



ORIGINAL ARTICLE

Risk factors of doxorubicin-induced cardiomyopathy in non-muscle- invasive bladder cancer

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ABSTRACT

BACKGROUND

Doxorubicin is an anthracycline antibiotic widely used as a chemotherapeutic agent to treat solid tumors and hematologic malignancies. Bladder cancer is the second most common genitourinary malignancy and can be classified into muscle-invasive bladder cancer and non-muscle-invasive bladder cancer (NMIBC). In Indonesia, NMIBC is treated by doxorubicin instillation. Several risk factors have been suggested to be associated with doxorubicin-induced cardiomyopathy, but on their quantitative effects no consensus has as yet been reached. This study aimed to determine the risk factors of doxorubicin-induced cardiomyopathy in NMIBC patients with intravesical doxorubicin instillation.

METHODS

A cross-sectional study was conducted involving 74 NMIBC patients who received local treatment by doxorubicin instillation after transurethral resection of bladder tumor (TURBT). Data were collected on the risk factors that may be favorable to doxorubicin-induced cardiomyopathy, namely age, sex, hypertension, type 2 diabetes mellitus, smoking, and NMIBC risk classification. The dependent variable was cardiomyopathy with decreasing left ventricular ejection fraction (LVEF) below 50 %. Multiple logistic regression was used to analyze the data.

RESULTS

The prevalence of cardiomyopathy was 6.75% (5/74). Type 2 diabetes mellitus was a significant risk factor for doxorubicin-induced cardiomyopathy among our subjects (aOR=34.30;95% C.I.:1.36-865-86;p=0.032). In contrast, age, sex, risk classification, hypertension, and smoking were nonsignificant predictors for doxorubicin-induced cardiomyopathy (p>0.05).

CONCLUSION

This study demonstrated that type 2 diabetes mellitus increased the risk of cardiomyopathy in doxorubicin users among patients with NMIBC. More research is necessary regarding the mechanisms underlying type 2 diabetes mellitus as a risk factor for doxorubicin-induced cardiomyopathy.

Keywords: NMIBC, bladder cancer, doxorubicin, echocardiography, Cardiomyopathy, diabetes mellitus

INTRODUCTION

Cancers of the urinary bladder are one of the most common malignancies throughout the world that particularly attack adults and the elderly. These cancers arise from the transitional epithelial cells lining the urinary bladder and are classified as non-muscle-invasive bladder cancers (NMIBC) or muscle-invasive bladder cancers (MIBC).⁽¹⁾ Non-muscle-invasive bladder cancers are defined as cancers that have not yet penetrated the muscular layer of the urinary bladder. These cancers comprise around 70% of newly-diagnosed cases of bladder cancer and have a high recurrence rate, thus requiring effective management strategies.⁽²⁾

Cancers of the urinary bladder are the second most common genito-urinary malignancies with a yearly increase in prevalence of 5 % in Indonesia.⁽³⁾ Because bladder cancers are classified based on the differences in treatment schedules, they are divided into MIBC and NMIBC. According to European guidelines, for intravesical instillation after maximal nonresidual transurethral resection of bladder tumor (TURBT0, it is recommended to use Bacille Calmette-Guérin (BCG), doxorubicin, epirubicin, gemcitabine, mitomycin C, or etoposide as treatment options.⁽⁴⁾

Doxorubicin is an anthracycline chemotherapeutic agent that is frequently used for various types of cancer, because of its ability to induce apoptosis in malignant cells. Although the drug is generally administered systemically, intravesical doxorubicin instillation has been explored as the treatment of choice for non-muscle-invasive bladder cancers.⁽⁵⁾ The intravesical approach allows a higher local drug concentration that minimizes systemic exposure, such as to reduce toxicity.⁽⁶⁾ Intravesical doxorubicin has been evaluated in a number of studies with regard to its effectiveness in the treatment of NMIBC, particularly in cases of superficial bladder cancers.^(5,6)

Doxorubicin is believed to be able to cause cardiomyopathy, with a mechanism of cardiotoxicity that is particularly caused by the accumulation of reactive oxygen species (ROS) that causes oxidative stress, inflammation, and apoptosis cardiac myocytes. Doxorubicin may also disturb mitochondrial function, thereby causing cell death.⁽⁷⁾

