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Long-term oncologic outcomes of epirubicin-based hyperthermic intravesical chemotherapy in BCG-naive patients with non-muscle-invasive bladder cancer: A multicenter retrospective observational study

Nicolas Arnold[1]*, Julien Blanc[2], Ilaria Lucca[2], Mihai Dorin Vartolomei[1,3], Laila Schneidewind[1], Nicola Giudici[1], Raphael Röthlisberger[1], George N. Thalmann[1], Bernhard Kiss[1], and Beat Roth[1]

[1]Department of Urology, University Hospital of Bern, Bern, Switzerland

[2]Department of Urology, University Hospital of Lausanne, Lausanne, Vaud, Switzerland

[3]The Institution Organizing University Doctoral Studies, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Cluj County, Romania

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***Corresponding author:**
Nicolas Arnold
(nicolas.arnold@insel.ch)

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Abstract

Introduction: Non-muscle-invasive bladder cancer (NMIBC) accounts for approximately 75% of bladder cancer cases and demonstrates substantial variability in recurrence and progression. Bacillus Calmette–Guérin (BCG) is the recommended adjuvant intravesical therapy in intermediate- and high-risk tumors; however, shortages and contraindications necessitate alternative treatments. Hyperthermic intravesical chemotherapy (HIVEC) has been mainly studied with mitomycin C, and data on epirubicin-based HIVEC are limited.

Objective: This study evaluated first-line epirubicin-based HIVEC in BCG-naive patients with NMIBC.

Methods: In this study, we included and retrospectively analyzed BCG-naive patients from our prospectively recorded, multicenter HIVEC database who received HIVEC in a first-line setting between March 2017 and September 2022. Treatment included six weekly induction instillations followed by six monthly maintenance instillations. The primary outcome was recurrence-free survival (RFS), while secondary outcomes included progression-free survival, extravesical RFS, disease-free survival, cancer-specific survival, and the need for radical cystectomy.

Results: Twenty-three patients with intermediate-, high-, or very high-risk NMIBC received epirubicin-based HIVEC in a first-line setting. The median follow-up was 35 months (IQR 29–52). Two patients (8.7%) experienced intravesical recurrence (both carcinoma *in situ*). Median RFS was 35 months (IQR 26–50), with 1- and 2-year RFS rates of 100.0% and 95.6%, respectively. No patient experienced progression, extravesical recurrence, cancer-specific death, or required radical cystectomy.

Conclusion: First-line epirubicin-based HIVEC in BCG-naive patients provided durable oncological control in predominantly high- and very high-risk NMIBC. These results indicate that epirubicin-based HIVEC may represent a potential alternative when BCG

is unavailable or contraindicated. However, the small sample size and observational design limit interpretability, underscoring the need for larger randomized trials to clarify the role of epirubicin-based HIVEC in this setting.

Keywords: Bladder cancer; Non-muscle-invasive bladder cancer; Bacillus Calmette–Guérin-naive; Hyperthermic intravesical chemotherapy; Epirubicin; Progression; Recurrence; Cystectomy

1. Introduction

Bladder cancer ranks as the ninth most common type of cancer worldwide, with men four times more likely to be affected than women.[1] Approximately 75% of newly diagnosed bladder cancer cases are non-muscle invasive bladder cancer (NMIBC), with a significantly better prognosis than muscle-invasive bladder cancer.[2] Nevertheless, NMIBC represents a biologically heterogeneous group of tumors, with 5-year recurrence rates ranging from 50% to 70%, and 5-year progression rates ranging from 10% to 30%.[3]

The European Association of Urology (EAU) and the European Organization for Research and Treatment of Cancer (EORTC) have developed different scoring systems to stratify NMIBC according to recurrence and progression risk. To prevent recurrence and delay progression, adjuvant intravesical therapy is recommended after complete resection of intermediate- and high-risk NMIBC.[4] While intermediate-risk NMIBC can be treated with intravesical chemotherapy or Bacillus Calmette–Guérin (BCG), high-risk NMIBC should be treated with BCG only for a duration of 1–3 years.[4,5-8] Nevertheless, the prognosis of NMIBC patients treated with BCG for 1–3 years varies widely, with recurrence risk driven by prior recurrence rate and number of tumors, and progression or cancer-specific mortality determined by stage and grade.[9]

