Comparison of intravesical instillation of Bacille Calmette-Guérin and epirubicin: a randomized controlled trial

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Research article

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Abstract

Background

The optimal regimen of instillation for patients with non-muscle invasive bladder cancer (NMIBC) and the recurrence-related factors are still needed to be clear.

Methods

The patients underwent transurethral resection of bladder tumor who diagnosed as intermediate or high risk NMIBC were randomized to receive bacillus Calmette–Guérin (BCG) 19, 15 times or epirubicin (EPI) 18 times (2:2:1). The primary end point was disease-free survival (DFS), the secondary end point was progression free survival (PFS). Associations between clinicopathological factors and prognosis were estimated, with accuracy of the prognostic models Spanish Urological Club for Oncological Treatment (CUETO) and European Organization for Research and Treatment of Cancer (EORTC) evaluated.

Results

A total of 93 patients (BCG19 for 35; BCG15 for 37 and EPI18 for 21) were included, with median follow-up time for 33.46 months. Recurrence and progression occurred in 22 and 8 of patients separately, and significant longer recurrence-free survival was noted in the BCG and primary bladder cancer groups. Higher general complication rate was seen in BCG group compared with EPI groups (83.33% and 61.90%, respectively; P = 0.022), but no grade 3–5 adverse events happened in both groups. Concordance indices for the CUETO and EORTC models were 0.766 and 0.741 for all our series and 0.812 and 0.817 for the BCG subgroup, respectively.

Conclusion

BCG instillation significantly reduced the rate of recurrence compared with epirubicin in this population. The EORTC and CUETO models exhibited high accuracies for the prediction of BCG treatment failure.

Trial registration:

This study was approved by Center for Drug Evaluation of National Medical Products Administration (CDENMPA, China) and Ethics Committee of our institute, with the whole process supervised. The registration number in CDE-NMPA was CTR20150840 (website of CDE: http://www.cde.org.cn/).

Background

Approximately 75% of patients with bladder cancer have non-muscle invasive bladder cancer (NMIBC; Ta or T1 disease) at the time of primary diagnosis(1). These patients can be divided into three risk groups (i.e., low, intermediate, and high risk). For intermediate- and high-risk patients, transurethral resection of bladder tumor (TUR-BT) and subsequent intravesical drug instillation are the standard treatments. However, there is currently no conclusion reached regarding treatment with instillation (2).

It has been confirmed that treatment with Bacillus Calmette–Guérin (BCG) following TUR-BT is superior to TUR-BT alone or combined with chemotherapy in Caucasian patients(3, 4). In addition, maintenance treatment with BCG has been recommended for intermediate- and high-risk patients(2). However, the use of BCG in Chinese patients has been limited by the high rate of intolerance and complications previously reported in clinical practice, and the design of trials of BCG instillation has been suboptimal. Moreover, despite the administration of maintenance therapy with BCG, 32.6% and 13.4% of patients continue to experience recurrence and tumor progression, respectively(5). In this study, we performed a randomized controlled trial to evaluate the efficacy and safety of adjuvant intravesical BCG or epirubicin (EPI) therapy for different regimes; we also estimated the predictive value for prognostic models to evaluate the prognostic factors for NMIBC.

Methods

Patients and treatment

A prospective, randomized, controlled, non-blinded study, conducted at West China Hospital, Sichuan University, compared intravesical BCG and EPI treatment. The study was approved by the ethics committee of the Center for Drug Evaluation of the National Medical Products Administration (China) and Ethics Committee of West China Hospital.

The inclusion criteria were: age 20–75 years; TUR-BT with completely tumor resection. BT was completely resected with pathologically proven intermediate or high-risk non-muscle invasive bladder urothelium carcinoma according to the European Association of Urology (EAU) guidelines for risk stratification of NMIBC(2).

