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ภาวะหัวใจเต้นช้ากว่าปกติจากการได้รับ 5-fluorouracil: กรณีศึกษา

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5-fluorouracil-induced Bradycardia: A Case Report

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บทคัดย่อ

หลักการและวัตถุประสงค์: การเกิดภาวะแทรกซ้อนต่อหัวใจ เป็นอาการไม่พึงประสงค์หนึ่งที่พบได้จากการได้รับ 5-fluorouracil (5-FU) อาการทางคลินิกซึ่งสัมพันธ์กับการใช้ 5-FU ที่อาจพบได้ เช่น ภาวะเจ็บเค้นอก ใจสั่น อาการหายใจลำบาก ภาวะกล้ามเนื้อหัวใจตาย ภาวะช็อกจากโรคหัวใจ และ ภาวะหัวใจหยุดเต้นเฉียบพลัน เป็นต้น แม้ว่าจะพบการเกิดความผิดปกติของคลื่นหัวใจโดยไม่มีอาการแสดง อย่างไรก็ตามภาวะหัวใจเต้นช้ากว่าปกติมักเป็นอาการที่ไม่ถูกรายงาน รายงานกรณีศึกษานี้จึงมีวัตถุประสงค์เพื่อรายงานผู้ป่วยที่เกิดภาวะหัวใจเต้นช้ากว่าปกติโดยไม่มีอาการแสดงจากการได้รับการรักษาด้วย 5-FU

กรณีศึกษา: ผู้ป่วยหญิงอายุ 47 ปีซึ่งมีโรคประจำตัวเป็นโรคหัวใจที่มีโครงสร้างหัวใจผิดปกติ ได้รับการวินิจฉัยว่าเป็นมะเร็งเยื่อบุโพรงมดลูกระยะ 4B เมื่อ 9 เดือนที่ผ่านมา โรคหัวใจของผู้ป่วยซึ่งได้รับการตรวจก่อนให้การรักษาด้วยยาเคมีบำบัดอยู่ในภาวะคงที่ อย่างไรก็ตามในวันที่ 3 ของการให้ยาเคมีบำบัดแบบประคับประคอง (รอบที่ 1) ด้วย 5-FU ขนาด 1000 มิลลิกรัม/ตารางเมตร ผู้ป่วยได้เกิดภาวะหัวใจเต้นช้ากว่าปกติโดยไม่มีอาการแสดง ซึ่งหลังจากเกิดเหตุการณ์ดังกล่าว ได้มีการหยุดยา 5-FU และไม่มีการให้ยาดังกล่าวอีก

สรุป: การเกิดภาวะหัวใจเต้นช้ากว่าปกติจาก 5-FU ถือเป็นอาการไม่พึงประสงค์ต่อหัวใจที่พบได้ไม่บ่อยนัก ผู้ป่วยที่มีโรคประจำตัวเป็นโรคหัวใจ ควรได้รับการประเมินโรคและปัจจัยเสี่ยงของการเกิดโรคหัวใจและหลอดเลือดก่อนเริ่มการรักษา นอกจากนี้การติดตามผู้ป่วยอย่างใกล้ชิดด้วยการตรวจคลื่นไฟฟ้าหรือการติดเครื่องบันทึกคลื่นไฟฟ้าหัวใจแบบพกพาก็มีความจำเป็นเช่นกัน เมื่อเกิดเหตุการณ์ดังกล่าวควรหยุด 5-FU ทันที การให้ยา 5-FU แก่ผู้ป่วยอีกครั้งสามารถทำได้ในผู้ป่วยบางรายที่มีอาการไม่รุนแรงเท่านั้น อย่างไรก็ตามควรมีการประเมินความเสี่ยงกับประโยชน์ที่ได้รับก่อนทำการให้ยาอีกครั้ง

คำสำคัญ: 5-Fluorouracil, ยากลุ่มต้านเมแทบอไลต์, ยาเคมีบำบัด, ความเป็นพิษต่อหัวใจ, ภาวะหัวใจเต้นช้ากว่าปกติ

Abstract

Background and Objective: Cardiotoxicity is one of the adverse effects associated with 5-fluorouracil (5-FU) based regimen. Diverse abnormal clinical manifestations such as angina, palpitation, dyspnea, myocardial infarction, cardiogenic shock and cardiac arrest have been linked to 5-FU. Although asymptomatic electrocardiogram (ECG) abnormalities were presented, the identify of bradycardia was rarely reported. This case report aimed to describe the case of asymptomatic bradycardia after receiving 5-FU treatment.