Since 2012, recurrent shortages of BCG have promoted the search for alternative treatment options.[10] In response, several institutions have investigated alternative intravesical treatment strategies.[11-19] Among these approaches, the combination of cytotoxic agents with intravesical hyperthermia, referred to as device-assisted hyperthermic intravesical chemotherapy (HIVEC), has been explored since the late 1990s.[20] The fact that patients with recurrent NMIBC may be unfit for or refuse radical cystectomy has led to HIVEC being investigated predominantly after BCG failure and recommended in guidelines as second-line therapy after BCG failure.[4,21] However, the use of device-assisted HIVEC with conductive heating has recently been increasingly investigated in BCG-naive patients, with mostly comparable oncological outcomes to those of intermediate- and high-risk NMIBC patients treated with BCG.[22,23] While data on HIVEC with mitomycin C predominate, studies on epirubicin-based HIVEC are relatively rare.[24-27] This prompted us to investigate our prospective, multicenter HIVEC database[28,29] to identify BCG-naive patients who received HIVEC with epirubicin in a first-line setting and to evaluate the oncological outcome of this subgroup.

2. Materials and methods

2.1. Study design

This was an observational, investigator-initiated, institutional review board-approved study (protocol number 121/08[28]). For this study, we included and retrospectively analyzed BCG-naive patients from our multicenter (Bern, Lausanne), prospectively managed HIVEC database who received HIVEC in a first-line setting between March 2017 and September 2022. The study complied with the Declaration of Helsinki and its amendments. Written informed consent was obtained from all participants prior to enrollment.

2.2. Patients

After experiencing the first BCG shortages in 2016, our institution developed a prospective protocol to standardize and evaluate epirubicin-based HIVEC, in which hyperthermia was generated using conductive heating. According to protocol and prior to HIVEC, patients were required to undergo transurethral resection of the bladder tumor or, in cases of positive cytology without visible tumor on cystoscopy, cold-cup bladder biopsies. In case of pT1 or high-grade pTa histology, repeat transurethral resection was performed within 2–4 weeks to rule out muscle invasion or residual tumor other than carcinoma *in situ* (CIS). All patients with EAU NMIBC intermediate-, high-, or very high-risk disease treated with HIVEC at our institution were recorded in our database. Patients categorized as very high risk were either unfit for or refused radical cystectomy prior to HIVEC treatment and database inclusion. To reduce cohort heterogeneity,

patients with non-urothelial histology were not eligible for inclusion. While the overall database cohort has been analyzed separately,[29] only BCG-naive patients were included in this study. These patients received HIVEC as first-line therapy due to BCG shortage, contraindications for BCG (e.g., immunosuppression), or administration of HIVEC for NMIBC low-grade recurrence.

2.3. Treatment

HIVEC was delivered with the UniThermia® system (Elmedical Ltd, Israel) with epirubicin (50 mg dissolved in 50 mL 0.9% saline) (Pfizer AG, Zürich, Switzerland), heated to 43 °C for 50 min. To maintain urinary alkalinization (target pH ≥ 6) and limit drug degradation, patients received 4g of sodium bicarbonate (Salmon Pharma GmbH, Basel, Switzerland) 12 hours before treatment, and the dose was adjusted for subsequent instillations according to urinary pH. Patients were additionally instructed to limit fluid intake to ≤200 mL within 4 h before instillation to avoid drug dilution.

2.4. Schedule

Treatment consisted of six weekly induction instillations followed by six monthly maintenance instillations. Follow-up included cystoscopy and cytology every 3 months for 2 years, then every 6 months for at least 5 years in patients without recurrence. Recurrences were confirmed by transurethral resection of the bladder tumor and histological evaluation. In the event of positive cytology without tumor detection, random cold-cup biopsies of the bladder and prostatic urethra, as well as upper tract cytology, were obtained. Ureteroscopy was performed as indicated. Late-phase abdominal computed tomography was performed at 6, 12, 24, and 60 months, or when recurrence was suspected (Figure 1).

