

Research Report

Hyperthermic Intravesical Chemotherapy for BCG Unresponsive Non-Muscle Invasive Bladder Cancer Patients

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Abstract.

Background: Adjuvant intravesical instillations with *bacillus Calmette-Guérin* (BCG) is the recommended treatment option for patients with intermediate- and high-risk non-muscle invasive bladder cancer (NMIBC). Despite adequate BCG treatment, a large proportion of patients experience a recurrence. Although radical cystectomy is the gold standard for BCG unresponsive NMIBC, some patients are unfit or unwilling to consider this option.

Objective: To assess the effectiveness of Hyperthermic IntraVESical Chemotherapy (HIVEC[®]) in BCG unresponsive NMIBC patients.

Methods: A *post-hoc* analysis was conducted of prospectively included intermediate- and high-risk NMIBC patients who were planned to receive HIVEC[®] treatment between October 2014 and November 2017. For the present analysis, only patients who met the BCG unresponsive definition were included. Patients were followed by cystoscopy and cytology every 3 months and a CT-urography scan yearly. The primary outcome was the disease-free survival (DFS). The Common Terminology Criteria for Adverse Events (CTCAE) was used to assess side-effects.

Results: The study population consisted of 55 BCG unresponsive NMIBC patients of whom 52 underwent ≥ 5 HIVEC[®] treatments. The median age and follow-up were 73 years and 14.0 months (IQR 7.6–24.6). The median DFS was 17.7 months (SE 6.72) and progression occurred in four patients. The 1-year cumulative incidence rate of disease recurrence/progression was 53%. Two patients experienced severe side-effects (CTCAE ≥ 3).

Conclusions: HIVEC[®] seems a valid treatment option for BCG unresponsive NMIBC patients. We report a median DFS of 17.7 months (SE 6.72), potentially avoiding or postponing the need for radical surgery in a proportion of these patients.

Keywords: BCG unresponsive, BCG, bladder cancer, chemo-hyperthermia

INTRODUCTION

The global incidence of bladder cancer is 430,000 patients per year [1]. Roughly 75% of patients present with non-muscle invasive bladder cancer (NMIBC)

[2]. Adjuvant intravesical instillations with *bacillus Calmette-Guérin* (BCG) is the recommended treatment option for patients with intermediate- and high-risk NMIBC [3]. Treatment with BCG typically includes a 6-week induction course followed by 3 weekly instillations at 3, 6, 12, 18, 24, 30 and 36 months. This BCG maintenance regimen has shown to reduce the risk of recurrence in intermediate- and high-risk NMIBC patients [4, 5]. Nonetheless,

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approximately 50% of patients will develop a recurrence within 5 years after BCG treatment and even a proportion of patients experience progression to muscle invasive bladder cancer (MIBC), which negatively impacts survival [6–8]. Some patients experience recurrent disease despite adequate BCG treatment, which is defined as having had ≥ 5 of 6 weekly induction instillations followed by ≥ 2 additional instillations of maintenance therapy or a second re-induction course of 6 BCG instillations. In addition, patients can experience disease recurrence because they did not receive adequate BCG treatment due to BCG intolerance or shortage [9]. A number of concepts have been published of how disease recurrence during or after BCG treatment should be defined [10–14]. Consequently, comparing salvage therapies in patients failing BCG has been hindered by the lack of standard definitions and studies that combined different classes of BCG-failure. Therefore, the International Bladder Cancer Group (IBCG) recently defined BCG unresponsive NMIBC to truly define patients who fail BCG. BCG unresponsive disease includes patients who experience high grade tumor recurrence within 6–9 months from the last BCG exposure despite adequate BCG treatment [9]. The prognosis of BCG unresponsive NMIBC patients is poor and radical cystectomy is currently the recommended treatment option in these patients [15]. However, many patients have comorbid conditions, are elderly or are simply not willing to undergo radical surgery. The optimal therapy in such cases is unknown, as established and effective salvage intravesical therapies are not yet available [15]. The European Association of Urology and International Consultation on Urologic Diseases (EAU-ICUD) does not endorse salvage intravesical gemcitabine, valrubicin, or IFN α , in patients who fail BCG, but chemo-hyperthermia is recommended as a promising treatment modality [16]. The objective of the present study was to assess the effectiveness and safety of hyperthermic intravesical chemotherapy (HIVEC[®]) in BCG unresponsive NMIBC patients, who were unfit or unwilling to undergo immediate radical cystectomy.

