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ARTICLE

Adverse events of hyperthermic intravesical chemotherapy for non-muscle invasive bladder cancer patients

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ABSTRACT

Introduction: Non-muscle invasive bladder cancer (NMIBC) is one of the most frequent neoplasms in Denmark. Treatment of high-risk NMIBC usually consists of transurethral resection of bladder (TUR-B) followed by intravesical Bacillus Calmette-Guérin (BCG) instillations. Unfortunately, some patients are BCG-unresponsive and will relapse over time. Radical cystectomy is the recommended salvage treatment following BCG-failure or BCG-intolerance. However, not all patients are candidates for surgery and thus, in need of other treatment. This study investigates the adverse events of Hyperthermic Intravesical Chemotherapy (HIVEC) treatment.

Methods: Twenty-three high-risk NMIBC patients, who were BCG-unresponsive or had contraindications for BCG, received HIVEC with Mitomycin C. Prior to each instillation, patients were interviewed by a nurse, using a systematic questionnaire regarding the adverse events. Patients were followed with cytology and cystoscopy every fourth month. The primary outcome was adverse event related to the HIVEC treatment.

Results: In general, the adverse events were mild to moderate and often self-limiting. The most common adverse events were urinary frequency (23.6%), incontinence (19.4%) and urinary tract pain (12.2%).

Conclusion: In the current study, we found that HIVEC was a well-tolerated treatment. HIVEC might be a feasible option for patients, who experienced BCG-failure or BCG-intolerance and could potentially postpone or avoid radical cystectomy.

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HIVEC; bladder cancer; NMIBC; BCG unresponsive; hyperthermia; Mitomycin C

Introduction

Bladder cancer is one of the most frequent neoplasms in Denmark, with approximately 2,000 new cases every year [1]. At the time of diagnosis, approximately 75% of patients have non-muscle invasive bladder cancer (NMIBC) and 25% of patients have muscle invasive bladder cancer [2].

Transurethral resection of bladder (TUR-B) is the cornerstone in the treatment for NMIBC, often supplemented with BCG-instillations (Bacillus Calmette–Guérin) or intravesical chemotherapy [3]. Intravesical BCG-instillation is the first-line treatment for high-grade Ta-T1 tumors, due to the lower risk of recurrence, compared to intravesical chemotherapy [4].

Although BCG reduces the risk of recurrence, some patients will relapse over time. Studies suggest that approximately 20–40% of the patients treated with BCG will have a recurrence after adequate BCG treatment [5]. In addition some patients will be BCG-intolerant, due to severe side effects which prevent further BCG instillation. In case of BCG-failure or BCG-intolerance, radical cystectomy is the recommended salvage treatment, according to the European association of Urology [6]. However, some patients are not candidates for radical cystectomy because of comorbidity or personal preferences. There is no standardized treatment for these patients, but in recent years new treatments have been developed. These treatments have focused on optimizing the delivery of already established therapies [7]. Hyperthermic Intravesical Chemotherapy (HIVEC) uses a conductive recirculation system to deliver chemotherapy at a constant temperature of 43 °C ± 0.5 °C to the bladder. The combination of thermotherapy and chemotherapy have a proven synergistic effect, which may be useful for treatment of NMIBC [8,9].

In the present study we will investigate the adverse events of HIVEC treatment in BCG-unresponsive NMIBC patients or patients where BCG were contraindicated.

Materials and methods

Patients

All patients treated with HIVEC between April 2018 and December 2019 at a single university hospital clinic were included in this study. Eligible patients had: (1) histologically

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confirmed Ta-T1 disease or carcinoma *in situ* (CIS), (2) received at least one HIVEC instillation.

A total of 23 patients were included.

Data registration and analysis was performed in accordance with the Danish Data Protection Agency under the Central Denmark Region common registration (file number 1-16-02-162-21). All patients provided written consent before study inclusion.

Treatment schedule and follow-up

Prior to the initial HIVEC treatment, a thorough TUR-B was performed. All visible tumors were deeply resected to ensure sufficient representation of detrusor muscle in the specimen. We used the Combat BRS V5 recirculation system to deliver the HIVEC treatment. The Combat BRS system is an external conductive recirculation system that uses an aluminum heat-exchanger for heat transfer. Mitomycin C is delivered to the bladder with a temperature of 43 °C ± 0.5 °C and the recirculation system ensures a constant temperature and a homogeneous distribution throughout the bladder [10].

