CASE REPORT

Gemcitabine-induced coronary vasospasm: A case report

Gemsitabinin tetiklediği koroner vazospazmı: Bir olgu sunumu

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Summary– Gemcitabine is a chemotherapy drug. It is a nucleoside analogue that is usually well tolerated by patients, with myelosuppression (especially thrombocytopenia) as dose-limiting side effect. Other mild to moderate side effects include alopecia, vomiting, nausea, rash, and fever. Coronary ischemia is the most common cardiotoxic effect of gemcitabine, which is due to its antimetabolites. While underlying cause of coronary ischemia following use of gemcitabine is uncertain, endothelial dysfunction and coronary thrombosis are potential explanations. To our knowledge, there are few published case reports of adverse cardiovascular side effects associated with gemcitabine. Presently described is case of acute inferior myocardial infarction in a female patient caused by gemcitabine.

Özet– Gemsitabin bir kemoteropi ilacıdır. Bu ilaç genellikle doza bağımlı iyi tolere edilebilen miyelosüpresyon (özellikle trombositopeni) yan etkisi görülebilen, bir nükleozid analoğudur. Hafif-orta düzeyde görülebilen diğer yan etkileri alopesi, kusma, bulantı, döküntü ve ateştir. Gemsitabinin en sık görülen kardiyotoksik etkisi koroner iskemisidir ki bunun bu ilacın antimetabolitlerine bağlı olduğu düşünülür. Koroner iskemisinin altında yatan neden belirsiz olmakla beraber, endotel fonksiyon bozukluğu ve koroner trombozu oluşumu olası açıklamalardır. Bizim bilgilerimize göre gemsitabin ile ilişkili kardiyovasküler yan etki bildirimi sınırlı sayıdadır. Bu yazıda gemcitabin alan bir kadın hastada gelişen bir akut inferiyor miyokart enfarktüsü olgusu sunuldu.

Gemcitabine is a nucleoside analogue commonly used as chemotherapy in various carcinomas, such as non-small cell lung cancer, pancreatic cancer, bladder cancer, and breast cancer. It is being investigated for use in esophageal cancer, and is being used experimentally in lymphomas and various other tumor types.[1,2] Gemcitabine represents an advance in cancer care, as it is not as debilitating as some other forms of chemotherapy.[3] Gemcitabine is administered intravenously, since it is extensively metabolized by the gastrointestinal tract. While gemcitabine is generally well tolerated by patients, myelosuppression (especially thrombocytopenia) is dose-limiting side effect. Other mild to moderate side effects include alopecia, vomiting, nausea, rash, and fever. In addition, drug-induced pulmonary toxicity is a rare but important complication of gemcitabine administration.[4] Gemcitabine-induced increase in serum transaminases, hematuria, and proteinuria are infrequent and non-serious side effects. Most common cardiotoxic effect of gemcitabine is coronary ischemia.[5] To our knowledge, there are only a few published case reports of adverse cardiovascular effects due to gemcitabine. Most frequently reported cardiovascular side effects of gemcitabine are associated with vasospasm and coronary ischemia, although in a few cases, it has been reported to trigger atrial fibrillation.[6]

Abbreviations:

5-FU	*5-fluorouracil*
AMI	*Acute myocardial infarction*
CAD	*Coronary artery disease*
ECG	*Electrocardiography*

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A 64-year-old woman began 6-session chemotherapy regimen for metastatic ovarian carcinoma with infusion of carboplatin and gemcitabine. No cardiovascular side effects were observed after first session. For

