

Outcome of intravesical doxorubicin installation in T1 non muscle invasive bladder cancer: experience from a tertiary hospital in Indonesia

Adhika Restanto Purnomo^{1*}, Andy Zulfiqqar²

¹Division of Urology, Soeradji Tirtonegoro General Hospital / Faculty of Medicine Public Health and Nursing Universitas Gadjah Mada. ²Division of Urology, Faculty of Medicine, Public Health and Nursing UGM, Yogyakarta, 55281, Indonesia

<https://doi.org/10.22146/inajbcs.v56i4.18139>

ABSTRACT

Submitted: 2022-12-14
Accepted : 2024-09-17

In Indonesia, the proportion of non-muscle bladder cancer is low compared to other countries. Doxorubicin is currently one of options for adjuvant therapy for nonmuscle invasive bladder (NMIBC) that underwent transurethral resection of bladder tumor (TURBT). This study is aimed to evaluate the oncological outcome of doxorubicin intravesical. Eight consecutive T1 bladder patients who underwent TURBT with complete tumor resection, and received intravesical chemotherapy were enrolled in this study. All the clinical data were gathered retrospectively. One of eight patients did not respond to intravesical doxorubicin instillation. Patients were recorded with univocal, low grade and female patients. In conclusion, doxorubicin intravesical may be one of options. Despite a small number of samples were enrolled. This preliminary data showed promising results on intravesical doxorubicin instillation.

ABSTRAK

Di Indonesia, proporsi kanker non-otot kandung kemih tergolong rendah dibandingkan negara lain. Doksorubisin saat ini merupakan salah satu terapi tambahan pilihan untuk *nonmuscle invasive bladder* (NMIBC) yang menjalani *transurethral resection of bladder tumor* (TURBT). Penelitian ini bertujuan untuk mengevaluasi luaran onkologis doksorubisin intravesika. Delapan pasien kandung kemih T1 berturut-turut yang menjalani TURBT dengan reseksi tumor lengkap, dan menerima kemoterapi intravesika dilibatkan dalam penelitian. Semua data klinis dikumpulkan secara retrospektif. Satu dari delapan pasien tidak merespons pemberian doksorubisin intravesika. Pasien tercatat sebagai pasien univokal, kelas rendah dan wanita. Kesimpulannya, doksorubisin intravesika mungkin merupakan salah satu pilihan. Meskipun jumlah sampel yang diteliti sedikit. Data awal ini menunjukkan hasil yang menjanjikan pada pemberian doksorubisin intravesika.

Keywords:

NMIBC;
TURBT;
doxorubicin;
intravesical;
oncological outcome

INTRODUCTION

Bladder cancer is reported as the 5th common diagnosed cancer in Europe, with almost 27.1% of new cases was diagnosed for non-muscle invasive bladder cancer (NIMBC) and the rest was muscle invasive bladder cancer as initial diagnoses.¹ Smoking is one of the factors that cause bladder cancer.^{2,3} Transurethral resection of bladder tumor (TURBT) or en-block resection followed

by mitomycin-c and Bacillus Calmette-Guerin (BCG) was used as gold standard of management.⁴ Despite the advance improvement of technology, the standard management of cancer has not changed and the recurrence rate still remains high. Therefore, left this cases remains as most expensive cancer and high risk of lifetime, and has not changed from the last decades. Thus, the newly published EAU guidelines still acknowledge that more research on emerging biomarker

*corresponding author: adhikarsst@gmail.com

is needed on this particular area to improve accuracy on both predicting end point in this cancer.^{5,6}

The shortage of BCG remains issues both in European and others countries.⁷ Although several alternative has been published recently. In the adjuvant treatment of NMIBC, two commonly used agents are BCG and doxorubicin. BCG immunotherapy is considered the gold standard that recommended by European Urology Association Guideline⁸ and American Urology Association⁹ guidelines for NMIBC. It has shown superior efficacy in reducing tumor recurrence and progression compared to other intravesical treatments. It stimulates the immune system to mount an immune response against cancer cells.