We used 40 mg Mitomycin C diluted in 40 ml NaCl 0.9%.

The HIVEC treatment regimen consisted of six once-weekly induction instillations of 60 min each, followed by three once-monthly maintenance instillations. Cystoscopy and cytology were performed before the first induction instillation and before the first and third maintenance instillation. Prior to each instillation, a nurse interviewed the patients, using a systematic questionnaire regarding the adverse events since the last instillation.

After treatment completion, all patients were followed by cystoscopy and cytology every fourth month until two years after the last recurrence. If the cystoscopy or cytology showed sign of recurrence, biopsy was performed to ensure histological diagnosis.

Outcomes and statistical analysis

The primary outcome was to investigate the adverse events of HIVEC treatment in patients with CIS or Ta-T1 low- or high-grade disease. Adverse events were estimated from the interviews and graded by the nurses, according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0 [11]. The secondary outcome was the disease-free survival (DFS), defined as the time from the last HIVEC treatment. Recurrences were histologically confirmed. The DFS was calculated using the Kaplan-Meier method. The tertiary outcome was complete treatment response in patients with CIS, defined as negative biopsies from narrow band imaging-guided TUR-B after induction therapy.

The statistical analysis was performed using the computer software MedCalc version 19.5.1.

Results

Patients

Table 1 shows patient and tumor characteristics.

Table 1. Patient and tumor characteristics of 23 NMIBC patients.

Characteristics		Total ($n = 23$)
Age	Median, years (IQR)[a]	74 (70–80.75)
Gender		
Male	*n* (%)	14 (60.9)
Female	*n* (%)	9 (39.1)
T-stage[b]		
Ta low-grade	*n* (%)	3 (13)
Ta high-grade	*n* (%)	4 (17.4)
CIS	*n* (%)	11 (47.8)
T1	*n* (%)	5 (21.7)
BCG		
Unresponsive	*n* (%)	16 (69.6)
Intolerance	*n* (%)	4 (17.4)
Other[c]	*n* (%)	3 (13)
HIVEC instillations		
≥6	*n* (%)	20 (87)
<6	*n* (%)	3 (13)

[a]Shapiro-Wilk test.
[b]Before start of HIVEC treatment.
[c]One patient did not receive BCG due to comorbidities, one due to a severe reaction in childhood and one did not receive BCG before HIVEC treatment.

In total, 16 patients were treated with HIVEC due to recurrence after previous BCG treatment. Four patients were offered HIVEC due to intolerance to BCG treatment and three patients did not receive BCG treatment prior to HIVEC because of comorbidity or severe reaction to BCG in childhood.

A total of 123 HIVEC induction instillations were administered. Of these, 108 instillations were fully completed for 60 min, nine had a duration of at least 40 min and six instillations had a duration of less than 40 min.

Adverse events

All reported adverse events after the induction instillations are shown in Table 2 and selected adverse events are shown in Figure 1.

In general, HIVEC treatment was well-tolerated and most of the adverse events were self-limiting. The adverse events were either grade 1 or 2 according to the CTCAE definitions and consisted of urinary frequency, incontinence, and urinary tract pain. Of the 123 installations given, 23 (18.7%) incidents of urinary frequency was observed in nine patients and six (4.9%) incidents, in three patients, to such an extent that it limited the patient's daily activities and required intervention. Fourteen (11.4%) incidents of incontinence were observed in two patients, nine (7.3%) incidents, in five patients, to such an extent that pads were needed and one (0.8%) incident where oral medical treatment was necessary (grade 2). Thirteen (10.6%) incidents of mild urinary tract pain was observed in seven patients and two (1.6%) incidents of moderate urinary tract pain that limited daily activities or required treatment, was observed in two patients.

Three patients had to stop before they had completed all six induction installations. One patient stopped treatment due to pollakiuria and incontinence and two patients due to small bladder capacity. One patient stopped treatment after the second maintenance instillation, due to a systemic reaction with universal rash and edema, which required 14 days of high-dose steroid treatment. Further investigation showed that the allergic reaction was due to allergy to Pivmecillinam,

Table 2. Reported adverse events during HIVEC induction instillations.