Studies show that there is an incidence of heart failure of around 5% to 10% after a cumulative doxorubicin dose of 300 mg/m², with

the risk rising to 20-30% at doses exceeding 500 mg/m².⁽⁸⁾

One hypothesis showed a lower incidence of cardiomyopathy in patients treated with intravesical doxorubicin than with systemic administration, because of the lower concentration of systemic drugs. There is a comparative study on systemic doxorubicin versus intravesical doxorubicin, but this study does not reveal significant differences in cardiotoxicity and supports the safety of intravesical doxorubicin from the cardiac point of view.⁽⁴⁾ The aforementioned study discusses the pharmacokinetic benefits of intravesical administration, that points to a potentially lower risk of cardiotoxicity because of the minimal absorption of systemic drugs. From the cardiac viewpoint, the mechanisms of doxorubicin-induced cardiotoxicity should be explored, such as oxidative stress and inhibition of topoisomerase 2 in cardiac cells. The conclusion of our study was that intravesical doxorubicin may be a safe choice for NMIBC in connection with cardiotoxic risk, providing effective local control without any significant systemic exposure.^(4,9)

One meta-analysis found that hypertension, diabetes mellitus, and obesity were associated with increased risk of anthracycline-induced cardiomyopathy, showing that appropriate protective strategies should be employed during and after anthracycline treatment.⁽¹⁰⁾ Other studies showed that there were several risk factors that could be associated with anthracycline-induced cardiotoxicity, including female sex, age under 18 years and over 65 years, radiation therapy involving the heart, and concomitant cardiotoxic chemotherapy.⁽¹¹⁾ Health complications such as diabetes mellitus, hypertension, dyslipidemia, obesity, and cardiovascular disorders, all are variables that may be risk factors of cardiotoxicity after doxorubicin-induction.⁽⁷⁾ Several risk factors are associated with anthracycline-induced heart failure, including female sex, age (>65 years, <18 years), radiation therapy involving the heart, simultaneous cardiotoxic chemotherapy, and pre-existing cardiovascular risk factors, such as smoking, hypertension, diabetes mellitus, and coronary artery disease.⁽¹²⁾ However, female sex is not a risk factor of heart failure caused by doxorubicin in patients with hematologic malignancies and sarcoma in Korea.⁽¹³⁾ Because of the inconsistent results from previous studies, a new study is needed to determine the risk factors of doxorubicin-induced cardiotoxicity in patients with cancers. Overall, knowledge about the effect

of various factors that may increase the risk of doxorubicin-induced cardiotoxicity is essential to support approaches in the treatment of patients with bladder cancer. The aim of the present study was to determine the risk factors of cardiomyopathy induced by the intravesical administration of doxorubicin in patients with NMIBC.

METHODS

Research design

This was a cross-sectional study conducted at Dr. Sardjito Central General Hospital from January 2020 to July 2024.

Research subjects

The study subjects consisted of 74 patients taken by total sampling, using the inclusion criteria of (1) diagnosed with NMIBC, (2) treated by intravesical doxorubicin-instillation (3) underwent echocardiographic evaluation, (4) had their informed consent form in the medical records and complete data on the variables to be studied. The exclusion criteria were (1) NMIBC conversion into MIBC or at advanced stage, (2) no available data, particularly from doxorubicin evaluation and echocardiography.

Data collection

The study subjects consisted of all patients with NMIBC, meeting the inclusion criteria comprising the following independent variables: (1) age, (2) sex, (3) comorbid hypertension, (4) type 2 diabetes mellitus, (5) NMIBC risk classification, (6) smoking status. The dependent variable was patients with echocardiographic examination results of left ventricular ejection fraction (LVEF) below 50% after intravesical doxorubicin instillation, defined afterwards as cardiomyopathy.⁽¹⁴⁾ Sex was categorized into male and female, while age was categorized into <60 and ≥60 years. Comorbid hypertension and diabetes mellitus were classified into patients with comorbid hypertension and without hypertension on the one hand and having diabetes mellitus or not having diabetes mellitus based on comorbid diagnosis. The classification of NMIBC risks in this study used two categories, namely low risk and high risk. Moderate risk and very high risk were placed in the high risk group. This grouping was based on the same follow-up strategies, such as time of cystoscopic evaluation and urinary cytological evaluation obtained from the initial cystoscopy, such as tumor size, focal or multiple

tumors, patient's age, where patients older than 70 years and having a tumor diameter of more than 3 cm or having multiple tumors, were subsequently classified as high risk. Smoking status in the risk factors were classified as patients with a history of habitual smoking, either by active or passive smoking.