Exclusion criteria were: a. Eastern Cooperative Oncology Group performance status score >1; b. patients with active tuberculosis or receiving treatment for anti-tuberculous; c. immune deficiency or undergoing immunosuppressive therapy; d. severe complication (e.g., serious cardiovascular and cerebrovascular disease), or presence of other types of cancer; e. previous diagnosis with muscle-invasive bladder cancer; f. patients underwent treatment (e.g., chemotherapy, radiotherapy or immunotherapy) during the previous 4 weeks which may influence the research results; f. serious intraoperative and postoperative complications (e.g., bladder perforation, serious postoperative hematuresis, bladder irritation, etc.); and g. patients not suitable to receive treatment or not able to participate in our trial due to pregnancy, severe disability, serious psychological problems, etc.

Post-operative immediate irrigation with EPI 50 mg was performed within 24 h after TUR-BT. After confirming the presence of intermediate- or high-risk NMIBC according to surgical findings and the final pathological report, patients who participated in the study were randomized into three bladder irrigation groups: a. BCG 19 group (BCG 120 mg weekly for six times, followed by biweekly irrigation for three times, and then monthly for 10 times, for a total of 19 irrigations with BCG); b. BCG 15 group (BCG 120 mg weekly for six times, followed by irrigations for the first 3 weeks and at 3, 6, and 12 months after surgery, for a total of 15 irrigations with BCG); and c. EPI 18 group (EPI 50 mg weekly for eight times, followed by monthly irrigation for 10 times, for a total of 18 irrigations). The randomization was performed within 14 days after surgery, at a 2:2:1 ratio (Das for IWRS Version 5.0, BioVoice & BioGuider, Beijing, China). Subsequently, irrigation was initiated on day 14 post operation and the duration of treatment was 1 year.

Follow-up and outcomes

For intermediate-risk patients, cystoscopy was performed 3 and 6 months after surgery, then biannually until 5 years. For high-risk patients, cystoscopy was performed trimonthly until 2 years after surgery, then biannually until 5 years. Urinalysis was performed prior to each irrigation. Patients were followed up until recurrence, progression, or discontinuation of treatment for any reason. Adverse effects were recorded at each follow-up according to the Common Terminology Criteria for Adverse Events Version 4.0(6).

The initiation time was the day TUR-BT was performed. The primary end point was recurrence during follow-up, while the secondary end point was progression to muscle-invasive bladder cancer or therapy-related discontinuation of treatment. Recurrence-free survival (RFS) and progression-free survival (PFS) times were recorded. BCG failure and intolerance were recorded according to the definitions of the EAU (2).

Data collection

Recorded clinical variants included gender, age and smoking history. Intraoperative recordings included tumor size, site, and number. Tumor histopathological type, T stage (8th American Joint Committee on Cancer TNM classification system)(7), tumor grade (2004 World Health Organization grading system), and carcinoma in situ status. All pathological reports were provided by the Pathology Department of West China Hospital.

Statistical methods

Differences in survival between two or more subgroups were evaluated using log-rank tests. Univariate and multivariate Cox regression analyses were performed to determine the clinicopathological parameters associated with the recurrence of patients with NMIBC. Patients were stratified using the European Organization for Research and Treatment of Cancer (EORTC) risk tables(8) and the Spanish Urological Club for Oncological Treatment (CUETO) scoring model(5). The predictive ability of these outcome prediction models was evaluated using the concordance index (c-index)(9).

Statistical analyses were performed using the SPSS Statistics version 25 (IBM, Armonk, NY, USA) and The R Programming Language 3.5.0 software (The R Foundation, Vienna, Austria). A P-value <0.05 denoted statistical significance.

Results

Patient baseline data

Totally 93 patients were enrolled for analysis (BCG19, BCG15 and EPI 18 groups for 35, 37 and 21 cases respectively, Table 1). The mean age was 62.96 years (standard deviation: 8.16 years), and the median follow-up time was 33.46 months (interquartile range: 18.30–44.80 months). There was no significant difference noted in baseline clinicopathological factors between the BCG and EPI treatment subgroups, except for T stage. Eight patients underwent radical cystectomy after NMIBC.