MATERIALS AND METHODS

Study design

A *post-hoc* analysis was conducted of prospectively included intermediate- and high-risk NMIBC (urothelial carcinoma) patients who were planned to

receive HIVEC[®] treatment between October 2014 and November 2017 at three institutions: Erasmus Medical Center, Rotterdam, the Netherlands, the Netherlands Cancer Institute, Amsterdam, the Netherlands and the Royal Surrey County Hospital, Guildford, United Kingdom. Protocol has been approved by a local Institutional Review Board, under number MEC-2015-077. Patients were eligible for inclusion in the present study if: i) the criteria for BCG unresponsive disease were met: i.e. adequate BCG treatment (at least 5/6 induction and 2/3 maintenance instillations) and high grade tumor within 6 to 9 months of the last BCG exposure [9], ii) had histologically confirmed high-grade NMIBC (WHO classification system 1973: Grade 2 or 3, WHO 2014: High-grade), including papillary NMIBC alone (Ta or T1), *carcinoma in situ* (CIS), or a combination of CIS and papillary disease.

Treatment schedule

The HIVEC[®] treatment schedule at the Erasmus Medical Center consisted of 10 intravesical instillations (four weekly induction instillations, followed by six monthly maintenance instillations). The treatment schedule at the Netherlands Cancer Institute and the Royal Surrey County Hospital consisted of 12 intravesical instillations (six weekly induction instillations, followed by six monthly maintenance instillations). Intravesical instillations with Mitomycin-C (MMC) were administered at a concentration of 80 mg diluted in 50 mL of distilled water. The solution was extravasically heated up to 41–43°C and recirculated during 60 min at 200 mL per min at stable pressure. All instillations were conducted with the Combat BRS system V2.0, which was used according to manufacturer's instructions (Combat Medical, Wheathampstead, UK). Only patients who completed at least 5 HIVEC[®] instillations were included in the effectiveness analysis. Safety was analyzed in all patients.

Follow-up, primary outcome and statistical analysis

All patients were followed by cystoscopy and cytology every three months and biopsies were performed if cystoscopy showed a recurrence or cytology showed a suspicion of the presence of urothelial carcinoma. A CT-scan of the urinary tract was performed once a year. The primary outcome was the disease-free survival (DFS), defined as the

time from start of first HIVEC[®] treatment until disease recurrence and/or progression. Recurrence was defined as histologically confirmed diagnosis of high-grade urothelial carcinoma, while progression was defined as histologically or radiologically confirmed diagnosis of MIBC or metastatic disease. For patients presenting with (concomitant) CIS, the secondary outcome was the complete response (CR) at 3 months, defined as the absence of CIS, high-grade disease or progression by cystoscopy and cytology or biopsy. The Kaplan-Meier method was used to generate estimates of DFS. Patients were censored at the date of disease recurrence/progression or date of last cystoscopy. Safety end points included: type, incidence, severity of adverse events (AEs) and severe (\geq grade 3) AEs (SAEs), as assessed by the Common Terminology Criteria for Adverse Events v5.0 (CTCAE). Adverse events were reported by the clinicians of each participating center. Risk of tumor recurrence was estimated by the cumulative incidence of recurrence/progression at 3,6,9 and 12 months. Statistical analysis was performed using IBM SPSS statistics for windows, version 24.