Adverse events[a]	1. instillation (%)	2. instillation (%)	3. instillation (%)	4. instillation (%)	5. instillation (%)	6. instillation (%)	Total no. of instillations (%)	Total no. of patients (%)
Urinary tract pain								
No symptoms	17 (77.3)	20 (90.9)	18 (90)	16 (84.2)	18 (87.7)	19 (100)	108 (87.8)	14 (60.9)
Grade 1	4 (18.2)	2 (9.1)	2 (10)	3 (15.8)	2 (9.5)		13 (10.6)	7 (30.4)
Grade 2	1 (4.5)				1 (4.8)		2 (1.6)	2 (8.7)
Urinary frequency								
Not present	15 (68.2)	17 (77.3)	14 (70)	15 (78.9)	16 (76.2)	17 (89.5)	94 (76.4)	11 (47.8)
Grade 1	7 (31.8)	3 (13.6)	3 (15)	3 (15.8)	5 (23.8)	2 (10.5)	23 (18.7)	9 (39.1)
Grade 2		2 (9.1)	3 (15)	1 (5.3)			6 (4.9)	3 (13)
Incontinence								
Not present	17(77.3)	17 (77.3)	15 (75)	15 (78.9)	18 (85.7)	17 (89.5)	99 (80.5)	15 (65.2)
Grade 1	4 (18.2)	5 (22.7)	1 (5)	2 (10.5)	1 (4.8)	1 (5.3)	14 (11.4)	2 (8.7)
Grade 2	1 (4.5)		4 (20)	2 (10.5)	2 (9.5)	1 (5.3)	10 (8.1)	5 (26)
Hematuria								
Not present	19 (86.4)	21 (95.5)	19 (95)	18 (94.7)	19 (90.5)	19 (100)	115 (93.5)	17 (73.9)
Grade 1	3 (13.6)	1 (4.5)	1 (5)	1 (5.3)	2 (9.5)		8 (6.5)	6 (26.1)
Urinary tract infection								
No symptoms	22 (100)	21 (95.5)	19 (95)	18 (94.7)	20 (95.2)	19 (100)	119 (96.7)	20 (87)
Grade 2		1 (4.5)	1 (5)	1 (5.3)	1 (4.8)		4 (3.3)	3 (13)
Abdominal pain								
No symptoms	19 (86.4)	20 (90.9)	19 (95)	18 (94.7)	19 (90.5)	19 (100)	114 (92.7)	15 (65.2)
Grade 1	3 (13.6)	2 (9.1)	1 (5)	1 (5.3)	2 (9.5)		9 (7.3)	8 (34.8)
Flu like symptoms								
No symptoms	19 (86.4)	18 (81.8)	19 (95)	18 (94.7)	20 (95.2)	18 (97.7)	112 (91.1)	19 (82.6)
Grade 1	3 (13.6)	3 (13.6)	1 (5)	1 (5.3)	1 (4.8)	1 (5.3)	10 (8.1)	3 (13)
Grade 2		1 (4.5)					1 (0.8)	1 (4.3)
Skin rash on genitalia								
No symptoms	22 (100)	22 (100)	19 (95)	19 (100)	21 (95.2)	19 (100)	121 (98.4)	21 (91.3)
Grade 1			1 (5)		1 (4.8)		2 (1.6)	2 (8.7)
Skin rash on hands/feet								
No symptoms	22 (100)	22 (100)	20 (100)	18 (94.7)	21 (100)	17 (89.5)	120 (97.6)	20 (87)
Grade 1				1 (5.3)		2 (10.5)	3 (2.4)	3 (13)
Skin rash other places								
No symptoms	22 (100)	20 (90.1)	18 (90)	18 (94.7)	20 (95.2)	19 (100)	117 (95.1)	20 (87)
Grade 1		2 (9.1)	2 (10)	1 (5.3)	1 (4.8)		6 (4.9)	3 (13)
Nausea								
No symptoms	19 (86.4)	18 (81.8)	18 (90)	19 (100)	21 (100)	19 (100)	114 (92.7)	18 (78.3)
Grade 1	2 (9.1)	3 (13.6)	2 (10)				7 (5.7)	3 (13)
Grade 2	1 (4.5)	1 (4.5)					2 (1.6)	2 (8.7)
Diarrhea								
No symptoms	21 (95.5)	20 (90.9)	19 (95)	19 (100)	20 (95.2)	19 (100)	118 (95.9)	20 (87)
Grade 1	1 (4.5)	1 (4.5)	1 (5)		1 (4.8)		4 (3.3)	2 (8.7)
Grade 2		1 (4.5)					1 (0.8)	1 (4.3)
Arthralgia								
No symptoms	21 (95.5)	21 (95.5)	20 (100)	19 (100)	21 (100)	19 (100)	121 (98.4)	21 (91.3)
Grade 1	1 (4.5)	1 (4.5)					2 (1.6)	2 (8.7)