Efficacy and safety for BCG and EPI treatment

After follow-up for more than one year, recurrence occurred in 12 BCG treated patients (16.67%), with 9 of them suffered recurrence in the course of BCG irrigation. Progression happened in 6 BCG treated patients (8.33%). Meanwhile, number of recurrence and progression for EPI were 10 (47.61%) and 2 (9.52%) respectively. 6 cases suffered recurrence during EPI therapy (28.57%). RFS was significantly longer in the BCG group (Figure 1, P=0.002), but no significant differences were seen between BCG19 and BCG15 regime subgroups (Figure 1, P=0.975). PFS differences between BCG and EPI therapy could not be evaluated since limited ending events.

Side effects were also collected (Table 2). Higher general complication rate was seen in BCG group compared with EPI groups (83.33% and 61.90%, respectively; P=0.022); however, most of complications for BCG group were treatment-free and there were no severe adverse events (grade 3-5) happened for these two treatment groups. Urocystitis was the most frequent complication for intravesical therapy, for which incidences were significant higher in BCG subgroup (75.00% vs 52.38%, P=0.047); fever was a unique complication after BCG therapy (16.67%), but all of them were treatment-free. Hematuresis occurred both after BCG and EPI treatment, with no significant difference demonstrated (43.1% vs 42.9%, P=0.987). There were more patients suffered rare complications such as respiratory infection, hypertension and hyperglycemia after BCG therapy, but difference wasn’t significant (29.17% vs 9.52%, P=0.122). Six patients didn’t complete full cycle of BCG therapy due to intolerance of complications, and all of them happened during the maintenance period (each had 3 patients for BCG 19 and 15 subgroups; five were due to urocystitis and one for hematuriesis); only one patient among them suffered disease recurrence two years after treatment had ended.

Influence of clinicopathological factors and treatment methods on recurrence

Among the 93 post-TUR-BT patients, the univariate analysis revealed that better survival was observed in those without smoking and previous bladder cancer history, with younger age, low tumor stage and less

tumor number (Table 3). However, only prior recurrent history was significantly correlated with poor RFS (P=0.001). Meanwhile, when we considered these in BCG treatment subgroups (n=72), we also found better PFS for male patients and those with well nuclear grade, but weren't significant; and PFS for those patients with prior recurrence rate less than one per year significant poorer than those with recurrence rate for more than one per year (P=0.033).

The EORTC risk tables and CUETO scoring model were used to predict recurrence in patients with postoperative NMIBC. For all 93 cases, the c-index of EORTC and CUETO was 0.766 and 0.741, respectively. These numbers were obviously higher than those of prediction according to tumor stage or grade alone or by EAU risk group stratification (Table 4). Meanwhile, higher predictive accuracy was recorded in the BCG subgroup (0.812 and 0.817, respectively) (Table 4).

Discussion

Recurrence of NMIBC is affected by numerous factors, including tumor size, number of tumors, prior recurrence rate, T stage, grade, and presence of carcinoma in situ (8). Patients at high risk of recurrence and progression can be identified through a comprehensive consideration of these factors. In the risk group stratification of EAU, patients with NMIBC are stratified into three risk groups (low, intermediate, and high risk) and different treatment strategies and follow-up measures are recommended(2). However, these strategies are not effective, with 47.8% of patients suffering at least one recurrence(8).

Since Morales first reported the irrigation treatment with BCG in bladder cancer(10), the efficacy of this method has been widely demonstrated and became the standard therapy for intermediate- and high-risk NMIBC(11). Lower recurrence rates were observed in BCG-treated patients compared with those who underwent chemotherapy(3, 12); however, higher complication rates also occurred(13). There is a limited number of studies on the use of BCG in Chinese patients due to the intolerance and contraindications of therapy with BCG. Nonetheless, this was gradually accepted by patients due to the improvement of supporting method. We firstly reported a randomized controlled trial of Chinese patients which compared the efficacy of BCG and EPI on NMIBC. The results suggested that, although six patients showed intolerance to therapy with BCG, this approach has advantages in preventing recurrence, without a significantly higher rate of side effects versus treatment with EPI.