RESULTS

A total of 55 BCG unresponsive NMIBC patients who were planned to receive HIVEC[®] treatment were included. Table 1 lists the baseline characteristics of the patient cohort. Three patients had not completed at least 5 HIVEC[®] instillations, so 52 patients were included in the effectiveness analyses. The median follow-up was 14.0 months (IQR 7.6 – 24.6) and did not significantly differ between patients who remained disease free (N=26), and patients who experienced recurrence or progression (N=26) during follow-up (12.8 vs 19.0 months, respectively) ($P=0.41$). The overall median DFS was 17.7 months (SE 6.72) (Fig. 1a). The median DFS in patients with papillary disease only (N=22) was 28.8 months (SE 11.9), while the median DFS in patients having (concomitant) CIS (N=30) was 17.7 months (SE 6.1) (Fig. 1b, $P=0.55$). The median DFS in ‘very high risk’ BCG unresponsive patients (T1 or T1+CIS, N=12) was 12.1 months (SE 4.6) (Fig. 1c). At 3 months, 21 out of 30 (70%) patients having (concomitant) CIS had a CR. The 1-year cumulative incidence rate of disease recurrence/progression was 53%. Table 2 lists the cumulative incidence rates at the 3,6,9 and 12 months of follow-up.

Table 1
Patient and tumor characteristics of 55 BCG unresponsive NMIBC patients

Baseline characteristics (N = 55)	
Age (median & range)	73 (34 – 87 yrs)
Hospital	
Erasmus Medical Center	21 (38%)
Netherlands Cancer Institute	17 (31%)
Royal Surrey County Hospital	17 (31%)
Gender	
Male	48 (87%)
Female	7 (13%)
T-stage	
Ta	15 (27%)
T1	9 (16%)
Ta + CIS	1 (2%)
T1 + CIS	3 (6%)
CIS only	27 (49%)
Tumor Grade	
G2 (HG)	4 (7%)
G3	24 (44%)
CIS only	27 (59%)
EAU Risk group	
High	55 (100%)
BCG	
Unresponsive	55 (100%)
HIVEC instillations	
≥ 5	52 (95%)
< 5	3 (5%)

Therapy for disease recurrence or progression

Overall, 26 patients (50%) remained disease free, 22 patients (42%) experienced recurrent disease and four patients (8%) experienced progression to MIBC or metastatic disease during follow-up. Of the 22 patients experiencing recurrent disease, 11 (50%) underwent radical cystectomy (pathology showed: pTisN0 in 7, pT1N0 + CIS in 2, pT3aN0 in one, and for one patient we could not retrieve pT-stage because he underwent cystectomy in another hospital. The last patient is currently planned for radical cystectomy. Four patients received rechallenge treatment with BCG, four remained under endoscopic surveillance, one patient underwent curative external beam radiotherapy and one patient received intravesical gemcitabine. Of the four patients who had progressive disease, one underwent palliative chemotherapy, one underwent palliative chemotherapy with radiotherapy, one is currently undergoing neo-adjuvant systemic chemotherapy and one received best supportive care due to liver metastases (Table 3). Bladder cancer related death during follow-up occurred in two patients.