2.5. Outcome measurements

Study endpoints were predefined at database initiation. The primary endpoint was intravesical recurrence-free survival (RFS), defined as recurrent NMIBC or recurrent/persistent CIS of the bladder. Secondary endpoints included progression-free survival (PFS; muscle-invasion or metastatic disease associated with intravesical recurrence), extravesical RFS (urothelial cancer recurrence of prostatic urethra or upper urinary tract), disease-free survival (DFS; intra- or extravesical urothelial cancer recurrence), cancer-specific survival (CSS; death caused by urothelial cancer at any location), overall survival (OS; death from any cause), and the need for radical cystectomy.

2.6. Statistical analysis

Categorical variables were reported as counts and percentages, and continuous variables as medians with interquartile ranges (IQR). Descriptive statistical analyses were performed using STATA v11 (StataCorp, United States of America) for demographic characteristics (age, sex), recurrence prior to HIVEC, indication for HIVEC administration, tumor stage and grade prior to HIVEC, EORTC score, EAU risk category, and number of HIVEC administrations. The small sample size precluded regression analysis.

3. Results

3.1. General results

Twenty-three patients were included: 20 males (87.0%) and three females (13.0%), with a median age of 73 years (IQR 64–78) and a median follow-up of 35 months (IQR 29–52). 11 patients (47.8%) had recurrent tumor disease, while 12 (52.2%) had a primary tumor prior to HIVEC. 17 patients (73.9%) received HIVEC due to BCG shortage, five (21.7%) due to low-grade recurrence, and one (4.4%) due to immunosuppression. The highest stage prior to HIVEC was pTa in 16 (69.6%), pT1 in five (21.7%), and CIS only in two (8.7%) cases. Low-grade disease was present in 9 patients (39.1%) and high-grade disease in 14 (60.9%). CIS was present prior to HIVEC in four patients (17.4%). Median EORTC recurrence and progression scores were five (IQR 5–6) and eight (IQR 5–12), respectively. According to the EAU risk stratification, 10 patients (43.5%) were intermediate-risk, seven (30.4%) high-risk, and six (26.1%) very high-risk. The median number of HIVEC instillations was six (IQR 6–8). Six patients (26.1%) discontinued instillation treatment during the induction cycle, four (17.4%) completed both induction and maintenance therapy (12 instillations), and 13 (56.5%) discontinued during the maintenance cycle (Table 1). Treatment discontinuation occurred exclusively due to side effects or unwillingness to continue treatment and not because of recurrence.

3.2. Primary endpoint

Two patients (8.7%) experienced intravesical recurrence at 12 and 28 months after the first HIVEC administration, respectively, with CIS detected in both cases. The former patient had primary CIS as the indication for HIVEC and was classified as EAU high-risk, whereas the latter had pTa high-grade disease as the indication and was also classified as EAU high-risk. In both cases, HIVEC was administered due to a BCG shortage. The former patient discontinued treatment after six instillations due to side effects, while the latter completed both induction and maintenance, receiving a total of 12 instillations. No intravesical recurrences were observed among patients receiving HIVEC due to low-grade recurrence (n = 5) and

