

Review

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Review

Epirubicin and Non-Muscle Invasive Bladder Cancer Treatment: A Systematic Review

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Abstract: (1) Background: Intravesical Chemotherapy is standard of care in intermediate risk non-muscle-invasive bladder cancer (NMIBC). Different agents are used across the world based on availability, cost and practice patterns. Epirubicin (EPI), one of these agents is used by many centers over many decades. However, its true differential efficacy compared to other agents and its tolerability is still poorly reported. We aimed to assess the differential efficacy and safety of intravesical EPI in NMIBC patients. **(2) Methods:** A systematic search of PUBMED, Webofscience, clinicaltrials.gov, and Google Scholar databases was performed on December 31, 2023. We reviewed 28 studies that included patients treated EPI after TURBT (transurethral resection of bladder tumors) for NMIBC and who compared oncological outcomes such as recurrence and progression to other adjuvant treatment such as Mitomycin C (MMC), Gemcitabine (GEM) and BCG. Further, we looked at the safety profile of EPI at room temperature under hyperthermia intravesically and at the oncological outcomes when administrated with hyperthermia; **(3) Results:** When compared to other chemotherapeutics (MMC/GEM), EPI seemed to be equally effective; however, EPI seems less effective in preventing disease management recurrence compared to BCG intravesical. The most common adverse events of EPI include cystitis, dysuria, and pollakiuria. **(4) Conclusions:** EPI exhibits similar oncological performances to Gemcitabine and Mitomycin C currently used for adjuvant therapy in NMIBC. Novel delivery mechanisms such as hyperthermia are promising newcomers.

Keywords: Epirubicin; intravesical instillations; bladder cancer; chemotherapy; adjuvant treatment

1. Introduction

Bladder cancer (BC) is the second most frequent urological malignancy affecting 573,000 patients yearly worldwide [1]. More than 75% of patients diagnosed with bladder cancer have a cancer confined to the mucosa or the lamina propria [2].

The standard treatment for NMIBC is Transurethral Resection of the Bladder Tumors (TURBT) followed by additional adjuvant treatment, which comprises single-shot intravesical chemotherapy dose induction +/- maintenance chemotherapy for up to three years [3–5]. For low-risk tumors, single instillations of drugs, such as single postoperative Mitomycin C (MMC), Epirubicin (EPI), or Gemcitabine (GEM) have been found to be effective in reducing disease recurrences [6,7].

For intermediate, high-risk and very high-risk bladder tumors, the most effective adjuvant therapy is with Bacillus Calmette-Guérin (BCG) [8]. BCG therapy is typically given as a series of 6 weekly instillations followed by a maintenance regimen up to 3 years.

In case of BCG ineligible or unresponsive patients, or in case of BCG shortage there are available some chemotherapeutic agents such as EPI, MMC or GEM for intravesical instillations [9], at least 6 times weekly, but a fixed regimen it has been not established yet. A full year regimen is nowadays considered as a minimum for best efficacy of the drugs (6 weekly instillations followed by instillation at 6 weeks intervals for a year) [10]. However, a shared decision-making regarding adjuvant therapy with the patient relies also on various factors, including age [11], stage, grade, and risk stratification of bladder cancer, as well as individual patient characteristics such as sarcopenia [12].

As a treatment for bladder cancer EPI still has a wide spectrum of use in many countries and geographical areas due to its therapeutic efficacy for NMIBC and lack of alternative approved treatments, on the other hand in other countries such as the US is not approved for intravesical treatment [13]. According to European Association of Urology (EAU) guidelines, EPI is an option in patient unfit for BCG or in case of BCG shortage [2]. In the US alone it is estimated that more than 8000 patients are not receiving BCG due to global shortage [14]. So, as an alternative adjuvant therapy after TURBT for bladder tumors, EPI has shown in time effectiveness in reducing recurrences. EPI works by interfering with the DNA of cancer cells, preventing their replication and growth [15].

Considering these facts, we aimed to look at all the relevant literature regarding the efficacy and toxicity of EPI. In this regard we searched for relevant literature regarding recurrence free survival (RFS) and progression free survival (PFS) rates after EPI treatment compared with those after BCG, MMC and GEM. A second focus was to analyze the impact of adding hyperthermia when using EPI in comparison to hyperthermia with MMC.