Six weeks inductive BCG instillations only are not enough for intermediate and high risk NMIBC treatment, and current evidences support 1–3 years maintenance schedule(14). A recent meta-analysis which included 1951 patients demonstrated that longer-maintenance therapy didn't increase side effect compared with induction therapy only, and longer maintenance (more than 1 years) wasn't superior to 1 years maintenance(15). However, the optimal number and frequency of maintenance intravesical therapy is still unknown(2). Since that, we compared two regime of 1 years BCG maintenance therapy, and found that there was no significant difference between BCG 15 and 19 regimes among recurrence and side effects.

Even treated with BCG, recurrence continues to occur in many patients treated with BCG; 32.6% as reported by Jesus et al.(5). Even after a full course of maintenance therapy with BCG, 15.7% and 26.3% of patients continue to experience early and late recurrence, respectively(16). Hence, considerable efforts were focused on the prognostic prediction of NMIBC to more rationally stratify patients, and identify those more suitable for individual surveillance and treatment programs. The EORTC scoring system, based on patients who underwent several instillation protocols, is used to predict recurrence and prognosis in patients with NMIBC (c-index of internal validation of 0.66 and 0.75, respectively)(8). Subsequently, the CUETO scoring model was designed to predict prognosis in patients receiving maintenance therapy with BCG (c-index of interval validation of 0.636 and 0.687 for early recurrence and progression, respectively)(5). Compared with risk group stratification, the tumor recurrence status (an important prognostic factor) was included in the CUETO and EORTC. Furthermore, in our study, these two models exhibited significantly better differentiations than risk group stratification, especially in BCG-treated patients, suggesting that CUETO and EORTC may be more suitable for the prediction and stratification of patients with NMIBC.

There are limitations for our study. For one thing, the sample size is relatively small for further subgroup analysis; for another, the follow-up time is short so that the secondary end point of progression could not be evaluated since limited positive events occurred. However, since all patients had completed more than 1 year's follow-up with complications recorded in detail, present results can well reflect the feasibility of BCG instillations in Asian NMIBC populations.

Conclusion

Maintenance treatment with BCG demonstrated better control of recurrence in Chinese patients with NMIBC after TUR-BT versus intravesical therapy with EPI. Prior recurrence status is an important prognostic factor for recurrence, while the EORTC and CUETO prognostic models exhibited higher prediction accuracy for recurrence than tumor stage, grade, or risk group stratification.

Abbreviations

NMIBC: non-muscle invasive bladder cancer; TUR-BT: transurethral resection of bladder tumor; BCG: Bacillus Calmette–Guérin; EPI: epirubicin; EAU: European Association of Urology; RFS: Recurrence-free survival; PFS: progression-free survival; EORTC: European Organization for Research and Treatment of Cancer; CUETO: Spanish Urological Club for Oncological Treatment.

Declarations

Ethics approval and consent to participate and publications

This study was approved by Center for Drug Evaluation of National Medical Products Administration (CDENMPA, China) and Ethics Committee of our institute, with the whole process supervised. The

registration number in CDE-NMPA was CTR20150840 (Registered 21 December 2015, website of CDE: http://www.cde.org.cn/). All the research registration and ethical approval documents were added below. Patients and their authorized family members had been fully informed before follow-up work was performed, with informed consent signed. All procedures adhere to CONSORT guideline.

Availability of data and materials

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy restrictions.

Competing Interests

The authors declare that they have no competing interests.

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Authors' contributions

X L managed the study. Y S, W Y, T L designed the study, X H, Z Y, S R and K W collected the data. Y S controlled the quality of data and algorithms. W Y, T L analyzed and interpreted the data. J L, W D, S X managed the statistical analysis. S F, Y W prepared the manuscript. Y S, W Y, T L edited the manuscript. X L reviewed the manuscript. All authors read and approved the final manuscript