Case presentation: We report a case of 47-year-old female who was previously diagnosed with mucinous adenocarcinoma of cervix clinical stage IVB for 9 months and had a history of structural heart disease. Her cardiac condition, which was investigated before chemotherapy treatment, showed stable disease. However, during 5-FU palliative chemotherapy (Cycle 1), she developed asymptomatic bradycardia on the third day of cycle with 5-FU 1000 mg/m^2. After occurrence of the cardiac event, 5-FU was discontinued, and reintroduction of 5-FU was not performed.

Conclusion: 5-FU induced bradycardia is an unusual cardiac event. In patients with history of cardiovascular disease, evaluating cardiac disease and cardiovascular risks should be performed before treatment initiation. Moreover, close monitoring with ECG or a 12-leads Holter monitoring are necessary as well. 5-FU should be immediate discontinued after the event is suspected. Reintroduction of 5-FU could be performed in some patients without serious problems. However, risk-benefit assessment should be done before performing rechallenge therapy.

Keywords: 5-Fluorouracil, antimetabolite, chemotherapy, cardiotoxicity, bradycardia

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Introduction

Cardiotoxicity is one of the complications that could arise following 5-fluorouracil (5-FU) based chemotherapy. Diverse cardiac events from 5-FU have been reported. Common features of 5-FU induced cardiotoxicity include chest pain, palpitation, dyspnea and hypotension.[1] The incidence of these common symptoms was up to 23%, whereas severe manifestations such as myocardial infarction, cardiogenic shock and cardiac arrest were presented with 0-2%. Although abnormal echocardiogram (ECG) change was reported, bradycardia was rarely identified. Because of 5-FU induced cardiotoxicity was first suggested in 1962,[2] PubMed was searched up for the articles published between January 1962 and August 2022, using the following search terms: (5-FU OR 5-fluorouracil OR capecitabine OR fluoropyrimidine) AND (arrhythmia OR bradycardia OR cardiotoxicity). The occurrence of bradycardia from 5-FU ranged from 1% to 21%.[3-13] These incidences varied according to study design and diagnostic criteria used.[14] Close ECG monitoring might lead to overestimated. The studies evaluating the incidence of 5-FU related bradycardia were summarized in Table 1.

5-FU induced cardiotoxicity seem to be affected by dosage use and different administration schedules. Continuous infusion was a risk factor associated with higher incidence of cardiotoxicity, whereas bolus administration showed lower event.[9, 11] Moreover, in multivariable analysis, cardiac comorbidity was presented as one of the predisposing factors related to 5-FU induced cardiotoxicity.[15] However, this significant association was not found in another study.[16]

Although various cardiac abnormalities have been reported, bradycardia was still an unusual event. Hence, we aimed to report the case of asymptomatic bradycardia after continuous infusion of 5-FU in a patient with pre-existing cardiac disease.

Table 1 Incidence of 5-FU induced bradycardia.

Article	Study design	Chemotherapy regimen	Incidence: n/N
Meyer et al. (1997)[3]	Prospective study	5-FU*	1/483
Tsavaris et al. (2002)[4]	Retrospective study	5-FU based regimen	3/14
Wacker et al. (2003)[5]	Prospective study	5-FU based regimen	Not reported
Talapatra et al. (2007)[6]	Case series	Cisplatin + 5-FU	6/6
Kosmas et al. (2008)[7]	Prospective study	5-FU based regimen	3/22
Stewart et al. (2010)[8]	Case series	5-FU	2/6
Khan et al. (2012)[9]	Retrospective study	5-FU based regimen	36/301
Lestuzzi et al. (2014)[10]	Prospective study	5-FU	2/231
Hafeez et al. (2017)[11]	Prospective study	5-FU	2/25
Peng et al. (2018)[12]	Prospective study	5-FU	11/196
Osterlund et al. (2022)[13]	Multicenter retrospective study	capecitabine or 5-FU	2/200