Doxorubicin is a chemotherapy drug that works by inhibiting DNA synthesis and cell proliferation as recommended in Indonesian Urology Association guideline.¹⁰ While BCG is primarily used for all cases NMIBC, doxorubicin is often considered as a second-line or salvage therapy in cases BCG has failed or is contraindicated. Both BCG and doxorubicin have demonstrated efficacy in reducing tumor recurrence rates. The used of doxorubicin was an alternative that has not widely reported. Several studies shown that the effectiveness of doxorubicin in term preventing recurrence, and progression. This study aimed to evaluate to evaluate the efficacy of doxorubicin for T1 patient in tertiary hospital in Indonesia.

MATERIAL AND METHODS

Patients

A total 8 patients whom diagnosed with urothelial bladder cancer from the Dr. Soeradji Hospital, Klaten, Central Java were enrolled on this study between, 2017-2020. Patient whom underwent complete resection, and underwent intravesical doxorubicin installation

chemotherapy were enrolled on this study.

Protocol

The primary end-point of this study was response to therapy towards Complete resection and six dosed doxorubicin intravesica as adjuvant therapy, the recurrence were described the as recurrent G3/HG (WHO 1973/2204) after completion of dosage doxorubicin, despite initial response. Unresponsive tumors toward chemotherapy were described as tumor recurrence within 3 mo, despite adequate chemotherapy exposures. The follow up programs were clinical evaluation, urinalysis, both cystoscopy and urine cytology according to EAU guideline 2019.⁸ Our research protocol were the installation of doxorubicin within 24 hr after completion initial TURBT, the installation were used 50 mg of doxorubicin in 50 mL normal saline that retrained at least 2 hr. The treatments were given on weekly schedule for 6 wk.

Analysis

Histological grade, cystoscopy, and clinical conditions (recurrence and upstaging) were used to evaluate of clinical outcome of patients.

RESULTS

On this pilot study, we found that the mean of ages patient was 64.1 + 8.39 y.o. with the majority of patient were males (87.5%). The characteristics of patients who enrolled on this study are presented in TABLE 1. On this pilot study, we found that the recurrence, and upstaging only found one patient with unifocal tumor, low-grade, and female patient (TABLE 2).

The recurrence was found on first cystoscopy evaluation on 3rd mo of therapy. Meanwhile, others patients did not show neither recurrence nor upstaging after one year evaluation on cystoscopy (TABLE 3).

TABLE 1. Characteristics of patients

Variable	Number
Ages (mean \pm SD yr)	64.1 \pm 8.39
Gender	
• Male	7
• Female	1
Histological grade [n (%)]	
• 1	4 (50.0)
• 2	1 (12.5)
• 3	3 (37.5)
Number of tumor lesion [n (%)]	
• 1	6 (75.0)
• > 1	2 (25.0)

TABLE 2. Characteristics of tumor

No. Case	Ages (yr)	Gender	Number of tumors	Histological grade	Recurrence	Upstaging
1	65	Male	Unifocal	Low	No	No
2	60	Male	Unifocal	High	No	No
3	72	Male	Multifocal	High	No	No
4	61	Female	Unifocal	Low	Yes	Yes
5	51	Male	Unifocal	High	No	No
6	61	Male	Unifocal	High	No	No
7	64	Male	Multifocal	High	No	No
8	79	Male	Unifocal	Low	No	No

TABLE 3. Characteristics of patients

No. cases	Ages (yr)	Gender	Cystoscopy evaluation (mo)			
			3 rd mo	6 rd mo	9 rd mo	12 rd mo
1	65	Male	No	No	No	No
2	60	Male	No	No	No	No
3	72	Male	No	No	No	No
4	61	Female	Yes	-	-	-
5	51	Male	No	No	No	No
6	61	Male	No	No	No	No
7	64	Male	No	No	No	No
8	79	Male	No	No	No	No

Patients with recurrence underwent other therapeutic modality such as re-TURBT and systemic chemotherapy.

