CASE REPORT

Cardiotoxicity Caused by Intravesical Doxorubicin (DOX) after TURBT: A Case Report

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Abstract

Introduction: Transurethral resection of bladder tumors (TURBT) remains the gold standard therapy for diagnosing and treating Non-Muscle Invasive Bladder Cancer (NMIBC). Post-operative intravesical chemotherapy with doxorubicin (DOX) is recommended to reduce recurrence. However, its cardiotoxic effects are underappreciated. The purpose of this case report is to raise awareness of the cardiotoxic effects of DOX during the treatment of bladder cancer.

Case Presentation: A 72-year-old woman with NMIBC underwent post-operative chemotherapy using intravesical DOX. The pre-chemotherapy cardiac function evaluation was normal. Two days after the 6th cycle of chemotherapy, the patient came to the emergency department of the Namira Islamic Hospital with complaints of chest pain and shortness of breath. The patient was diagnosed with Acute Myocardial Infarction (AMI). One day after hospitalization, the patient died due to cardiogenic shock.

Discussion: Cancer treatment can cause cardiotoxicity. This occurs in a quarter of cancer patients depending on cardiovascular risk factors and the type of chemotherapy drug used. DOX has been postulated to induce cardiotoxicity through various mechanisms. However, the use of DOX intravesically is expected to have minimal toxic effects compared to systemic administration.

Conclusions : Surgical treatment with TURBT followed by intravesical chemotherapy is the treatment of choice in this case of NMIBC. Based on our case, intravesical administration of DOX in chemotherapy presumably can cause cardiotoxicity in a bladder cancer patient. Therefore, early and continued monitoring of the patient's cardiac function during and after treatment of DOX is necessary for better outcomes.

Keywords: Bladder cancer, Intravesical chemotherapy, Doxorubicin, Cardiotoxicity

Introduction

Transurethral Resection of Bladder Tumor (TURBT) is a diagnostic and therapeutic treatment for bladder tumors. It is considered the gold standard in the treatment of non-muscle invasive bladder cancer (NMIBC).[1,2] Intravesical chemotherapy administered 24 hours after TURBT surgery has an ablation effect on residual tumors at the resection site and on small, unseen tumors. It can reduce the recurrence rate by 11.7% compared to TURBT alone. However, it is more effective in low-risk tumors than in high risk. Mitomycin C (MMC), epirubicin, and DOX are agents for intravesical chemotherapy.[2]

Bladder cancer is the tenth most common neoplasm worldwide. It constitutes 2,1% of all cancer death. It is more common in men than women, with a ratio of 4:1.[3] Based on GLOBOCAN data in 2020, five years prevalence of bladder cancer in Indonesia for all ages is 7.33 per 100.000.[4] In 2021, there are three bladder cancer patients at Namira Islam Hospital. All of these patients underwent TURBT, and two of

them were given chemotherapy with intravesical DOX. Administration of intravesical chemotherapy after TURBT is the main choice for reducing NMIBC recurrence.[2]

DOX is one of the most commonly used chemotherapy drugs because it has a broad spectrum.[5,6] It is used clinically to prevent tumor recurrence, with an average response rate of 45%.[6] However, its clinical use is limited by its dose-dependent cardiotoxicity.[5,6,7] Intravesical therapy is one of the main treatments for bladder cancer, with minimal toxic effects compared to systemic use, by administering drugs into the bladder through a catheter.[5] However, in this case report, applying DOX intravesical therapy after TURBT showed adverse cardiotoxic effects. We aim to raise awareness of the cardiotoxic effects of DOX during the treatment of bladder cancer.

Case Presentation

A 72-year-old woman came to the Emergency Room at Namira Islam Hospital complaining of chest pain and shortness of breath for 12 hours. Chest pain is felt in the substernal area and radiates to the back, aggravated by deep breathing and lying down. Complaints are relieved by sitting and leaning forward. The patient admits that she often experiences sharp chest pains when lying in bed. Two days before entering the emergency room, the patient had undergone the 6th cycle of chemotherapy with intravesical DOX. She was diagnosed with NMIBC based on previous ultrasound, TURBT, and anatomical pathology examination. There was no history of similar complaints previously and no history of hypertension, diabetes mellitus, and heart problems before chemotherapy with DOX. The cardiac function evaluation was normal before DOX administration.