[a]All treatment related adverse events were graded according to the Common Terminology Criteria for Adverse Events (CTCAE).

administered prophylactic prior to each of the patients' treatments, and not a result of the HIVEC treatment itself.

Some patients experienced systemic adverse events, but to a lesser extent than local adverse events. Ten (8.1%) incidents of mild flu-like symptoms were observed and one (0.8%) incident of moderate flu-like symptoms that limited daily activities or required treatment was observed. Nine (7.3%) incidents of mild abdominal pain were reported. Furthermore, seven (5.7%) incidents of nausea was observed and two (1.6%) incidents where nausea resulted in decreased oral intake.

Efficacy

Ta-T1 tumors

Twelve patients were diagnosed with Ta or T1 disease prior to treatment initiation. During follow-up, five of these patients experienced a recurrence. The recurrences occurred after one, four, four, seven and eight months. No patients progressed to muscle invasive disease in the follow-up period. After four months of follow-up, 70% were disease-free (Figure 2). One patient died during follow-up, but for a cause unrelated to bladder cancer.

Cis

Eleven patients were diagnosed with CIS prior to treatment initiation. At the first cystoscopy after treatment completion, all patients had a complete response. During the follow-up period, three (27.3%) patients relapsed after seven, seven and nine months (Table 3). No patients progressed to muscle invasive disease in the follow-up period. Two patients died during follow-up, but both died of causes unrelated to bladder cancer.