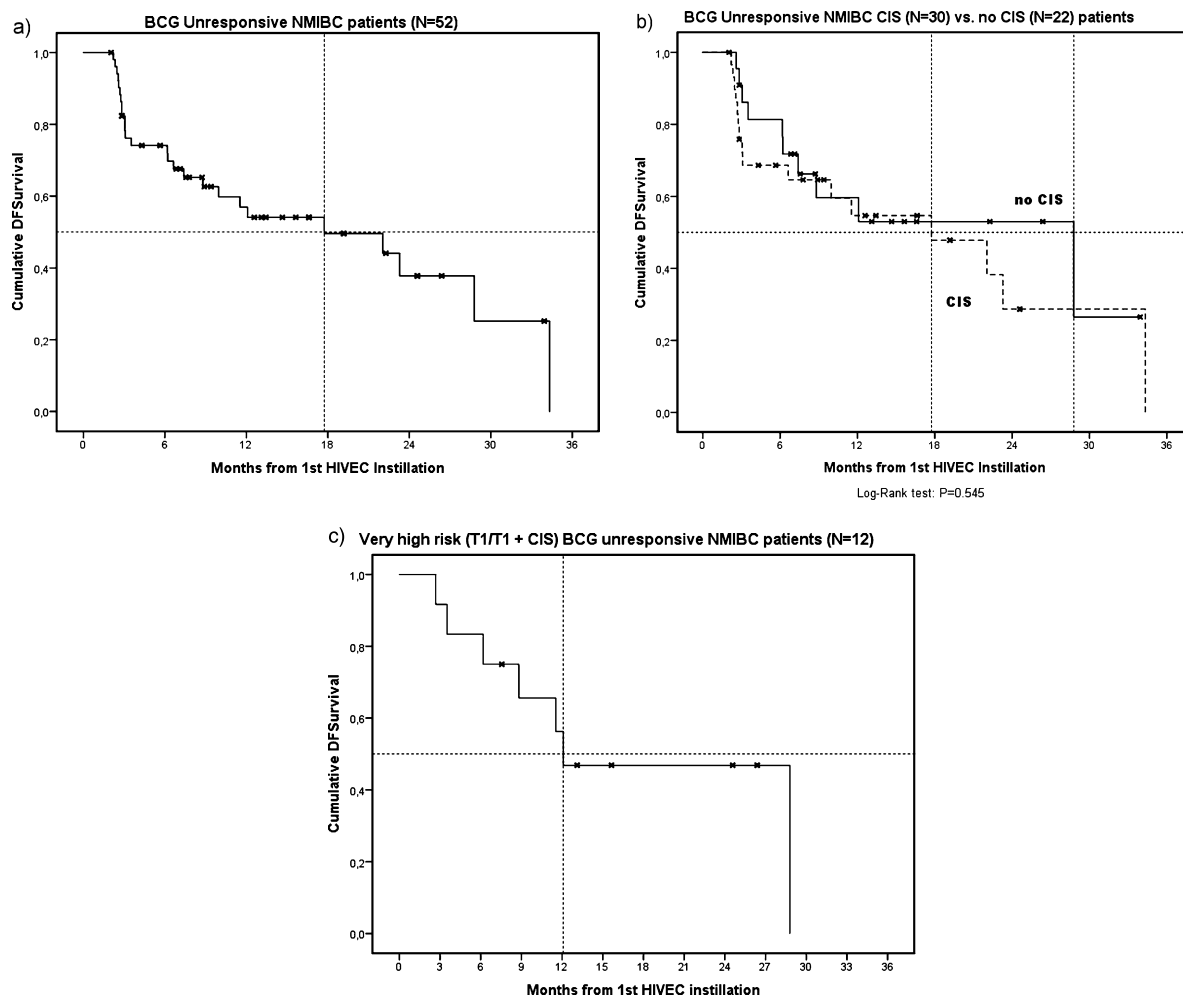


Fig. 1. Kaplan Meier curves showing DFS after HIVEC® treatment in BCG unresponsive NMIBC patients (a), BCG unresponsive NMIBC CIS versus no CIS patients (b) and 'very high risk' BCG unresponsive NMIBC patients (c).

Table 2
Cumulative incidence rates of patients who underwent ≥ 5 HIVEC® instillations (N = 52) at 3,6,9 and 12 months of follow-up

Follow-up moment	No of recurrent patients	Patients still under FU	Cum. Patients censored	Cum. Incidence rate
3 months	13 (6 persistent CIS)	52	0	25% (13/52)
6 months	4	48	4	35% (17/48)
9 months	2	43	9	44% (19/43)
12 months	2	40	12	53% (21/40)

Adverse events

Of the 55 patients, three (5%) did not complete at least 5 HIVEC® instillations, because of an AE – facial swelling, urticaria, and urinary tract pain, respectively). For 38 patients (69%) at least one AE during the instillation course was reported, whereas 17 patients (31%) had no side effects. Table 4 lists

all experienced AEs. All treatment-related AEs were CTCAE graded and no patients had grade IV or V AEs. Two SAEs (\geq grade 3) were reported (severe urinary tract pain and a urinary tract infection for which IV antibiotics were indicated) and occurred among the patients who did complete a minimum of 5 HIVEC® instillations. In the patient with severe urinary tract pain, HIVEC® treatment was stopped