* Concomitant with nifedipine

Case presentation

A 47-year-old female who was previously diagnosed with mucinous adenocarcinoma of cervix clinical stage IVB for 9 months, presented with abnormal vaginal bleeding. She had a history of chronic symmetrical polyarthralgia, inferior vena cava (IVC) thrombosis with pulmonary embolism. Severe mitral stenosis (MS), mild tricuspid regurgitation (TR) with severe pulmonary hypertension S/P percutaneous balloon mitral valvuloplasty (PBMV) was diagnosed approximately 15 years ago. She was taking ferrous fumarate, amitriptyline prn for insomnia, tramadol prn for arthritis pain and life-long enoxaparin. She received a total of nine cycles of cisplatin/paclitaxel chemotherapy. The patient experienced no complications during each treatment cycle. The

computed tomography of whole abdomen (CTWA) after ninth cycle of chemotherapy revealed a large, ill-defined, and extending lesion involving the cervix and upper third vagina that could be residual / recurrent tumour and enlarged nodes at both common iliac and left external iliac regions. Hence, she was admitted to the hospital for 5-FU palliative chemotherapy (cycle 1). The initial physical examinations did not show any abnormal signs and symptoms and baseline electrolytes were within normal limits as well. Baseline ECG showed normal sinus rhythm and baseline heart rate was between 76 and 88 beats per minute (bpm). The treatment with continuous infusion of 5-FU 1000 mg/m^2 was planned for 4 days. The prophylactic administration of dexamethasone and ondansetron were given. The medications that were previously taken, including ferrous fumarate and enoxaparin, were continued, whereas amitriptyline and tramadol which can cause cardiac arrhythmia were withdrew. On the third day of chemotherapy, the patient developed flushing. 5-FU infusion was stopped and intravenous chlorpheniramine was started. After that, her symptom was almost completely resolved, and chemotherapy was resumed. The vital sign before restating 5-FU was shown as following: BP 107/55 mmHg, PR 60 beats/minute, RR 22 breaths/minute and O2 saturation 100% room air. The ECG and vital sign were monitored every hour. About 8 hours later, her heart rate of 46 bpm was detected with no cardiac symptoms. 5-FU chemotherapy was discontinued immediately and bedside ECG revealed sinus bradycardia. Ferrous fumarate and enoxaparin were continued. No additional abnormality was established on physical examination. Laboratory investigations showed normal renal and liver functions. Electrolytes were within normal limits. After cessation of 5-FU administration, her heart rate was measured every hour and found to be less than 50 bpm intermittently (ranged from 39 to 48 bpm) during the 5-hour monitoring. Then, her heart rate reverted to higher than 50 bpm. 5-FU chemotherapy was not rechallenged and a further treatment with radiation therapy was considered.

Discussion

Cardiotoxicity is one of the adverse effects reportedly associated with 5-FU. The incidence of 5-FU induced cardiotoxicity was up to 30%.[15] The most common symptom was chest pain followed by palpitation, dyspnea and hypotension.[1] Although the complication is rare, serious and life-threatening events must be considered. Bradycardia is an unusual cardiac event, occurring in 1% to 21%.[3-13] The event is commonly developed during the first cycle of treatment with onset of 3 days after 5-FU initiation.[6] Our patient developed asymptomatic bradycardia on the 3rd day of first cycle 5-FU chemotherapy, which was similar to the previous case series.

The precise mechanisms of 5-FU induced cardiotoxicity remain unclear. However, coronary vasospasm, direct toxicity to myocardium and endothelial dysfunction have been proposed.[17] Coronary vasospasm is the most well recognized theory for describing myocardial ischemic complication. Endothelial-dependent and endothelial-independent dysfunction are other mechanisms which can be associated with vasoconstriction.[18, 19] Endothelial dysfunction leads to impaired vessel lumen regulation, platelet aggregation and fibrin formation. It was postulated that oxygen free radicals also play a role in endothelial dysfunction. Furthermore, 5-FU causes erythrocyte membrane changes leading to reduction in erythrocyte's ability to deliver and transport oxygen, resulting in myocardial ischemia and injury. Direct myocardial injury is another proposed mechanism. Alpha-fluoro-beta-alanine (FBAL), suggested as a mediator of the direct toxic effect of 5-FU was found in increased level in a patient with 5-FU induced myocardial infarction.[20]

Presently, the underlying risk factors for cardiotoxicity in patients receiving 5-FU are not fully identified since most evidence collected are from retrospective studies with low power to achieve statistical significance, case reports and case series. However, prior cardiovascular diseases, high dose 5-FU, and administration schedules were discussed as predisposing factors of 5-FU induced cardiotoxicity. A pre-existing cardiovascular disease (CAD) or cardiovascular risks are emphasized as the contributing factor for chemotherapy induced cardiotoxicity by the