DISCUSSION

Currently there are two issues related to management NMIBC in Indonesia i.e. 1) the low numbers of cases and the low clinical trial regarding the outcome of this diseases, and 2) unavailability of BCG strains that recommended by EAU and AUA guidelines as immunotherapy. Several agents of chemotherapy are suggested i.e. prevented the recurrence of T1 diseases, and doxorubicin alternative therapy.^{11,12} On this pilot study, doxorubicin demonstrated good efficacy to prevent recurrence and upstaging on T1 diseases, despite small number of cases that enrolled. Among 8 cases enrolled this study, only 1 case of recurrence and upstaging was observed. This case is found in low-grade tumor and female patients. In the treatment of NMIBC, both intravesical chemotherapy and BCG immunotherapy have been utilized. Intravesical chemotherapy involves the direct administration of chemotherapeutic agents such as mitomycin or doxorubicin into the bladder to target and destroy cancer cells. It is commonly used in patients with low to intermediate-risk NMIBC. On the other hand, BCG, originally developed as a tuberculosis vaccine, has emerged as the gold standard immunotherapeutic agent for high-risk NMIBC. The BCG works by stimulating the immune system to mount an immune response against cancer cells and has shown superior efficacy in reducing tumor recurrence and progression compared to intravesical chemotherapy. Several studies have demonstrated the superiority of BCG over intravesical chemotherapy in terms of reducing tumor recurrence rates and improving long-term outcomes in high-risk NMIBC patients.^{13,14}

Bladder cancer was also found

predominantly diagnoses in male compared to female. Several epidemiology studies reported that male have three or four times risks to develop bladder cancer in compare to female.^{15,16} In addition, there are widely data that supports females that developed urothelial bladder cancer have potential to developing tumor with more aggressive behavior and worse outcome compares males patients. The distinct difference of aforementioned tumor natures is hypotheses due to multifactorial results of environmental factors such as carcinogens (tobacco, and chemical) as well genetic, hormonal and dietary factors.¹⁷

This preliminary study showed that the recurrence and upstaging patient NMIBC that underwent intravesical doxorubicin installation chemotherapy is low compared to standard therapy BCG.^{18,19} This indicated that doxorubicin may be cheap alternative of adjuvant therapy to NMIBC. Even though small number of samples is the limitation of this study, further study is warrant to confirmed these findings. The conclusion that can be drawn from this study indicates that intravesical administration of doxorubicin can be an option in NIMBC chemotherapy. These preliminary data showed promising results with intravesical administration of doxorubicin.

CONCLUSION

In conclusion, the choice between intravesical chemotherapy and BCG depends on several factors, including the patient's risk profile and treatment response. Doxorubicin demonstrates a good efficacy to prevent recurrence and upstaging on T1 diseases. This finding highlight the importance of individualized treatment strategies for NMIBC patients to optimize outcomes and improve long-term prognosis.

ACKNOWLEDGMENT

I am very grateful to Allah for the completion of this research, I am grateful for the assistance of one of my residents, dr. Andy Zulfiqqar, who has helped me compile this research. Hopefully I will be able to continue this research with more samples to be able to corroborate the results of this preliminary study.