Statistical analysis

Simple logistic regression analysis was used to analyze the relationship between the dependent and independent variables. The results of the analysis were presented as Odds Ratio (OR), 95% Confidence Interval (CI) and p-value. Significant results were those with a p-value of less than 0.05. The independent variables with $p < 0.25$ in the bivariate analysis were entered in the multivariate logistic regression analysis, and the results presented as Adjusted Odds Ratio (aOR), 95% Confidence Interval (CI) and p-value, the results being deemed significant at $p < 0.05$. All analyses were done using the Stata ver.17 application. A p-value of < 0.05 was considered significant.

Ethical clearance

This study obtained ethical clearance from the Medical and Health Research Ethics Committee (*Komite Etik Penelitian Kedokteran dan Kesehatan*, KEK), Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada – Dr. Sardjito Regional General Hospital and received ethical approval to conduct the study under Reference No. KE/FK/0975/EC/2024.

RESULTS

A total of 74 patients fulfilled the inclusion criteria of being patients with NMIBC who had been treated with intravesical doxorubicin instillation and evaluated by echocardiography, among whom 5 patients had cardiomyopathy with a left ventricular ejection fraction (EF) below 50%. Patient characteristics were varied and the majority of the sample or 82.43% were males and most or 54.05% were <60 years of age. Several general risk factors that may worsen bladder cancer and cardiological problems were also collected, with 44.59% hypertension, 68.92% diabetes mellitus, and 63.51% smokers being found in the whole sample. For the risk of bladder cancers in NMIBC it was found that 48.65% were of high risk, while the remaining 51.35% were of low risk. The average number of cystoscopic evaluation that was done on each patient was 3 times. (Table 1)

Table 1. Characteristics of NMIBC patients undergoing intravesical doxorubicin instillation (n=74)

Characteristics	n (%)
Sex	
Male	61 (82.43)
Female	13 (17.57)
Age (years)	
< 60	40 (54.05)
≥ 60	34 (45.95)
Risk	
High	36 (48.65)
Low	38 (51.35)
Hypertension	
Yes	33 (44.59)
No	41 (55.41)
Diabetes mellitus	
Yes	51 (68.92)
No	23 (31.08)
Smoking	
Yes	47 (63.51)
No	27 (36.49)
EF on echocardiography (%)	
40-50	5 (6.76)
>50	69 (93.24)

Data presented as n (%)

EF = Left Ventricular Ejection Fraction

The investigators also analyzed the variables that may be possible risk factors of lowered EF on echocardiography, ultimately leading to cardiomyopathy. Among the six variables analyzed by simple logistic regression, there were

the independent variables of sex, age, NMIBC risk classification, hypertension, and diabetes mellitus, having a significant p value of <0.25, as listed in Table 2.

Subsequent to the simple logistic regression analysis, by entering the significant independent variables, followed by multiple logistic regression analysis, among all variables with significantly different results, only diabetes mellitus was found to affect the EF category (aOR=22.33;95% CI: 1.02 – 489.01; p=0.049) (Table 3).

DISCUSSION

According to the treatment of choice found in the literature, intravesical instillation chemotherapy should be given within the first two hours after the first TURBT, with the longest recommended time of initial instillation being 24 hours after the first TURBT. This would then be followed by serial instillations and cystoscopic evaluations, depending on the NMIBC risk classification.⁽¹⁵⁻¹⁷⁾ In Indonesia intravesical doxorubicin chemotherapy is also performed in Dr Sardjito Central General Hospital, Yogyakarta. However, the instillation procedure in which patients are given doxorubicin is conditioned by echocardiographic evaluation on the assumption that doxorubicin influences the Left Ventricular Ejection Fraction (LVEF), thereby resulting in cardiomyopathy.^(18,19)

Table 2. Simple logistic regression analysis of risk factors for cardiomyopathy in NMIBC patients receiving intravesical doxorubicin instillation

Variable	Cardiomyopathy (+)	Cardiomyopathy (-)	OR	p value
	n (%)	n (%)		
Sex				
Male	3 (4.92)	58 (95.08)	3.52	0.195
Female	2 (15.38)	11 (84.62)		
Age				
< 60 years	1 (2.50)	39 (97.50)	0.19	0.150
≥ 60 years	4 (11.76)	30 (88.24)		
Risk				
High	4 (11.11)	32 (88.89)	0.22	0.181
Low	1 (2.63)	37 (97.37)		
Hypertension				
Yes	4 (12.12)	29 (87.88)	0.18	0.136
No	1 (2.44)	40 (97.56)		
Diabetes mellitus				
Yes	1 (1.96)	50 (98.04)	10.53	0.041
No	4 (17.39)	19 (82.61)		
Smoking				
Smoker	3 (6.38)	44 (93.62)	1.17	0.866
Non-smoker	2 (7.41)	25 (92.59)		