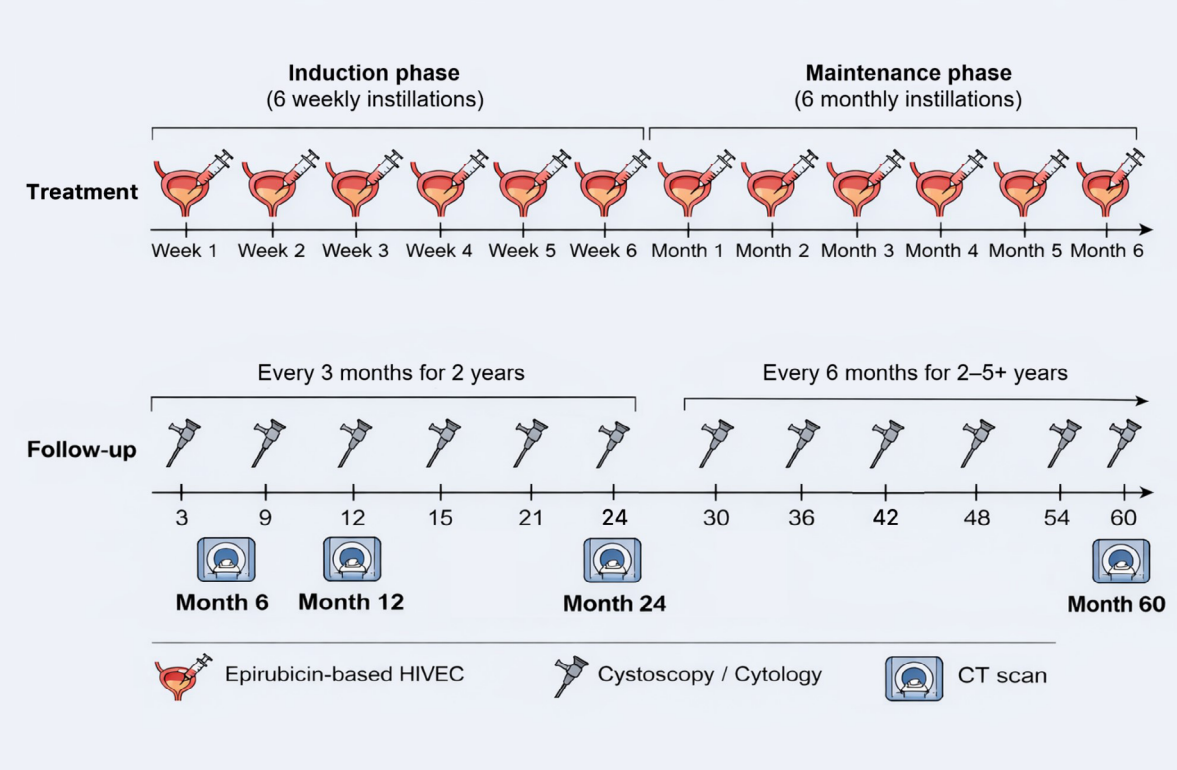

Figure 1. Treatment and follow-up schedule
Abbreviations: CT: Computed tomography; HIVEC: Hyperthermic intravesical chemotherapy.

immunosuppression (n = 1). Median intravesical RFS was 35 months (IQR 26–50), with 1- and 2-year intravesical RFS rates of 100.0% and 95.6%, respectively.

3.3. Secondary endpoints

No patients experienced disease progression, resulting in a median PFS of 35 months (IQR 29–52) and 1- and 2-year PFS rates of 100.0% each. No extravesical recurrences were observed, yielding a median extravesical RFS of 35 months (IQR 29–52). Median DFS was 35 months (IQR 29–50) with 1- and 2-year DFS rates of 100.0% and 95.6%, respectively. No cancer-specific deaths were recorded. Accordingly, median CSS and OS were both 35 months (IQR 29–50). None of the patients required radical cystectomy for oncologic or functional reasons.

4. Discussion

Our multicenter, retrospective, observational study shows promising oncological outcomes in BCG-naive patients who received epirubicin-based HIVEC as first-line therapy, indicating its potential value as a treatment alternative to BCG. This is clinically relevant because BCG shortages have become increasingly common in recent years[10] and some patients are unable to receive BCG for various reasons. Our study and its results are also meaningful because studies on epirubicin-based HIVEC are generally rare.

In our study investigating HIVEC with epirubicin in 23 BCG-naive patients with NMIBC, most of whom were classified as EAU high- or very high-risk (n = 13, 56.5%), we identified intravesical recurrences in only two patients (8.7%), with a median intravesical RFS of 35 months (IQR 26–50) and 1- and 2-year intravesical RFS rates of 100.0% and 95.6%, respectively. These outcomes not only meet but clearly surpass the International Bladder Cancer Group's definition of clinically meaningful results for emerging therapies, which are set at recurrence-free rates of 50% at 6 months, 30% at 12 months, and 25% at 18 months for papillary tumors.[30] Notably, no cases of progression, extravesical recurrence, cancer-specific mortality, or need for radical cystectomy due to oncologic or functional reasons were observed.