Table 3

Treatment modality for patients who experienced recurrence or progression under HIVEC[®] treatment (N = 26)

Treatment modality	No of patients (%)
Recurrent disease (N = 22)	
Radical Cystectomy	11 (50%)
Planned for Radical Cystectomy	1 (4%)
BCG rechallenge	4 (19%)
Endoscopic surveillance	4 (19%)
Curative external beam radiotherapy	1 (4%)
Intravesical gemcitabine	1 (4%)
Progressive disease (N = 4)	
Neo-adjuvant chemotherapy	1 (25%)
Palliative chemotherapy	1 (25%)
Palliative chemotherapy + radiotherapy	1 (25%)
Best supportive care	1 (25%)

Table 4

Reported adverse events during HIVEC[®] instillations

Adverse events (N = 55)	No of patients (%)
No side effects reported	17 (31%)
Bladder spasms	
Grade 1	4 (7%)
Urinary frequency/urgency	
Grade 1	6 (11%)
Grade 2	13 (24%)
Urinary tract infection	
Grade 2	4 (7%)
Grade 3	1 (2%)
Urinary tract pain	
Grade 1	2 (4%)
Grade 2	5 (9%)
Grade 3	1 (2%)
Rash acneiform	
Grade 1	4 (7%)
Urticaria	
Grade 1	1 (2%)
Flu-like symptoms	
Grade 1	3 (5%)
Abdominal pain	
Grade 1	1 (2%)
Edema face	
Grade 1	1 (2%)
Dry skin	
Grade 1	1 (2%)

after the fifth instillation. It settled in two weeks with conservative treatment. The patient with severe urinary tract infection was successfully treated with IV antibiotics. Hematuria was reported among all patients with a urinary tract infection. One patient experienced a transient ischemic attack during the course of HIVEC[®] treatment, but not on the day of instillation, so this event was considered as not directly related to treatment.

DISCUSSION

BCG unresponsive NMIBC is a clinical challenge in daily urologic practice because of the high risk of

recurrence and progression. The gold standard for BCG unresponsive NMIBC is radical cystectomy, which is a surgical procedure with high morbidity rates. Many patients therefore seek bladder sparing cancer management. So, the management of BCG unresponsive NMIBC has been identified as an unmet clinical need by the FDA [15]. We report a median DFS of 17.7 months and a 1-year cumulative incidence rate of 53% in 52 BCG unresponsive NMIBC patients, who were treated with HIVEC[®]. Furthermore, data from previous studies suggest that immediate cystectomy after BCG failure is not strictly mandatory, but rather that modest and efficient radical cystectomy after an attempt at salvage intravesical therapy can be an effective strategy [15]. Many salvage therapy options have already been investigated as alternatives to radical surgery in the BCG failure setting [17, 18], but the various definitions of BCG failure precluded comparison of studies. Implementing a uniform definition for BCG unresponsiveness is necessary to be able to make a comparison between single armed trials, evaluating the efficacy of new agents after BCG immunotherapy. Therefore, the IBCG defined BCG unresponsive disease with the aim to encourage uniformity in clinical trial design. Furthermore, given the high risk of disease recurrence, a placebo-controlled arm is not ethical in BCG unresponsive disease, so experimental single armed trials with new agents are now being conducted [19]. Kamat et al. stated that agents showing DFS rates of 30% at 12 months in such trials are considered to have a clinically meaningful magnitude of effect [9]. In the present study, we report a 53% cumulative incidence, meaning 47% of the patients being disease-free at 12 months of follow-up (Table 2). As compared to other agents investigated in BCG unresponsive trials, HIVEC[®] has a similar performance. For example, Shore et al. reported 35% of the patients remaining free of high-grade recurrence at 1 year after intravesical rAd-IFN α /Syn3 treatment, and Li et al. reported a DFS of 34.8% at 1 year with Mycobacterium phlei Cell wall-Nucleic Acid complex (MCNA) [20, 21]. Valrubicin is currently the only Food and Drug Administration (FDA) approved intravesical agent, although only approved for BCG-refractory CIS, showing a modest DFS rate of approximately 10% at 12 months [22].