NMIBC: non-muscle-invasive bladder cancer; OR: odds ratio

Table 3. Multiple logistic regression analysis of risk factors for cardiomyopathy in NMIBC patients receiving intravesical doxorubicin instillation

Risk Factor	aOR (95% CI)	P value
Sex		
Male	9.64 (0.61 – 152.33)	0.108
Female	Reference	
Age		
< 60 years	0.40 (0.03 – 5.59)	0.498
≥ 60 years	Reference	
Risk		
High	0.10 (0.01 – 1.78)	0.118
Low	Reference	
Hypertension		
Yes	0.07 (0.00 – 2.02)	0.122
No	Reference	
Diabetes mellitus		
Yes	22.33 (1.02 – 489.01)	0.049
No	Reference	

NMIBC: non-muscle-invasive bladder cancer; aOR: adjusted odds ratio; CI: confidence interval

This hypothesis finds support in a case report by Akbar et al.⁽²⁰⁾ who found cardiotoxicity after administration of the sixth doxorubicin instillation, with the patient having acute myocardial infarction two days after instillation, and succumbing to cardiogenic shock.

From the results of the present study it is apparent that cardiomyopathy may be affected by intravesical doxorubicin in patients with NMIBC. A total of 74 patients undergoing weekly routine doxorubicin treatment, who were evaluated by echocardiography, were found to have an LVEF below 50 %, signifying that they were in an early stage of cardiomyopathy prior to the doxorubicin treatment. The literature review by Trasca et al.⁽¹⁴⁾ states that in the cardiomyopathy cases evaluated by echocardiography, one of the indications for echocardiography was an LVEF of less than 40%. Furthermore, Lam and Yancy⁽²¹⁾ defined universal heart failure that is classified into three categories, namely LVEF <40% for cardiomyopathy, 40-50% for borderline cardiomyopathy (onset of cardiomyopathy), and >50% for normal LVEF, slightly different from Mathew et al.⁽²²⁾ A person with an LVEF <45% may be diagnosed as having idiopathic dilated cardiomyopathy. In our study, borderline was also grouped as cardiomyopathy, because it is probable that this borderline condition may change into cardiomyopathy after intravesical doxorubicin instillation.

In our study, the proportion of patients with cardiomyopathy was 6.76%. We found diabetes

mellitus to be a risk factor of cardiomyopathy in patients with NMIBC who were treated with intravesical doxorubicin instillation and who according to multivariate analysis had a 22.33-fold greater risk, after adjustment for all other independent variables. Diabetes mellitus as independent variable has long been known as an independent risk factor of cardiomyopathy. According to the literature review by Jia et al.,⁽²³⁾ patients with diabetes mellitus have a relative risk of 1.3 for heart failure after 43 months of observation.

This study has one limitation in comparing by echocardiographic evaluation the group of NMIBC patients who did not receive doxorubicin with those who did, because at Dr. Sardjito Central General Hospital this is not yet possible because the treatment of NMIBC patients with intravesical doxorubicin chemotherapy must be done after TURBT.

The clinical implication of this study is that the results may be applied to hospital treatment and follow-up. Not all patients who are diagnosed with NMIBC need to be regularly evaluated for cardiac function by echocardiography, because of considerations of effective utilization of time and ambulatory treatment, because not all populations have the same cardiotoxicity or cardiomyopathy risks after intravesical doxorubicin instillation. However, in several high risk populations with comorbid diabetes, it is recommended that patients with NMIBC be evaluated by echocardiography to monitor the risk of low EF that may change into heart failure with an EF of less than 50%.

CONCLUSION

This study revealed that patients with NMIBC who were treated with intravesical doxorubicin instillation had a higher risk of cardiomyopathy in subjects with comorbid diabetes. More research is necessary regarding the mechanisms underlying diabetes as a confounding factor for doxorubicin-induced cardiotoxicity, because this may benefit the management of diabetic patients receiving doxorubicin.

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Conflict of Interest

The authors declare that there were no conflicts of interest in conducting this study.

Author Contributions

Both authors contributed equally to this study. IMNGS collected and analyzed the data. AZH conceived and developed the idea for this study, revised the manuscript, and completed the discussion. Both authors discussed the results, and wrote up the discussion and conclusion. Both authors approved the final version before submission of the manuscript.

Data Availability Statement

The supplementary datasets of this study are available upon request from the corresponding author.

Declaration of Use of AI in Scientific Writing

There was no AI involved in the writing of this study.

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