2. Materials and Methods

A systematic search of MEDLINE, Web of Science, clinicaltrials.gov and Google Scholar databases was performed on December 31, 2023, using any combination of the terms: Epirubicin (EPI) AND Bladder Cancer (EXP) OR Epirubicin (EPI) AND non-muscle invasive bladder cancer (NMIBC). All original articles that fulfilled the inclusion criteria were included. We performed additional cross checking of reference lists, and “hand searched” for any additional references.

Studies were considered eligible if they included patients with NMIBC, had a prospective or retrospective design, included at least 10 patients, and assessed the oncological impact of EPI treatment compared with those after BCG, MMC and GEM or EPI standard treatment alone or using chemohyperthermia. Language of publication was not an exclusion criterion. Primary outcomes were comparison of recurrence and progression rates between EPI and MMC or GEM or BCG. The secondary outcome was to evaluate the safety profile of EPI and the impact of using device assisted intravesical administration of EPI. For each selected study, the following items were recorded: first author's name, year of publication, country, study design, number of patients, patients' characteristics, variables included in multivariable analysis, recurrence rate, progression rate, follow-

up, and adverse events (AEs), when reported. Two investigators (SC and MF) independently conducted literature search and extracted data from included full-text articles; disagreements were resolved by consensus with a third investigator (MDV).

3. Results

3.1. Adverse Events after Intravesical instillations with Epirubicin

A number of 11 studies reported adverse events after adjuvant intravesical instillations with EPI, using a regimen of at least 6 weekly instillations. They included 1165 patients in total, of which 207 were females. The instillation regimen was not uniform as it is no clear recommendation and varied from 6 installations until 17 instillations [16–18]. The most frequently reported adverse events were cystitis (34%), followed by dysuria, pollakiuria, hematuria, bladder irritation/spasms, fever, nausea and vomiting, and generalized skin rash (2.3%) [19], see Table 1.

Table 1. Reported adverse events after intravesical instillation with Epirubicin.

Study/year	Country	No pts. m/f	No. Instillations	Adverse reactions no. patients (%)
Melekos et al.1993	Greece	84/15	6-8 (50mg EPI in 50 ml saline)	cystitis (34%) and hematuria (15%)
Eto et al.1994	Japan	98/16	(30mg EPI/30ml saline) Twice a week/4 weeks 1 monthly/11 months	micturition pain 6 (10.0%), pollakiuria (9 (15.0%)), and hematuria 3 (5.0%)
Ryoji et al.1994	Japan	97	20 mg in 30 ml physiological saline, 17 times for 1 year: once immediately after TUR, once every 2 weeks for the next 4 months, and then once per month for the following 8 months	9.3% (9/97) of the patients pain on urination, pollakiuria, and hematuria.
Watanabe et al.1994	Japan	40/13	(20 mg EPI) was dissolved in 40 ml physiological saline. 17 instillations seven times at intervals of 2 weeks. Finally, eight intravesical instillations were performed at 1-month intervals. A total of 17 intravesical injections were given over a period of about 1 year	3 cases (5.7%), and most were symptoms of bladder irritation such as pollakiuria
Ali-El-Dein et al.1997	Egypt	206/47	8 (1/week) (50 mg EPI/40ml saline) 1 monthly for 12 months (maintenance)	40 to 56% local side effects (contracted bladder)
Okamura et al.1998	Japan	110/28	(40 mg/ml in normal saline) Arm A (17 instillations) Vs. Arm B (6 instillations)	Miction pain and frequency in 10 (7.2%) patients and gross hematuria in 1 (0.7%)
Melekos et al. 1992	Greece	55/10	6 weeks, 1/monthly	Cystitis: 27.9%pts, Hematuria 14%, Fever 2.3%, Nausea and