Hyperthermia is thought to have several beneficial effects on the treatment of bladder cancer with MMC, such as increasing the penetration of MMC into the urothelium and increasing its cytotoxicity [23,

24]. In their meta-analysis, Lammers et al. showed 59% less recurrences after chemo-hyperthermia compared with MMC alone in NMIBC patients [25]. The most studied application of chemo-hyperthermia is the Synergo HT[®] system, in which local hyperthermia is administered via microwave irradiation of the urothelium. During HIVEC[®], MMC is extravasically heated by the Combat BRS system and recirculated, maintaining a high bladder temperature. No randomized comparisons between both systems have been performed yet. Several studies with proportions of BCG failure patients included using the Synergo HT[®] system, have been performed [26–29]. The overall reported 1-year DFS rates were higher than reported in the present study, but how many of these patients failing BCG therapy, actually met the definition of BCG unresponsive NMIBC is unclear. In a study conducted by Witjes et al. 45 out of 49 (92%) patients having (concomitant) CIS, had a CR at 3 months after treatment with the Synergo HT[®] system, but this was not a BCG unresponsive CIS population [30]. Sousa et al. studied the efficacy of HIVEC[®] in a heterogeneous NMIBC population and showed a 4-year cumulative incidence of recurrence (CIR) of 20.8% in patients who received HIVEC[®] as a neoadjuvant treatment (before transurethral resection of a bladder tumor (TURB)) versus a 2-year CIR of 12.5% in patients who received HIVEC[®] as adjuvant therapy (post-TURB) [31]. However, how many patients from their cohort met the BCG unresponsive definition was also not defined.

Regarding the HIVEC[®] safety profile, most AEs were mild or moderate (CTCAE ≤ 2) in severity and only 3 patients did not complete at least 5 HIVEC[®] instillations, because of an AE. No patients had grade IV or V AEs and in two patients SAEs (\geq grade 3) were reported. The observed treatment related AE rate (69%) is comparable to instillations with MCNA (65.9%) and lower than intravesical rAd-IFN α /Syn3 treatment (85%) in BCG unresponsive NMIBC patients [20, 32].

Our study has several limitations. First, patients were retrospectively classified to the criteria of BCG unresponsive disease. So, in cases of inaccuracies on the number and regimen of BCG treatments prior to referral, patients had to be excluded, leading to a reduced sample size. However, the data on the 52 included patients was all prospectively recorded, so documentation during follow-up was accurately conducted. Second, the three participating hospitals did not apply a similar regimen for HIVEC[®] treatment. However, both regimens applied the first 5

instillations weekly, which made us use this as a criterion when considering a patient as ‘treated’ in the effectiveness analysis. Of note, the median DFS did not significantly differ between the two treatment regimens ($P=0.83$). A prospective observational study on HIVEC[®] treatment in BCG unresponsive patients would overcome these issues.

CONCLUSION

In a cohort of 52 BCG unresponsive NMIBC patients, who received ≥ 5 HIVEC[®] instillations, including 30 patients with (concomitant) CIS, 50% of the patients remained disease free after a median follow-up of 14.0 months. This corresponds to a median DFS of 17.7 months. HIVEC[®] treatment was well tolerated and only three patients had to stop treatment because of side-effects. Therefore, we conclude that HIVEC[®] treatment might be a feasible option in BCG unresponsive NMIBC patients, potentially avoiding or postponing the need for radical surgery in a proportion of these patients.

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CONFLICT OF INTEREST

JJJ received travel grants from Combat medical to attend scientific meetings, KH, MR and HM have no conflicts of interest to report, JLB received travel grants from Combat medical to attend scientific meetings and has received honoraria by MSD, Roche, BMS and Janssen Pharmaceuticals for consultancy work. Combat medical had no participation in the design of the study, the collection of the data and data analysis, and writing process of this manuscript.

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