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Tables

Table 1. Clinicopathological data of patients with NMIBC

Clinicopathological variants	BCG group (n=72)	EPI group (n=21)	Total (n=93)	P-value
Gender				0.390
Male	57	19	76	
Female	15	2	17	
Preoperative age (years)				0.930
≤60	24	8	32	
60–70	34	10	44	
>70	14	3	17	
Smoking history				0.089
No	43	8	51	
Yes	29	13	42	
Prior recurrence rate				0.232
Primary	44	13	57	
Recurrent, ≤1 rec/yr	18	2	20	
Recurrent, >1 rec/yr	10	6	16	
T category				0.002
Ta	51	21	72	
T1	21	0	21	
Grade				0.331
Low grade	32	12	44	
High grade	40	9	49	
Tumor size				0.465
<3 cm	38	9	47	
≥3 cm	34	12	46	
No. tumors				0.793
≤3	49	13	62	
>3	23	8	31	
Risk stage				0.453
Intermediate risk	27	10	37	

High risk	45	11	56	
Recurrence				0.006
No	60	11	71	
Yes	12	10	22	
EORTC risk tables				0.218
1–4	28	5	33	
5–9	39	16	55	
10-17	5	0	5	
CUETO scoring model				0.962
0-4	21	7	28	
5-6	26	8	35	
7-9	20	5	25	
10-16	5	1	6	

NMIBC: non-muscle invasive bladder cancer; n: number of patients; yr: year; No: number; Recurrent, ≤1 rec/yr: prior recurrence rate of less than one per year; Recurrent, >1 rec/yr: prior recurrence rate of more than one per year; EORTC: European Organization for Research and Treatment of Cancer; CUETO: Spanish Urological Club for Oncological Treatment.

Table 2. Complications for intravesical therapy.

Complication	BCG19 n (%)	BCG15 n (%)	EPI18 n (%)	P value BCG19 vs 15	P value BCG vs EPI
Urocystitis	27(73.0%)	27(77.1%)	11(52.4%)	0.683	0.047
Hematuresis	17(48.6%)	14(37.8%)	9(42.9%)	0.358	0.987
Fever	5(14.3%)	7(18.9%)	0(0.0%)	0.598	0.062
Others	9(24.3%)	12(34.3%)	2(9.5%)	0.353	0.122
CTCAE grade					
Grade1	29(82.9%)	24(64.9%)	13(61.9%)	-	-
Grade2	2(5.7%)	6(16.2%)	0(0.0%)	-	-
Grade3-5	0(0.0%)	0(0.0%)	0(0.0%)	-	-
Total adverse events	31(88.6%)	30(81.1%)	13(61.9%)	0.226	0.022

BCG: Bacillus Calmette–Guérin; EPI: epirubicin; n: number, CTCAE: Common Terminology Criteria for Adverse Events; Others: rare complications including respiratory infection, hypertension and hyperglycemia.

Table 3. Univariate analysis of the NMIBC cohort and BCG subgroup

Clinical pathological data	Total patients (n=93)		BCG subgroup (n=72)	
	P-value	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)
Males[a]	0.538	1.466 (0.434–4.958)	0.718	0.786 (0.213–2.905)
60–70 years[b]	0.255	0.592 (0.240–1.459)	0.546	0.682 (0.197–2.360)
>70 years[c]	0.310	0.512 (0.140–1.865)	0.647	0.682 (0.132–3.514)
Smoking history[d]	0.071	2.226 (0.933–5.314)	0.473	1.514 (0.488–4.695)
Recurrent[e]	0.001	9.781 (3.281–29.164)	0.003	21.864 (2.818–169.651)
Recurrent, ≤1 rec/yr[f]	0.062	3.282 (0.944–11.412)	0.033	10.827 (1.209–96.991)
Recurrent, >1 rec/yr[g]	0.001	15.121 (5.297–43.167)	0.001	53.346 (6.522–436.343)
T1[h]	0.892	1.072 (0.394–2.915)	0.246	1.972 (0.626–6.215)
High grade[i]	0.920	0.958 (0.415–2.212)	0.359	1.754 (0.528–5.825)
Tumor size ≥3 cm[j]	0.009	0.266 (0.098–0.722)	0.068	0.193 (0.042–0.884)
No. tumors >3[k]	0.344	1.509 (0.644–3.540)	0.397	1.644 (0.520–5.197)
High-risk tumor stage[l]	0.504	1.345 (0.564–3.210)	0.108	3.482 (0.762–15.912)
BCG 15 group[m]	0.956	0.969 (0.312–3.005)	0.975	1.018 (0.328–3.158)
EPI 18 group[n]	0.019	3.378 (1.225–9.313)	-	-

[a]: compared with females; [b] and [c]: compared with age ≤60 years; [d]: compared with non-smokers; [e], [f], and [g]: compared with incipient patients; [h]: compared with Ta; [i]: compared with low grade; [j]: compared with tumor size <3 cm; [k]: compared with number of tumors ≤3; [l]: compared with intermediate-risk patients; [m]: compared with the BCG 19 group; [n]: compared with the BCG cohort.