				vomiting 2.3%, Generalized skin rash 2.3%
Torelli et al. 2001	Italy	130/39	(80 mg/institution) started within 20 days after TUR-1 monthly for 11 months	chemical cystitis in 9 patients (6.7%), bacterial cystitis in 2 (1.5%)
Bassi et al. 2002	Italy	26/4	6 80 mg EPI (in 50 ml sterile saline)	Grade of toxicity G1 G2 G3 G4 Bladder spasms/dysuria 4(13.7%) 9(31%) 2(6,89%) - Hematuria - 3(10.3%) - - Fever - 1(3%) - -
Mitsumori et al. 2004	Japan	51/18	A, delayed instillation (first instillation 7 days after TURBT) and low-dose (30 mg once every 2 weeks, six times B, early instillation (three instillations before 7 days after TURBT) and low-dose C, delayed and high-dose (30 mg once weekly 12 times) instillation D, early and high-dose	18 patients (26%) irritated bladder 13pts (18.84%), haematuria 1 pt (1.44%), and bacterial cystitis 4 pts (5.79%)
Kato et al. 2015	Japan	71/17	30 mg of EPI plus 200 mg of Ara-C dissolved in 20 mL of physiological saline weekly for the first year, then every 2 weeks for the second year, once a month for the third year, and once every 3 months during the fourth and fifth years	Severe, reversible cystitis 2 pts (4.5%)
Legend	EPI: Epirubicin; TURBT: Trans Urethral Resection of Bladder Tumor, Ara-C: Cytosin Arabinoside			

3.2. Epirubicin versus BCG

Nine studies compared EPI to BCG in terms of recurrence and progressions rates. They included 1422 patients, of which 316 were females. Prognostic factors included age, gender, number, tumor stage pTa-pT1 and grade G1-G3 (12-19). The recurrence rate was lower for patients treated with BCG instillations [20–24] and regarding progression the difference was limited or no difference was noticed [20,21], see Table 2.

Table 2. Studies comparing recurrence and progression rates after treatment with Epirubicin and Bacillus Calmete Guerin.

Study/year	Country	Design (Period)	No pts. m/f	Age Median (IQR)	Stage	Grade	Variables	Recurrence	Progression	Follow-up
Duchek et al. 2009	Sweden	Prospective study February 1999 - December 2006	256	67	T1	BCG G2 35%(28) 32%(26) EPI G3 91%(72) 92%(74)	Drug, Size, Multifocality Age, Re-TUR, Grade, Concomitant CIS	34 pts (BCG) Vs 47 pts (EPI&iFN)	no difference regarding the progression	2 years
Marttila et al. 2016	Finland	1997 - 2008.	272	71/70	pTa/pT1/urothelial neoplasm 103/10/2 (90/9/2) 108/6/0 (95/5/0)	BCG G1 75%(65) G2 27%(24) EPI/IFN G1 79%(69) G2 24%(21)	gender, age, no. of recurrences, time to recurrence, multifocality, cytology grade, tumor diameter, perioperative Epirubicin	After 5 yr, the recurrence-free estimate of the BCG group was significantly better than that of the EPI/IFN group, 59% versus 38%, respectively	There was no significant difference in the probability of progression or overall survival	BCG/EPI 7.5yr/7,4yr
Tozawa et al. 2001	Japan	March 1990 to February 1999	72	70 years	BCG pTa 13 pT1 37 EPI pTa 7 pT1 57	BCG G1 14 G2 34 G3 2 EPI G1 6 G2 50 G3 8	age, sex, tumor grade, stage, number of recurrences before TURBT,	32.0% (16/50) in BCG-treated patients 26.1% (6/23) of patients with chemoimmunotherapy	However, the comparison of Kaplan-Meier curves at the 3-year time point revealed a lower tumor recurrence in the BCG monotherapy group,	2 years