Several studies have investigated oncologic outcomes of HIVEC administered in a first-line setting. Guerrero-Ramos *et al.*[22] randomized 50 patients with high-risk NMIBC 1:1 to either BCG therapy or device-assisted mitomycin C-based HIVEC and were the first to show

Table 1. Patient characteristics

		EAU		
	Overall	**Intermediate-risk**	**High-risk**	**Very high-risk**
Number of patients, *n* (%)	23 (100)	10 (43.5)	7 (30.4)	6 (26.1)
Follow-up				
Median, months (IQR)	35 (29–52)	35 (26–49)	35 (32–47.5)	52 (34–57)
Mean, months (SD)	39.7 (20.2)	38.5 (21.8)	36.7 (13.6)	45.2 (22.5)
Age				
Median, years (IQR)	73 (64–78)	76 (62–80)	70 (67–74)	74 (66–79)
Mean, years (SD)	71.6 (9.9)	72.5 (12.4)	69.0 (6.4)	73.2 (7.9)
Sex, *n* (%)				
Male	20 (87.0)	9 (90.0)	6 (85.7)	5 (83.3)
Female	3 (13.0)	1 (10.0)	1 (14.3)	1 (16.7)
Recurrent tumor disease, *n* (%)				
Yes	11 (47.8)	9 (90.0)	0 (0.0)	2 (33.3)
No	12 (52.2)	1 (10.0)	7 (100.0)	4 (66.7)
Reason for HIVEC, *n* (%)				
BCG shortage	17 (73.9)	5 (50.0)	7 (100.0)	5 (83.3)
Low-grade recurrence	5 (21.7)	5 (50.0)	0 (0.0)	0 (0.0)
Immunosuppression	1 (4.4)	0 (0.0)	0 (0.0)	1 (16.7)
Highest tumor stage prior to HIVEC, *n* (%)				
pTa	16 (69.6)	10 (100.0)	5 (71.4)	1 (16.7)
pT1	5 (21.7)	0 (0.0)	0 (0.0)	5 (83.3)
pTis only	2 (8.7)	0 (0.0)	2 (28.6)	0 (0.0)
Highest grade (2004/2016) prior to HIVEC, *n* (%)				
Low-grade	9 (39.1)	9 (90.0)	0 (0.0)	0 (0.0)
High-grade	14 (60.9)	1 (10.0)	7 (100.0)	6 (100.0)
CIS prior to HIVEC, *n* (%)				
Yes	4 (17.4)	0 (0.0)	2 (28.6)	2 (33.3)
No	19 (82.6)	10 (100.0)	5 (71.4)	4 (66.7)
EORTC scores				
Recurrence score, quantitative (IQR)	5 (5–6)	5 (5–6)	5 (3–5)	7 (6–10)
Progression score, quantitative (IQR)	8 (5–12)	5 (5–5)	8 (8–11)	14 (12–17)
Number of HIVEC instillations				
Median, *n* (IQR)	6 (6–8)	6 (5–6)	6 (6–7)	8 (5–12)
Discontinuation of HIVEC, *n* (%)				
No discontinuation	4 (17.4)	1 (10.0)	1 (14.3)	2 (33.3)
During the induction cycle	6 (26.1)	3 (30.0)	0 (0.0)	3 (50.0)
During the maintenance cycle	13 (56.5)	6 (60.0)	6 (85.7)	1 (16.7)

Abbreviations: BCG: Bacillus Calmette–Guérin; CIS: Carcinoma *in situ*; EAU: European Association of Urology; EORTC: European Organization for Research and Treatment of Cancer; HIVEC: Hyperthermic intravesical chemotherapy; IQR: Interquartile range; SD: Standard deviation.