NMIBC: non-muscle invasive bladder cancer; BCG: Bacillus Calmette–Guérin; CI: confidence interval.; Recurrent, ≤1 rec/yr: prior recurrence rate of less than one per year; Recurrent, >1 rec/yr: prior recurrence rate of more than one per year.

Table 4. Predictive value of prognostic models

Prognostic grading systems	Total NMIBC cohort		BCG subgroup	
	c-index	(95% CI)	c-index	(95% CI)
T stage	0.526	(0.514–0.538)	0.592	(0.575–0.609)
Nuclear grade	0.534	(0.521–0.547)	0.590	(0.575–0.605)
Risk group stratification	0.572	(0.561–0.583)	0.635	(0.623–0.647)
CUETO scoring model	0.766	(0.753–0.779)	0.812	(0.800–0.827)
EORTC risk table	0.741	(0.729–0.753)	0.817	(0.805–0.829)

NMIBC: non-muscle invasive bladder cancer; BCG: Bacillus Calmette–Guérin; CI: confidence interval; c-index: concordance index; EORTC: European Organization for Research and Treatment of Cancer; CUETO: Spanish Urological Club for Oncological Treatment.

Figures

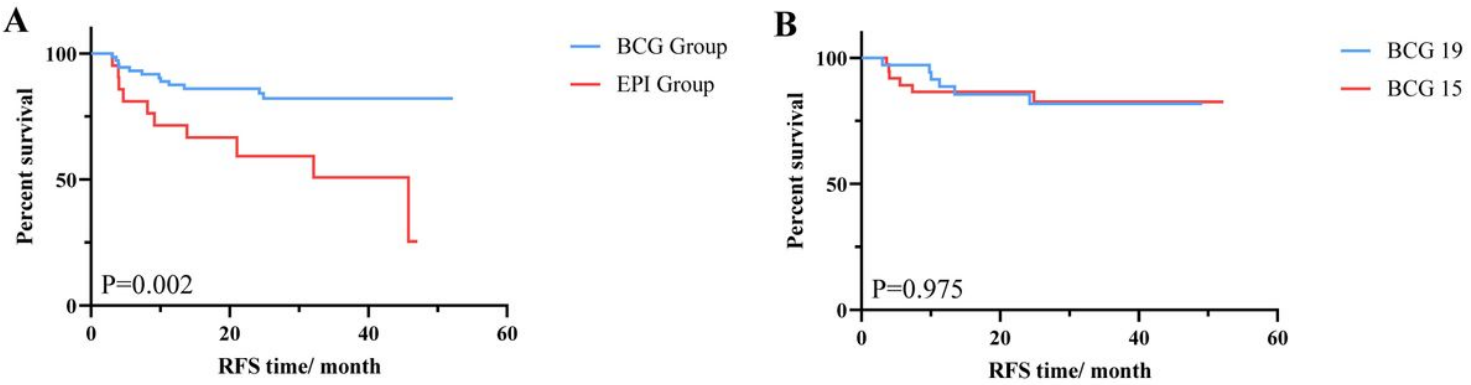

Figure 1

Comparison of recurrence-free survival for different intravesical instillation groups (A) Comparison of RFS between BCG and epirubicin groups. (B) Comparison of RFS between different BCG regime subgroups. RFS: recurrence-free survival; NMIBC: non-muscle invasive bladder cancer; BCG 19: BCG 19 times group; BCG 15: BCG 15 times group; EPI 18: epirubicin 18 times group.

Supplementary Files

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- CONSORT2010Checklist.doc
- CONSORT2010FlowDiagram.doc