									significant at a level of p = 0.026	
Melekos et al.1996	Greece	Prospective Study	132	BCG/EPI 65.3/67.2	BCG Ta 34 T1 24 EPI Ta 38 T1 23	BCG G1 12 G2 34 G3 12 EPI G1 12 G2 35 G3 14	gender, age, primary tumors, multiple tumors, stage, grade, previous intravesical therapy, concomitant CIS	Free of recurrence 44% for Epirubicin vs 55% for BCG 10 (16.4%) in the Epirubicin group and 7 (12%) in the BCG	10(16.4) EPI Vs 7(12) BCG	2 years
Chi Wai Cheng et al. 2004	China	Between July 1988 and September 1999	36	71.6 years	T1	G3	NA	16 pts (44.4%)	9 pts (25%)	12 years
Chi Wai Cheng et al. 2005	China	Between October 1991 and September 1999	209	69.9 years	BCG Ta 63 T1 39 EPI Ta 77 T1 29	BCG G1 19 G2 47 G3 33 EPI G1 30 G2 55 G3 20	NA	59 pts had recurrence with EPI VS 30 pts with BCG	The 10-year Kaplan-Meier estimate for progression-free survival was 78% in BCG Vs The 10-year Kaplan-Meier estimate for progression-free survival was 74% in EPI	23 months
Iida et al. 2009	Japan	Retrospective study between January 1991	93	73.95 years	EPI T1/G3 69pts BCG T1/G3 24pts	G3	sex, age, multifocality, stage, grade, and previous intravesical therapy	31 pts (33%)	14 pts-cancer progression	68.7 months

		and September 2005								
Hemdan et al. 2013	Sweeden	Prospective study Between 1999 and 2006	256		BCG T1G2-3 126pts EPI+IFN T1G2-3 124pts	G2-3	risk of recurrence, treatment failure, cancer-specific death	5 years BCG vs Epi+IFN 59%vs38%	free of progression 78% and 77%	6.9 years
Melekos et al. 1993	Greece	Prospective trial	190	Epi 65.8y BCG 67.1y	EPI Ta: 42 T1: 25 BCG Ta: 41 T1: 21	EPI G1:31 G2:25 G3:11 BCG G1:27 G2:27 G3:8	gender, age, primary tumors, multiple tumors, stage, grade, previous intravesical therapy, concomitant CIS	EPI 27 (40.3) BCG 20 (32.2)	EPI 6 (9) BCG 4 (6.5)	32.9 months

Legend: BCG: Bacillus Calmete Guerin, EPI: Epirubicin, IFN: Interferon, CIS: Carcinoma in situ.

3.3. Epirubicin versus Mitomycin C

Two studies [25,26] had investigated the effect of EPI compared to that of MMC and they showed that there is no significant differences between the two drugs (EPI vs. MMC) regarding progression and recurrence, see Table 3.

3.4. Epirubicin versus Gemcitabine

Two studies [27,28] had investigated the effect of EPI compared to that of GEM. They included 459 patients, of which 135 were female. Zhang et.al [28] has shown a statistical significance of low recurrence and progression in patients with high risk NMBIC, treated with GEM with a (HR of 0.165, 95% CI 0.069–0.397, $p= 0.000$) for recurrence and (HR = 0.160, 95% CI 0.032–0.799, $p= 0.026$) for progression. On the other hand, Wang et.al [27] found no statistical significance regarding recurrence and progression, see Table 4.

3.5. Chemohyperthermia with Epirubicin

Chiancone et al. [29] looked at the oncological results of EPI as adjuvant treatment using hyperthermic intravesical chemotherapy (HIVEC) administration. They included 26 patients, of which 18 males and 8 females. Recurrence occurred in two patients (7.69%) from the high-grade group and in one (3.85%) from low grade group, and two patients (7.69%) had progression. They concluded that EPI with HIVEC is a valid option of treatment for high grade NMBIC with BCG intolerance, and there was no difference in oncological outcomes compared to MMC. Similar results were reported also by Arends et al. [30] when using the Synergo device to administrated EPI or MMC into the bladder, see Table 5.

Table 3. Studies comparing recurrence and progression rates after adjuvant treatment with Epirubicin or MMC in patients with non-muscle invasive bladder cancer.