that HIVEC was noninferior to BCG in patients with these tumor characteristics. In this study, RFS and PFS rates at two years were 86.5% and 95.7%, respectively, with a mean time to recurrence of 21.5 months. Examining primarily tolerability and compliance, Magalhães *et al.*[23] also reported promising oncologic efficacy data for mitomycin C-based HIVEC in 57 patients with intermediate- and high-risk NMIBC, of whom 40 had primary disease, and 17 had recurrent disease following prior chemotherapy-based instillation therapies. After a median follow-up of 31 months, 32 patients (61.4%) were disease-free, while 22 (38.6%) experienced recurrent disease. Kastner *et al.*[31] investigated mitomycin C-based HIVEC in 51 patients, of whom 16 were BCG-naive, and reported no significant difference in RFS between BCG-unresponsive and BCG-naive patients and 1- and 2-year RFS rates of 69.2% and 35.1% in BCG-naive patients (n = 16). All of the above studies show promising oncological results for HIVEC in first-line treatment settings of BCG-naive patients, even when directly compared with BCG. Although a direct comparison with our study is difficult due to differing study designs and small patient cohorts, the oncologic outcomes of our study should at least be considered encouraging. In contrast to the studies mentioned above, which all investigated mitomycin C-based HIVEC, we used HIVEC with epirubicin, an anthracycline chemotherapeutic agent that acts as a cytostatic drug, stopping tumor growth by directly interfering with the DNA of cancer cells.[32] However, to date, based on a few studies with small patient numbers, there is no evidence indicating reduced efficacy of mitomycin C compared with epirubicin when used in the context of HIVEC.[24,25] Another possible explanation for our promising results is the optimized treatment protocol, which included restricting fluid intake and alkalinizing the urine prior to therapy to reduce drug dilution and biodegradation, thereby improving efficacy.

This study has several limitations, including the relatively small cohort size and absence of a controlled comparator, as HIVEC was performed as first-line therapy only in cases of BCG shortage, contraindication, or low-grade recurrence. The heterogeneity of the cohort with regard to treatment indications is another limitation, as varying indications may be associated with different oncological outcomes. Moreover, despite encouraging oncological outcomes, treatment adherence was suboptimal, with a notable proportion of patients not completing maintenance therapy. In contrast to BCG maintenance therapy, data on maintenance instillation with chemotherapeutic agents remain limited and inconclusive.[33] These factors warrant cautious interpretation of our findings. The purely descriptive approach of our study also precludes causal conclusions. Additional possible sources of bias include selection bias related to treatment allocation based on clinical assessment and information bias inherent to retrospective analyses. These limitations were partly addressed by using a prospective database and inclusion criteria defined at database initiation.

Nevertheless, to our knowledge, this study is the first to investigate epirubicin-based HIVEC as first-line therapy and demonstrates promising oncological outcomes in the context of existing studies on HIVEC in BCG-naive patients. Key strengths include a standardized treatment protocol, a prospectively maintained database, a multicenter study design, and consistent oncological results, which together support the clinical relevance of our findings. Although our study design and small patient number do not allow clinical recommendations, our data indicate the potential value of epirubicin-based HIVEC as a therapeutic alternative to BCG and position it alongside other emerging BCG alternatives.

5. Conclusion

In our cohort of BCG-naive patients with predominantly high- and very high-risk NMIBC, first-line epirubicin-based HIVEC showed promising oncological outcomes, indicating its potential value as a treatment alternative in cases of BCG shortage, contraindications, or intolerance. However, due to the absence of comparators, the small and heterogeneous cohort, and potential confounding factors, the generalizability of these findings is limited, and the results should be interpreted with caution. Further validation in large randomized trials is required to clarify the role of epirubicin-based HIVEC in the first-line management of NMIBC.

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Conflict of interest

The authors declare no conflict of interest to declare.

Author contributions

Conceptualization: Nicolas Arnold, Beat Roth
Formal analysis: Mihai Dorin Vartolomei
Investigation: Nicolas Arnold, Julien Blanc
Methodology: Nicolas Arnold, Beat Roth
Supervision: Beat Roth, Ilaria Lucca
Writing–original draft: Nicolas Arnold
Writing–review & editing: Raphael Röthlisberger, Nicola Giudici, George N. Thalmann

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the Canton of Bern, Switzerland (protocol number 121/08). Written informed consent for participation was obtained from all participants prior to enrollment.

Consent for publication

Written informed consent for publication was obtained from all participants prior to enrollment.

Availability of data

The datasets generated and/or analyzed during the current study are not publicly available due to data protection regulations but are available from the corresponding author on reasonable request.

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