability of positive cultures for mycobacteria than earlier systemic diseases [33], [34], [35], [36], [37], [38], [39], [40]. While most localized complications occurred in areas in contact with the urinary tract (penis, prostate, bladder, kidney), distant localizations in the vasculature [41], [42], [43], [44], [45], [46], [47], [48], [49], [50], [51], vertebrae [28], [29], [30], [49], chest wall [52], and other granulomatous abscess in rarer localizations have been reported [53], [54], [55] [56].

Granulomas are uniformly present, and the disease appears to have been spread by either contiguous or hematogenous means.

Genitourinary complications presented as abscesses or ulcerations in tissue in direct contiguous contact. Bladder [35], penile [57], prostate [58], and renal [40], [59], [60], [61] generally present as a localized abscess with a benign course of disease. However, rare complications involving the vasculature, resulting in aneurysms have shown poorer prognosis with mortality rate of 15.8% [41], [42], [62].

4 Diagnosis

Microbiologic and histologic diagnosis can be performed, however, some cases are reported solely based on clinical manifestations. Diagnosis by acid-fast bacilli staining was 25.3%, 40.9% for mycobacterial culture, and 41.8% for PCR-based assays [16]. Granulomatous inflammation was present in 86.3% of biopsied cases.

5 Treatment

With an overall lack of clinical trials, as well as due to the paucity of cases reported, there is no clear guideline. However, most reports suggest the use of antituberculosis medications with or without corticosteroids or surgery. Standard recommended therapy for *M. tuberculosis* of INH and RIF for 6 months with a 2 month intensive phase including EMB is generally recommended [63], [64]. Alternatively, Gonzalez et al. recommended the treatment regimen of 9 months, as BCG is intrinsically resistant to PZA, requiring a longer treatment period [13]. Some strains (Connaught, Tice, RIVM) have shown to be resistant to cycloserine [65]. Connaught BCG strain is susceptible to fluoroquinolones, and reports have shown successful treatment replacing RIF and INH [13], [57], [65], [66], [67]. Corticosteroids were mostly used in the presence of miliary tuberculosis [18], [64].

No trial has tested whether or not terminating, delaying or continuing BCG instillation was appropriate. However, the consensus suggests discontinuation of BCG instillation in case of previous systemic BCG infection [13], [64], [68].

6 Outcomes

The overall prognosis is good, however, Asín et al. presented an overall mortality of 5.4%. No studies reported risk factors for poorer outcomes, while Asín et al. found age older than 65, disseminated infection, and vascular involvement to be significantly related to higher mortality in a composite study of collected patients from a single institute and comparable case review of the literature [16].

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Corresponding authors: MD, PhD Tae-Hyoung Kim, Chung-Ang University, Urology, 102, Heukseok-ro, Dongjak-gu, 06973 Seoul, South Korea, Phone: 82-2-10-8870-2099, E-mail: kthlmk@nate.com

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