THE USE OF HALF DOSE BCG FOR INTRAVESICAL IMMUNOTHERAPY IN NON MUSCLE INVASIVE BLADDER CANCER

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Abstract

Introduction: Intravesical Bacillus Calmette-Guérin (BCG) immunotherapy is now considered as the treatment of choice for intermediate and high-risk non muscle-invasive bladder cancer (NMIBC), but there are variations with regard to the optimal use of BCG in NMIBC adjuvant treatment.

Material and methods: In a prospective observational study 23 patients with intermediate and high-risk NMIBC underwent adjuvant intravesical Bacillus Calmette-Guerin instillation therapy after a complete TUR-BT. Patients received six weekly instillations of half dose BCG, 3 mo rest, and three further weekly instillations of half dose BCG. Maintenance therapy with three weekly instillations at 6, 12, 18, 24, 30 and 36 months.

Results and limitations: Twenty-three patients were included, complete response rate at the first control (recurrence free cystoscopy at 3 months after start of treatment) was 100%. Based on a median follow up of 29 month, no BCG-refractory (progression in stage or grade by 3 mo after first cycle of BCG) and no BCG-resistant (recurrence or persistence after 3 mo after the induction cycle) patients were observed. At one year no tumor recurrence or progression was observed. None of the patients receiving intravesical therapy stopped treatment do to toxicity.

Conclusions: Bacillus Calmette-Guerin maintenance with half dose BCG proved effective. Complete response rate with half dose intravesical BCG immunotherapy were similar to those with complete dose from literature. The half dose had acceptable toxicity, mainly local side effects: cystitis 76% respectively and grade 1 gross haematuria 10%.

Keywords: Bacillus Calmette-Guerin, Intravesical immunotherapy, Non-muscle-invasive bladder cancer

Introduction

The primary approach to the management of intermediate and high risk non muscle invasive bladder cancer (NMIBC) is transurethral resection of the bladder tumor (TURBT) followed by intravesical immunotherapy with Bacillus Calmette-Guerin [1,2]. The intravesical administration of BCG produce an immune response cascade, which is responsible for the tumoral apoptosis [3,4].

Intravesical BCG immunotherapy is now considered as the treatment of choice for intermediate and high-risk non muscle-invasive bladder cancer (NMIBC), but there are variations with regard to the optimal use of BCG in NMIBC adjuvant treatment. In a prospective observational study 23 patients with intermediate and high-risk NMIBC underwent adjuvant intravesical Bacillus Calmette-Guerin instillation therapy after a complete TUR-BT. Patients received six weekly instillations of half dose BCG, 3 mo rest, and three further weekly instillations of half dose BCG. Maintenance therapy with three weekly instillations at 6, 12, 18, 24, 30 and 36 months.
risk NMIBC [5], but there are variations with regard to the optimal use of BCG in NMIBC immunotherapy [6]. The optimal dose is unknown, most studies used the standard dose which is a global standard of care based on the Southwest Oncology Group (SWOG) maintenance schedule [7]. To decrease the toxicity of BCG and improve patients long time adherence, some authors have proposed reducing the dose of instilled BCG [8], showing no overall difference in efficacy [9].

**Objectives**

Evaluate the efficacy of half dose intravesical BCG in our patients and to provide more information regarding the “half dose” in the prevention or delay of disease progression and tumor recurrence.

**Material and methods**

23 male patients with intermediate and high-risk NMIBC (Table I) underwent adjuvant intravesical Bacillus Calmette-Guerin instillation therapy after a complete TUR-BT and single, immediate instillation of 50mg Epirubicin [2].

The tumoral stage and grade, significant prognostic factors for recurrence, progression and survival were established at our hospital’s Pathological Department, according to tumor-node-metastases (TMN) system for tumoral stage (depth of invasion), and according to the World Health Organization (WHO) 1973 classification and WHO 2004 classification for tumoral grade.

Based on number of tumors, tumor diameter, stage and grade patients were categorized into intermediate- and high-risk groups according to EORTC scoring system [1]. Six patients were with high risk (TaT1 high grade (G2/G3) papillary urothelial neoplasms with or without CIS) and the other eighteen were considered as intermediate risk group (TaT1 low grade G1/G2 large or/and multiple and recurrent tumor) patients.