The patient had NMIBC and underwent TURBT surgery on December 9, 2021. Anatomic pathological results showed infiltrating urothelial carcinoma. Patients also received chemotherapy with intravesical DOX at a dose of 50 mg weekly. The first cycle started 24 hours after her surgery. During treatment, the patient complained of hematuria and dysuria on the fourth cycle of chemotherapy and was treated with oral antibiotics, analgesics, and antifibrinolytics. Patients also suffer from fatigue, nausea, and no appetite.

The patient was diagnosed with acute myocardial infarction, presumably due to intravesical DOX administration. Diagnosis is based on electrocardiogram findings that showed sinus tachycardia with the presence of left bundle branch block (LBBB), left ventricular strain pattern with ST elevation on lead V1-V3, which was associated with acute myocardial infarction. One day after being hospitalized, the patient had a cardiogenic shock and was

declared dead. In this case, echocardiography, troponin I test, and cardiac catheterization have not been performed.

Discussion

Cancer treatment can lead to cardiac complications due to cardiotoxicity. Treatment-induced cardiotoxicity is the direct effect of cancer treatment on the structure and function of the heart. This occurs in a quarter of cancer patients depending on cardiovascular risk factors and the type of chemotherapy drugs used. Incidence varies for each chemotherapeutic agent, including an anthracycline, with rates ranging from 1 to 26%. One of the drugs in the anthracycline class is DOX.[8] Our patient came to the emergency room with complaints of chest pain and shortness of breath. The patient had NMIBC and felt these complaints two days after undergoing the 6th cycle of chemotherapy with intravesical DOX. The patient was diagnosed with acute myocardial infarction based on clinical signs and electrocardiogram findings. However, echocardiography, cardiac enzyme test, and cardiac catheterization were not performed on this patient. The patients in this report had no significant risk factors for coronary heart disease, so the use of a chemotherapy regimen was suspected of causing the cardiac complication.

The mechanism by which DOX causes cardiotoxicity is not fully understood.[9,10] DOX has been postulated to induce cardiotoxicity through multiple mechanisms including autophagy, apoptosis, necroptosis, ferroptosis, pyroptosis, and others.[10] Apoptosis-mediated loss of cardiomyocytes and oxidative stress is stated as the main cause of doxurubicin-induced cardiomyopathy.[11] A case of acute myocardial infarction following systemic DOX therapy has been reported previously. A 67-year-old woman with recurrent breast cancer received chemotherapy with liposomal DOX. During the liposomal DOX infusion, she developed substernal chest pain, crushing, hypotension, and diaphoresis, and was diagnosed with acute myocardial infarction. It was found that her right coronary artery was blocked in the middle vessel based on angiography.[12]

In cases of NMIBC, the current treatment of choice is TURBT followed immediately by intravesical chemotherapy.[5] Intravesical chemotherapy installation at Namira Islam Hospital uses DOX, with 50 mg doses in every cycle. DOX was selected for its local availability. Intravesical use of DOX has minimal toxic effects compared to systemic administration.[5] A study by Hodovan evaluated the appearance of manifestations of cardiotoxicity in bladder cancer patients receiving intravesical and systemic DOX therapy. The study involved 96 patients who were divided into three groups. This study found that systemic administration of DOX to patients with bladder cancer caused

significant changes in the myocardium after the first chemotherapy. In contrast, the group of patients treated with a single intravesical instillation of DOX did not cause cardiac complaints, nor did changes in laboratory results and instrumental heart rate. The intravesical route of administration is expected to result in almost no drug reabsorption from the bladder into the systemic bloodstream, and hence accumulation in the heart.[9]

The cardiotoxic side effects of intravesical DOX are expected to be minimal or non-existent. However, in our case report, the cardiac complications experienced by the patient were suspected due to intravesical administration of DOX after receiving six cycles of chemotherapy. Studies on cardiotoxic side effects of intravesical administration have been carried out in animals. Research conducted by Yu et al found that mice given DOX had a 28.6% incidence of cardiotoxic side effects with inflammation of heart muscle cells.[6] Therefore, further studies on the mechanism of cardiotoxicity due to intravesical administration of DOX are needed.