European Society for Medical Oncology.[1] In previous study, the only independent risk factor for serious cardiotoxicity was a history of cardiac disease (OR 4.108, 95% CI 2.778-6.074, p<0.001).[15] Moreover, higher occurrence of 5-FU induced cardiotoxicity in patients with pre-existing cardiac disease was established.[3] Subgroup analysis based on different types of cardiovascular disease in prospective study with multivariable analysis revealed the relative risk of 8.2 and 7.6 for patients with ischemic heart disease and myocardial infarction, respectively.[3] However, this significant association did not find in other studies.[6, 16] Moreover, known risk factors for ischemic heart disease were not related to the development of cardiotoxicity from 5-FU.[3, 7, 21] Among the patients who experienced bradycardia from 5-FU, none of them had any history of cardiac disease or cardiovascular risk factors.[6] Nonetheless, the presence of CAD may worsen the clinical symptom in the patient developed cardiotoxicity.[10] In this case report, our patient had an underlying structural heart disease. However, she showed asymptomatic bradycardia and ECG was necessary to monitor the abnormality changes.

It is worth mentioning that adverse cardiac event is reportedly lower in patients receiving bolus 5-FU infusion than in patients receiving continuous administration.[7, 22] The lower incidence of cardiotoxicity can be explained by rapid excretion of 5-FU with half-life of 15-20 minutes. Rapid clearance leads to less drug accumulation or lower exposure. Hence, the appearance of cardiotoxicity might be lower in bolus infusion.[17] Nevertheless, one study found that patients with bolus administration had a greater tendency to develop cardiac symptoms.[5]

When cardiac toxicity from 5-FU is suspected, immediate discontinuation is recommended. Reintroduction of 5-FU in patients who had experienced 5-FU induced cardiotoxicity is not advised due to high incidence of recurrence. Recurrence rate of 82-100% with 13% mortality had been previously observed.[17] Some studies found success with re-administration of 5-FU with dose reduction and CCBs, nitrates or nitroglycerine prophylaxis in patients who had developed coronary vasospasm.[17, 23, 24] 5-FU reintroduction was done in 6 patients who had developed transient asymptomatic bradycardia after 5-FU infusion.[6] Persistent bradycardia during the first and second cycle of treatment was found in 2 patients, while the other 4 patients continued the chemotherapy with no major problem after 5-FU was resumed. However, proper consideration and risk-benefit assessment should be done before performing rechallenge therapy. Besides, Holter monitoring should be performed for observing adverse event during drug re-administration.[6, 17]

Conclusion

5-FU induced bradycardia, although unusual, is one of the serious adverse cardiac toxicity events. In patients with history of CAD, evaluating cardiac disease and cardiovascular risks should be performed before starting 5-FU treatment. Moreover, close monitoring with ECG or a 12-leads Holter monitoring are necessary as well. Reintroduction of 5-FU after the occurrence of bradycardia should be performed only after well consideration.

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References

1. Jurczyk M, Król M, Midro A, Kurnik-Łucka M, Poniatowski A, Gil K. Cardiotoxicity of Fluoropyrimidines: Epidemiology, Mechanisms, Diagnosis, and Management. J Clin Med 2021;10(19).
2. Lee AD, McKay MJ. Symptomaitc 5-fluorouracil-induced sinus bradycardia. Intern Med J 2011; 41(7):566-70.
3. Meyer CC, Calis KA, Burke LB, Walawander CA, Grasela TH. Symptomatic cardiotoxicity associated with 5-fluorouracil. Pharmacotherapy 1997; 17(4):729-36.
4. Tsavaris N, Kosmas C, Vadiaka M, Efremidis M, Zinelis A, Beldecos D, et al. Cardiotoxicity following different doses and schedules of 5-fluorouracil administration for malignancy-a survey of 427 patients. Med Sci Monit 2002;8(6):PI51-7.
5. Wacker A, Lersch C, Scherpinski U, Reindl L, Seyfarth M. High incidence of angina pectoris in patients treated with 5-fluorouracil. A planned surveillance study with 102 patients. Oncology 2003;65(2):108-12.