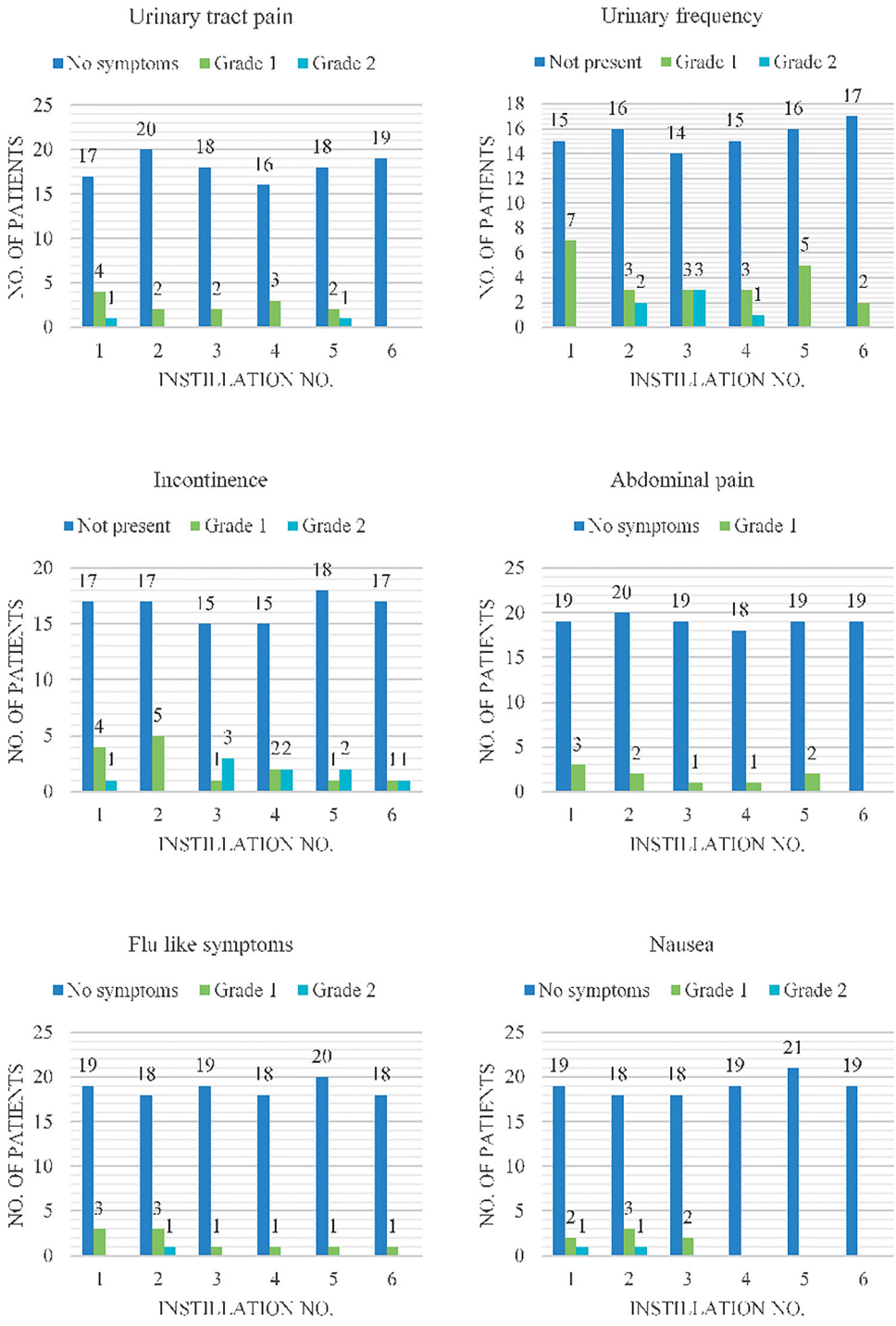

Figure 1. Selected adverse events during HIVEC induction instillations.

Discussion

BCG-unresponsive NMIBC pose a major problem, as there currently is no standardized bladder sparing treatment. New treatment options are needed, to treat the patients who do not want radical cystectomy or who are surgically unfit. In this study, we investigated the safety of HIVEC treatment. Of the 23 patients who received HIVEC, only three patients discontinued the treatment, one patient due to adverse events and two patients due to small bladder capacity. The most common adverse events were urinary frequency (23.6%), incontinence (19.4%) and urinary tract pain (12.2%).

The HIVEC treatment generally showed a tolerable safety profile. All reported adverse events were CTCAE grade 1 or 2. Compared to a large EORTC study reporting adverse events of intravesical BCG treatment, the patients in the present study experienced fewer adverse events [12].

The observed adverse events after HIVEC treatment reported in this study, is similar to the observed adverse events, which de Jong et al. described in their study, regarding adjuvant HIVEC treatment [13]. Chiancone et al. also showed that HIVEC is a very well tolerated treatment. In their study, urinary frequency, pelvic pain, hematuria, and urinary urgency were the most reported adverse events. A total of

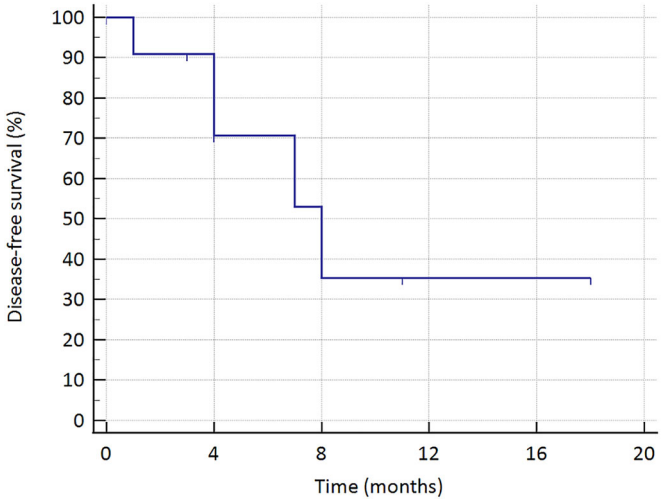

Figure 2. Kaplan-Meier curve showing DFS after HIVEC treatment in NMIBC Ta-T1 patients.