BCG was administered at minimum 4wk after TUR-BT, but in the most cases the 6 wk interval was preferred. Patients included were without urinary tract

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infections (UTI) and without haematuria before instillations. Two different BCG stains were used (BCG-medac and ImmuCyst). The standard dose of 81 mg was reduced to half, regarding toxicity and financial considerations.

The BCG maintenance schedule was based on the Southwest Oncology Group (SWOG) regimen of six weekly instillations followed by three weekly instillations at 3 and 6 months and every 6 months for three years [7].

Patients were informed about possible side effects for an early recognition, and educated for post instillations behavior: the solution containing BCG to be held in bladder for two hours, to change position in every 15 minutes for an optimal contact with the bladder wall and voiding in sitting position.

The BCG containing serum was administered with a proper catheterization technique into an empty bladder passively by gravity. Ofloxacin 200 mg and Indometacin suppository were administered twice at each instillation after the first urination to reduce the local discomfort and side effects [10].

Results

On the basis of a median follow-up of 29 months, with a mean of 29.17±18.88 months, no BCG-refractory (progression in stage or grade by 3 months after first cycle of BCG) and no BCG-resistant (recurrence or persistence after 3 months after the induction cycle) patients were observed. At one year no tumor recurrence or progression was observed. One BCG relapsing patient at 13 months with a nested subtype developed in submucosal layer.

The complication rate associated with BCG instillations was 37% (95%CI [32%-42%]) from overall instillations and includes mainly local side effects. 76% of the complications were cystitis 76% (95%CI [67%-93%]), grade 1 gross haematuria 10% (95%CI [5%-16%]), orhiepididimitis 2% (95%CI [0%-6%]), and fever with or without general malaise 11% (95%CI [6%-19%]) resolved in 48 hours with or without antipyretics. 64% (95%CI [58%-69%]) from absolute number of instillations had no adverse events.

BCG-associated systemic side effects were less frequent. One patient presented after the second cycle of maintenance systemic BCG reactions treated with ethambutol, pirazinamin, and sinerdol for 3 months. Instillations were suspended but restarted at patient’s strong demand.

Discussions

Initially the instillations were started between 3-6 weeks after a complete TUR-BT according to the SWOG regimen [7,10], but at the 6 week starters the intensity of local side effects was less higher than in the others, so we decide to make the first instillation at 6 weeks after TUR-BT in all patients who undergo intravesical immunotherapy.

Several studies suggest that a 6-wk induction course alone is not sufficient to an optimal response and the...
maintenance therapy is mandatory [11,12,13,14]. The Southwest Oncology Group (SWOG) reported the most significant impact of maintenance therapy with full dose BCG on disease free survival [7], the 3-wk maintenance schedule leads to the best outcomes in terms of reducing progression, recurrence and mortality in NMIBC, are further supported by the European Organization for Research and Treatment for Cancer (EORTC) 30911 trial [13], and the Japanese Cooperative Study [14]. For this reason we adopt for our patients the SWOG regimen.

A consensus about the optimal dose and schedule for BCG has not been established. Morales replying to an editorial comment “this regimen is arbitrary, and may be modified in the future as additional data become available” [19]. Most studies and meta-analyses have utilized the full 81 mg dose, and this remains the global standard of care. Evidence suggests that one-half and one-third dose produce similar benefits in preventing recurrence and progression as the standard dose [15,16,17,18].

Because our median follow up is only 29 mo comparing to the 77 mo of the SWOG study, the recurrence free survival is not comparable, but in the SWOG study two thirds of the patients stopped BCG due to side effects in the first six months and many patients failed to complete the full course of treatment. In our small group none of the patients receiving intravesical therapy stopped treatment do to toxicity. Our initial tumor-free response rate was complete (100%) comparing to the literature 84% [20, 21].

Some authors consider the use of quinolones as a potential effectiveness lowering factor because may affect the viability of BCG [22], but the International Bladder Cancer Group recommendations contains the use of ofloxacin twice after each BCG for prevention of Bacillus Calmette-Guerin associated adverse events. In our patients the frequency and intensity of adverse events decreased markedly after the usual administration at each patient.

Conclusions

Bacillus Calmette-Guerin maintenance with half dose BCG proved effective. There was no need to stop BCG administration for toxicity reasons. Dose reduction, use of ofloxacin and patient education are strategies that help prevent BCG-associated adverse events. The first step in improving compliance with maintenance BCG is to ensure that physicians are both believe and trust in value of BCG instillational therapy.

References