Cardiotoxicity is likely to be prevented or treated with better early monitoring and intervention during cancer treatment, and continued monitoring after treatment.[8] In the clinical setting, cardiac imaging surveillance is used for the early detection of cardiotoxicity. Echocardiography can be used to prevent and monitor early signs. Therefore, cardiac magnetic resonance imaging (MRI) is the gold standard for determining cardiac volume and function because of its superior image quality. Current guidelines recommend this imaging modality for confirmation of cardiac dysfunction associated with cancer therapy.[13]

Conclusion

Surgical treatment with TURBT followed by intravesical chemotherapy is the treatment of choice in this case of NMIBC. Based on our case, intravesical administration of DOX in chemotherapy presumably can cause cardiotoxicity in a bladder cancer patient. Therefore, early and continued monitoring of the patient's cardiac function during and after treatment of DOX is necessary for better outcomes.

References

1. Alrabadi, A, Abuhamad, M, Mansi, H, et al. Delayed Bladder Perforation Related to Immediate Single Dose Intravesical Doxorubicin Instillation After TURBT: A Case Report and Literature Review. *Clinical Medicine Insights: Case Report*. 2021;14:1179547620986158.. doi:10.1177/1179547620986158
2. Porten, SP, Leapman, MS, Greene, KL. Intravesical chemotherapy in non-muscle-invasive bladder cancer. *Indian Journal of Urology*. 2015;31(4):297-303. doi:10.4103/0970-1591.166446

3. Saginala, Kalyan et al. "Epidemiology of Bladder Cancer." Medical sciences (Basel, Switzerland). 2020; 8(1): 15. doi:10.3390/medsci8010015

4. International Agency for Research on Cancer World Health Organization (WHO). *The Global Cancer Observatory (GLOBOCAN) 2020: Indonesia fact sheets*. 2021.

5. Jin, Xun et al. Efficient Intravesical Therapy of Bladder Cancer with Cationic Doxorubicin Nanoassemblies. *International Journal of Nanomedicine.* 2016; 11: 4535-4544. doi:10.2147/IJN.S103994

6. Yu, Dah-Shyong., Yan, Hui-Yu., Wu, Chia-Lun. and Hung, Shun-Hsing. Comparison of Therapeutic Efficacyo Lipo-Doxorubicin and Doxorubicin in Treating Bladder Cancer. *Urological Science*. 2017; 28(4), pp.200–205. doi:https://doi.org/10.1016/j.urols.2016.08.001.

7. Zhang, S., et al. Identification of The Molecular Basis of Doxorubicin-Induced Cardiotoxicity. *Nature Medicine*. 2012; 18(11), pp.1639–1642. doi:https://doi.org/10.1038/nm.2919.

8. Clark, R.A., et al. Cardiotoxicity after cancer treatment: a process map of the patient treatment journey. *Cardio-Oncology*. 2019; 5(14). https://doi.org/10.1186/s40959-019-0046-5

9. Hodovan, N. L. Evaluation of changes in instrumental and biochemical markers of heart diseases in patients with bladder cancer under the condition of intravenous and intravesical doxorubicin administration. *Biomedical and Biosocial Anthropology*. 2021; (43), 40-44. https://doi.org/10.31393/bba43-2021-07

10. Christidi, E. and Brunham, L.R. Regulated cell death pathways in doxorubicin-induced cardiotoxicity. Cell Death & Disease. 2021; 12(4), pp.1–15. doi:https://doi.org/10.1038/s41419-021-03614-x.

11. Rawat, P.S., Jaiswal, A., Khurana, A., Bhatti, J.S. and Navik, U. Doxorubicin-induced cardiotoxicity: An update on the molecular mechanism and novel therapeutic strategies for effective management. *Biomedicine & Pharmacotherapy*. 2021; 139, p.111708. doi:https://doi.org/10.1016/j.biopha.2021.111708.

12. Winchester, D.E. and Bavry, A.A. Acute Myocardial Infarction During Infusion of Liposomal Doxorubicin for Recurrent Breast Cancer. *The Breast Journal*. 2010; 16(3), pp.313–314. doi:https://doi.org/10.1111/j.1524-4741.2009.00898.x.

13. Gabani, Mohanad et al. Association of Cardiotoxicity With Doxorubicin and Trastuzumab: A Double-Edged Sword in Chemotherapy. *Cureus*. 2021; 13(9): e18194. doi:10.7759/cureus.18194