75 patients received HIVEC with MMC. Of these, four patients (5.33%) experienced a grade 3 adverse events (CTCAE definitions). No grade 4 or 5 adverse events were reported [14].

The effect of HIVEC treatment cannot be properly estimated based on the present study. The study only included a relatively small study population, the follow-up time was short, and the patient group was heterogeneous regarding tumor characteristics. For the time being, only single-arm observational studies have looked at the effectiveness of HIVEC. Sousa et al. found a two-year cumulative incidence of recurrence of 12.5% and de Jong et al. found a one-year cumulative incidence rate of recurrence/progression of 53% [13,15]. Shang et al. published a meta-analysis in 2011, with five randomized controlled trials (RCTs) comparing BCG with standard adjuvant chemotherapy. They found that 35.5% of the patients treated with BCG had recurrence [4]. Based on the currently available data, this indicates that BCG is superior to HIVEC when it comes to effect. HIVEC may however prove to be a feasible alternative for patients who do not have effect or tolerate BCG and thereby possibly avoid radical cystectomy.

Several other device-assisted therapies for treatment of NMIBC have been tested in recent years. Radiofrequency-Induced Thermochemotherapy (RITE) is an already established treatment for several other cancers, like lung-, colorectal- and thyroid cancer [16–18]. RITE is administered in combination with chemotherapy, which leads to a higher concentration of chemotherapy in the tumor tissue, compared to chemotherapy alone [19]. Like HIVEC, RITE is a relatively tolerable treatment, with most adverse events being self-limiting. Several studies have described the adverse events. The most commonly reported adverse events are non-infective cystitis (32%), suprapubic pain (29.5%) and bladder spasms or urgency (20.3%) [7]. No studies comparing RITE with HIVEC have been performed.

Electromotive drug administration (EMDA) is another way to increase the effect of Mitomycin C. This is done by making an electrical charge between a urinary catheter electrode and two cutaneous electrodes on the lower abdomen. A RCT compared EMDA Mitomycin C, passive Mitomycin C and BCG. They found significantly more local- and systemic adverse events in the BCG group compared to both the EMDA and Passive Mitomycin C groups [20]. No studies comparing EMDA with HIVEC have been performed.

Table 3. Effect of HIVEC treatment on CIS patients.

Effect parameter	HIVEC *n* (%)
Complete response after treatment completion[a]	11 (100)
Recurrence during follow up	3 (27.3)[b]

[a]Defined as the first cystoscopy after ended treatment.
[b]Two patients experienced recurrence after 7 months and one patient after 9 months.

We intend to continue HIVEC treatment in selected patients, as it is easy and tolerable. Expanding to larger patient groups will await ongoing studies, to see if the clinical effect, compared to current standard, justifies this.

Limitations

The main limitation of the current study is the sample size. Only 23 patients were included and only 123 induction instillations were performed. Furthermore, the study population had heterogeneous tumor characteristics, which further limited our findings. Moreover, follow-up time was relatively short and with considerably variations in the study population. Another limitation concerns the interviews done by the nurses, regarding the adverse events. The adverse events were self-reported and contains several potential biases like selective memory, telescoping, attribution, and exaggeration. Not all interviews were completed, and therefore not included in the analysis. If the patients stopped the treatment before the six induction instillations, they did not get interviewed after the last HIVEC treatment they had received. Thus, fewer adverse events could potentially be reported. However, this is the most comprehensive collection of data after each installation, regarding the adverse events, that has been compiled to date.

Conclusion

In the present study, we found that HIVEC was a well-tolerated treatment with relatively few and often self-limiting adverse events. Furthermore, it suggests that HIVEC may be a possible treatment for patients who experienced BCG-failure or BCG-intolerance and thereby potentially avoid or postponing the need for radical cystectomy.

Disclosure statement

JBJ is conducting research in collaboration with medac and Photocure ASA. The other authors report no conflicts of interest.

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