REFERENCES

1. Umbas R, Safriadi F, Mochtar CA, Djatisoesanto W, Hamid ARAH. Urologic cancer in Indonesia. *Jpn J Clin Oncol* 2015; 45(8):708-12.
<https://doi.org/10.1093/jjco/hyv066>
2. Freedman ND, Silverman DT, Hollenbeck AR, Schatzkin A, Abnet CC. Association between smoking and risk of bladder cancer among men and women. *JAMA* 2011; 306(7):737-45.
<https://doi.org/10.1001/jama.2011.1142>
3. Van Osch FH, Jochems SH, Van Schooten FJ, Bryan RT, Zeegers MP. Quantified relations between exposure to tobacco smoking and bladder cancer risk: a meta-analysis of 89 observational studies. *Int J Epidemiol* 2016; 45(3):857-70.
<https://doi.org/10.1093/ije/dyw044>
4. Jiang S, Redelman-Sidi G. BCG in bladder cancer immunotherapy. *Cancers* 2022; 14(13):3073.
<https://doi.org/10.3390/cancers14133073>
5. Izumi K, Taguri M, Miyamoto H, Hara Y, Kishida T, Chiba K, *et al.* Androgen deprivation therapy prevents bladder cancer recurrence. *Oncotarget* 2014; 5(24):12665-74.
<https://doi.org/10.18632/oncotarget.2851>
6. Mostafid H, Kamat AM, Daneshmand S, Palou J, Taylor JA, McKiernan J, *et al.* Best practices to optimise quality and outcomes of transurethral resection of bladder tumours. *Eur Urol Oncol* 2021; 4(1):12-9.
<https://doi.org/10.1016/j.euo.2020.06.010>
7. Abufaraj M, Mostafid H, Shariat SF, Babjuk M. What to do during Bacillus Calmette-Guérin shortage? Valid strategies based on evidence. *Curr Opin Urol* 2018; 28(6):570-6.
<https://doi.org/10.1097/MOU.0000000000000544>
8. Babjuk M, Burger M, Capoun O, Cohen D, Compérat EM, Dominguez Escrig JL, *et al.* European Association of urology guidelines on non-muscle-invasive bladder cancer (Ta, T1, and carcinoma in situ). *Eur Urol* 2022; 81(1):75-94.
<https://doi.org/10.1016/j.eururo.2021.08.010>
9. Chang SS, Boorjian SA, Chou R, Clark PE, Daneshmand S, Konety BR, *et al.* Diagnosis and treatment of non-muscle invasive bladder cancer: AUA/SUO Guideline. *J Urol* 2016; 196(4):1021-9.
<https://doi.org/10.1016/j.juro.2016.06.049>
10. Hendri AZ, Hamid ARAH, Hakim L, Warli SM, Prasetyawan W, Danarto HR, *et al.* Panduan penanganan kanker kandung kemih tipe urotelial. *Ikatan Ahli Urologi Indonesia (IAUI)* 2014; 1-56.
11. Al-Gallab MI, Naddaf LA, Kanan MR. The management of non-invasive bladder tumours with doxorubicin intravesical instillation after transurethral resection. *Sultan Qaboos Univ Med J* 2009; 9(1):53-8.
12. Fukuokaya W, Kimura T, Miki J, Kimura S, Watanabe H, Bo F, *et al.* Effectiveness of intravesical doxorubicin immediately following resection of primary non-muscle-invasive bladder cancer: a propensity score-matched analysis. *Clin Genitourin Cancer* 2020; 18(2):e55-61.
<https://doi.org/10.1016/j.clgc.2019.09.005>
13. Lamm DL, Blumenstein BA, Crissman JD, Montie JE, Gottesman JE, Lowe BA, *et al.* Maintenance bacillus calmette-guerin immunotherapy for recurrent Ta, T1 and carcinoma in

- situ transitional cell carcinoma of the bladder: a randomized southwest oncology group study. *J Urol* 2000; 163(4):1124-9.
14. Sylvester RJ, Van Der Meijden APM, Oosterlinck W, Witjes JA, Bouffouix C, Denis L, *et al.* Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC Risk Tables: a combined analysis of 2596 patients from seven EORTC trials. *Eur Urol* 2006; 49(3):466-77.
<https://doi.org/10.1016/j.eururo.2005.12.031>
 15. Gontero P, Comperat EAB, Dominguez Escrig JL, Mariappan LE, Masson-Lecomte A, Mostafid AH, *et al.* EAU Guidelines on non-muscle-invasive (TaT1, CIS) bladder cancer. Congress Milan 2023. ISBN 978-94-92671-19-6.
 16. Reid LM, Leav I, Kwan PW, Russell P, Merk FB. Characterization of a human, sex steroid-responsive transitional cell carcinoma maintained as a tumor line (R198) in athymic nude mice. *Cancer Res* 1984; 44(10):4560-73.
 17. Marks P, Soave A, Shariat SF, Fajkovic H, Fisch M, Rink M. Female with bladder cancer: what and why is there a difference? *Transl Androl Urol* 2016; 5(5):668-82.
<https://doi.org/10.21037/tau.2016.03.22>
 18. Zlotta AR, Vooren JPV, Huygen K, Drowart A, Decock M, Pirson M, *et al.* What is the optimal regimen for BCG intravesical therapy? Are six weekly instillations necessary? *Eur Urol* 2000; 37(4):470-7.
<https://doi.org/10.1159/000020170>
 19. Soloway MS. Overview of treatment of superficial bladder cancer. *Urol* 1985; 26(4 Suppl):18-26.