Study/year	Country	Design (Period)	No pts. m/f	Age Median (IQR)	Stage	Grade	Variables	Recurrence	Progression	Follow-up
Bono et al. 1996	Italy	October 1986- April 1989	108	65.5 years	Study (30864) (MMC) Ta-82 patients (76%) T1 in 26 (24%) Study (30869) (EPI) Ta in 35 patients (87.5%) T1 in 5 patients (12.5%)	Study (30864) (MMC) G1 in 33 cases (30.6%), G2 in 67 cases (62.0%) and G3 in 8 cases (7.4%). Study (30869) (EPI) G1 in 15 cases (37.5%), G2 in 22 cases (55.0%) and G3 in 3 cases (7.5%)	<85 years, good general health, multiple primary or recurrent Ta-T1	Treated with MMC 19pts – 19.79%	progression in 20% of patients	N.A
Calais da Silva et al. 1992	Portugal	N.A	46/14	68 years	EPI Ta- 6 patients T1 23 patients MMC Ta 1 patient T1 17 patients	EPI G1-11 patients G2-14 patients G3-7 patients MMC G1-10 patients G2-16 patients G3-2 patients	Single/multiple tumor Primary-recurrent	EPI Primary Ta 6 patients with 1 recurrence; primary T1- 23 patients with 8 recurrences, and recurrent T3 patients with 3 recurrences. MMC Ta 1 patient with no recurrence; primary T1 17 patients with 5 recurrences; recurrent Ta 2 patients with no recurrences, and T 8 patients with 3 recurrences.	N.A	17.7 months
Legend	MMC: Mytomicin C; EPI: Epirubicin; N.A: not available									

Table 4. Studies comparing recurrence and progression rates after adjuvant treatment with Epirubicin or Gemcitabine in patients with non-muscle invasive bladder cancer.

Study/year	Country	Design (Period)	No pts. m/f	Age Median	Stage	Grade	Variables	Recurrence	Progression	Follow-up
Wang et al.2019	China	January 1996 to July 2018	91/33f	NA	NA	GEM Low 42(57.53%) High 31(42.47%) EPI Low 19(51.35%) High 18(48.65%)	gender, age, multifocality, size, grade, risk, re-TURBT	Gemcitabine intravesical chemotherapy group was significantly related to a lower rate of recurrence in GEM (HR = 0.165, 95% CI 0.069–0.397, P = 0.000)	lower rate of progression with GEM (HR = 0.160, 95% CI 0.032–0.799, P = 0.026)	GEM 34.8 months EPI 35.9 months
Zhang et al. 2021	China	Retrospective study from October 2015 to October 2019	233/102f	62y	Ta A29 B30 C36 T1 A38 B51 C38	Low Grade A34 B40 C48 High Grade A33 B41 C26	gender, age, size, number of tumors, stage, grade	P=1.00-no statistical significance	P=0.69-no statistical significance	
Legend	GEM: Gemcitabine, EPI: Epirubicin, TURBT: Transurethral Resection of Bladder Tumors, N.A: not available									

Table 5. Studies comparing recurrence and progression rates after adjuvant treatment with Epirubicin or MMC using hyperthermia in patients with non-muscle invasive bladder cancer.

Study/year	Country	Design (Period)	No. patients male/female	Chemo hyperthermia	Characteristics	Age years Mean/SD	Stage/Grade	Variables	Recurrence	Progression	Follow-up
Chiancone et al. 2020	Italy	Retrospective March 2017- February 2020	98/33 (33.7%)	HIVEC 72 pts. MMC vs 26 pts. EPI	BCG failure or intolerance patients with high-risk NMIBC	67.54 ±7.96 vs. 64.35 ±8.56	Ta G3 15(79.17%) vs 11(57.69%) T1G3 57(20.83%) vs 15(42.31%)	Age, gender, smoking status, BMI, diabetes, number of tumors, tumor size, recurrence rate, pathologic state, Concomitant CIS, Tumor on RE-TURB, previously treated with MMC, BCG failure group.	High-grade 14/72 (19.44%) MMC vs. 2/26 (7.69%) EPI Low-grade 3/72 (4.17%) MMC vs. 1/26 (3.85%) EPI	MMC 4/72 (5.56%) vs. EPI 2/26 (7.69%)	10.5 vs. 14 months
Arends et al. 2014	Netherlands	Prospective maintain database 2002 - 2013	160/ 36 (22.5%)	Synergo SB-TS 101 system 20 EPI 140 MMC	NMIBC refractory to regular intravesical treatment	65 (range 34 to 87)	pT1 75 (46.9%), pTa 85 (53.1%), high- grade 104 (65.0%) low-grade 56 (35.0%).	Age, gender, CIS history, No. preCHT TURBTs, PreCHT T1 on histology, PreCHT highly recurrent NMIBC, PreCHT grade	1 year RFS 64% EPI vs. 59% MMC 2 year RFS 55% EPI vs. 46% MMC, (p=0.303)	NA	75.6 months
Legend	HIVEC: Hyperthermic intravesical chemotherapy; MMC: Mitomycin C; EPI: Epirubicin; SD: standard deviation; NMIBC: non-muscle invasive bladder cancer, TURBT: transurethral resection of the bladder tumors; CIS: carcinoma in situ; CHT: chemo hyperthermia; BCG: Bacillus Calmette Guerin; BMI: Body Mass Index; NA: not available										