6. Talapatra K, Rajesh I, Rajesh B, Selvamani B, Subhashini J. Transient asymptomatic bradycardia in patients on infusional 5-fluorouracil. J Cancer Res Ther 2007;3(3):169-71.
7. Kosmas C, Kallistratos MS, Kopterides P, Syrios J, Skopelitis H, Mylonakis N, et al. Cardiotoxicity of fluoropyrimidines in different schedules of administration: a prospective study. J Cancer Res Clin Oncol 2008;134(1):75-82.
8. Stewart T, Pavlakis N, Ward M. Cardiotoxicity with 5-fluorouracil and capecitabine: more than just vasospastic angina. Intern Med J 2010;40(4):303-7.
9. Khan MA, Masood N, Husain N, Ahmad B, Aziz T, Naeem A. A retrospective study of cardiotoxicities induced by 5-fluouracil (5-FU) and 5-FU based chemotherapy regimens in Pakistani adult cancer patients at Shaukat Khanum Memorial Cancer Hospital & Research Center. J Pak Med Assoc 2012; 62(5):430-4.
10. Lestuzzi C, Vaccher E, Talamini R, Lleshi A, Meneguzzo N, Viel E, et al. Effort myocardial ischemia during chemotherapy with 5-fluorouracil: an underestimated risk. Ann Oncol 2014;25(5): 1059-64.
11. Hafeez I, Lone AA, Beig J, Alai M, Dar M, Tramboo N. Effect of 5-fluorouracil on sinoatrial node and conduction system of heart. J Adv Med Med Res 2017;4:184.
12. Peng J, Dong C, Wang C, Li W, Yu H, Zhang M, et al. Cardiotoxicity of 5-fluorouracil and capecitabine in Chinese patients: a prospective study. Cancer Commun (Lond) 2018;38(1):22.
13. Osterlund P, Kinos S, Pfeiffer P, Salminen T, Kwakman JJM, Frödin JE, et al. Continuation of fluoropyrimidine treatment with S-1 after cardiotoxicity on capecitabine- or 5-fluorouracil-based therapy in patients with solid tumours: a multicentre retrospective observational cohort study. ESMO Open 2022;7(3):100427.
14. Lestuzzi C, Tartuferi L, Viel E, Buonadonna A, Vaccher E, Berretta M. Fluoropyrimidine-Associated Cardiotoxicity: Probably Not So Rare As It Seems. Oncologist 2020;25(8):e1254.
15. Jin X, Bai Y, Gao L, Wu S. Incidence of and risk factors for cardiotoxicity after fluorouracil-based chemotherapy in locally advanced or metastatic gastric cancer patients. Cancer Chemother Pharmacol 2019;84(3):599-607.
16. Jensen SA, Hasbak P, Mortensen J, Sørensen JB. Fluorouracil induces myocardial ischemia with increases of plasma brain natriuretic peptide and lactic acid but without dysfunction of left ventricle. J Clin Oncol 2010;28(36):5280-6.
17. Yuan C, Parekh H, Allergra C, George TJ, Starr JS. 5-FU induced cardiotoxicity: case series and review of the literature. Cardiooncology 2019;5:13.
18. Kanduri J, More LA, Godishala A, Asnani A. Fluorouracil-Associated Cardiotoxicity. Cardiol Clin 2019;37(4):399-405.
19. Sara JD, Kaur J, Khodadadi R, Rehman M, Lobo R, Chakrabarti S, et al. 5-fluorouracil and ancrdiotoxicity: a review. Ther Adr Med Oncol 2018;10.
20. Layoun ME, Wickramasinghe CD, Peralta MV, Yang EH. Fluoropyrimidine-Induced Cardiotoxicity: Manifestations, Mechanisms, and Management. Curr Oncol Rep 2016;18(6):35.
21. Jensen SA, Sørensen JB. Risk factors and prevention of cardiotoxicity induced by 5-fluorouracil or capecitabine. Cancer Chemother Pharmacol 2006;58(4):487-93.
22. Tsavaris N, Kosmas C, Vadiaka M, Skopelitis E, Kopterides P, Pamouki S, et al. 5-Fluorouracil cardiotoxicity is a rare, dose and schedule-dependent adverse event: A prospective study. J BUON 2005;10:205-11.
23. Clasen SC, Ky B, O'Quinn R, Giantonio B, Teitelbaum U, Carver JR. Fluoropyrimidine-induced cardiac toxicity: challenging the current paradigm. J Gastrointest Oncol 2017;8(6):970-9.
24. Redman JM, Rhea L, Brofferio A, Whelpley M, Gulley JL, Gatti-Mays ME, et al. Successful 5-fluorouracil (5-FU) infusion re-challenge in a metastatic colorectal cancer patient with coronary artery disease who experienced symptoms consistent with coronary vasospasm during first 5-FU infusion. J Gastrointest Oncol 2019;10(5):1010-4.

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