4. Discussion

We found out by analyzing the current available data that the most common adverse event after adjuvant intravesical instillation with EPI are cystitis, dysuria, pollakiuria and hematuria [31]. Similar after MMC were reported as follows: cystitis (34%), skin rash, pruritis and local irritation [25]. After Gemcitabine were reported the most nausea/vomiting (44.2%) and constipation/diarrhea (23.4%) [32]. It seems that the overall toxicity of EPI is in the same range as other therapeutic options for intravesical chemotherapy.

However, it is well known that the treatment with BCG is more efficient in terms of preventing progression as we showed in the summary table of the included studies (Table 2). Data that was already confirmed by the meta-analysis of You et al.[33].

In terms of adjuvant chemotherapy, it was not observed a clinically significant difference between EPI, MMC or GEM. The RFS and the PFS rates are slightly similar. However, a recent meta-analysis showed that among 22 studies that adopted induction followed by maintenance intravesical therapy, with reference to the lower-dose BCG, EPI was associated with a significantly higher risk of recurrence (Odds ratio [OR]: 2.82, 95% CI: 1.54-5.15), but not other intravesical chemotherapies, with no significant differences in risk of progression among the intravesical therapies [34]. Further prospective studies are needed to answer this key question, which drug has the best tolerability, safety, and impact on oncological outcomes. Some trials are already recruiting patients to test in vitro the drug with the most antitumor efficacy [35]. Until then, clinicians should use all the therapies available based on shared decision making with the patient and based on guidelines recommendations.

In the case of using chemohyperthermia it seems that might be a certain benefit, however not quantifiable yet. In case of MMC, a recent Randomized Clinical Trial (RCT) showed that RFS at 24 months was 61% (95% CI 51-69%) in the chemohyperthermia arm and 60% (95% CI 50-68%) in the control arm (HR 0.92, 95% CI 0.62-1.37; log-rank $p = 0.8$) [36]. These results should be interpreted taking into account that it was used for chemohyperthermia instillations only the Combat bladder recirculating system (Combat Medical, St. Albans, UK) and there are many other systems available for hyperthermia intravesical instillations [37], and their use may lead to other results. Further, from the all available data it was observed no difference in case of RFS estimates between patients treated with EPI and patients treated with MMC [38]. Regarding comparison with standard of care, this is BCG treatment. A recent meta-analysis showed no statistical significant difference between chemohyperthermia and BCG, as adjuvant treatment [39]. However, there is a paucity of data regarding this question and a solid conclusion cannot be drawn.

Limitation of this current review lays on the retrospective nature of the included studies, lack of sufficient data published to confirm a difference between drugs used for adjuvant intravesical instillation, heterogeneity of reported data, number of patients included and no prospective head-to-head comparison.

5. Conclusions

Epirubicin has meaningful efficacy in addressing NMIBC; however, its efficacy and indications are limited to selected patients, mainly with an intermediate risk according to EAU guidelines stratification and to those unfit or unresponsive to BCG therapy. Retrospective studies highlight that BCG stands out as more effective than Epirubicin in terms of preventing recurrence. Epirubicin exhibits similar oncological performances to Gemcitabine and Mitomycin C currently used for adjuvant therapy in NMIBC. Novel delivery mechanisms such as hyperthermia are promising newcomers.

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