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her second cycle of chemotherapy, she was admitted to the hospital so that she could be closely monitored. After 30 minutes of gemcitabine infusion, she experienced severe chest pain accompanied by ST segment elevation in inferior derivation and lateral ST segment depression, as well as progressive shortness of breath. Her risk factors for cardiovascular disease included positive family history of ischemic heart disease and previous regular hypertension. She presented to the emergency department of our hospital with mildly elevated cardiac troponin level (17 pg/mL), and was given probable diagnosis of acute inferior myocardial infarction (Figure 1). Unfractionated heparin (5000 IU) and oral acetylsalicylic acid were administered. Cardiac catheterization confirmed angiographically normal coronary arteries. Transthoracic echocardiogram revealed moderately inferior wall hypokinesia, ejection fraction of 40% to 45%, normal valves, and no pericardial effusion. She was transferred to coronary care unit, where she received anticoagulant and antithrombotic therapy consisting of aspirin, clopidogrel, low molecular weight heparin, and nitroglycerin. Within 3 hours of admission to coronary care unit, chest pain resolved and ST segment elevation in D2 and D3, and aVF derivation had disappeared (Figure 2). Physical examination was normal, and echocardiogram indicated ejection fraction of 60%. Approximately 18 hours after procedure, cardiac enzymes were as follows: creatine kinase was 189 U/L, creatine kinase MB was 19 U/L, and troponin was 12 pg/mL. She was discharged after only 1 day without any adverse cardiac event and no cardiac treatment. For remaining 5 sessions of her metastatic ovarian cancer treatment, gemcitabine was replaced with bevacizumab. After her last session of chemotherapy, her electrocardiography (ECG) and echocardiography results were normal; no cardiovascular medicine was prescribed.

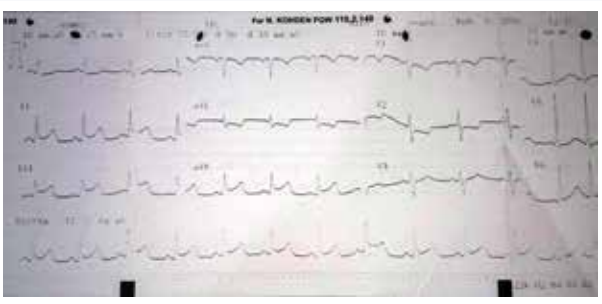

Figure 1. Electrocardiogram recorded after gemcitabine infusion indicated acute inferior myocardial infarction.

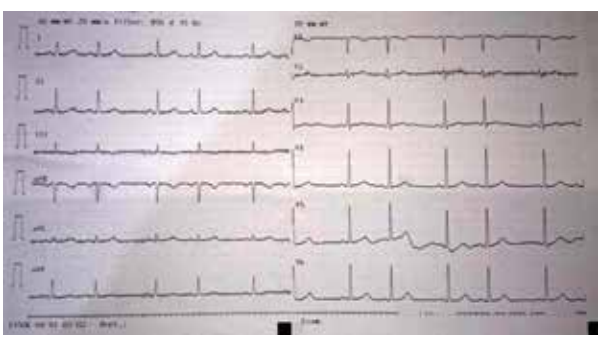

Figure 2. Electrocardiogram recorded after anticoagulant and antithrombotic therapy was normal.

DISCUSSION

Cardiotoxicity is frequent complication of antineoplastic therapy. Some of the most popular anticancer medications are known to cause cardiovascular complications, such as heart failure, myocardial ischemia, hypertension, thromboembolism, QT prolongation, and bradycardia.[5,7] These complications can occur during treatment, shortly thereafter (within days or weeks after treatment), or may not be apparent for months or sometimes years after completion of chemotherapy. Incidence and severity of chemotherapy-induced adverse cardiac reactions are dependent on characteristics of both the drug (e.g., type of drug, cumulative or total dose, and schedule) and the patient, including age, prior chest-mediastinal irradiation history, concurrent administration of cardiotoxic agents, electrolyte imbalances (e.g., hypokalemia and hypomagnesemia), history of cardiac diseases, and other risk factors of atherosclerosis.

Chest pain is cardiac event commonly experienced by cancer patients. These patients often undergo workup for myocardial ischemia. Several forms of cancer treatment (e.g., radiation, chemotherapy) are associated with increased risk of coronary artery disease (CAD) and/or acute coronary syndrome. There are several underlying mechanisms of cardiac ischemia. Anthracycline-induced cardiomyopathy is the most well known cardiac event.[7] In addition, other agents have been reported to cause several adverse cardiac events, including alkylating agents (e.g., cyclophosphamide, ifosfamide, and cisplatin) and others (e.g., paclitaxel, etoposide, teniposide, Vinca alkaloids, and fluorouracil).[5,7]

Most common symptom associated with 5-fluorouracil (5-FU) cardiotoxicity is angina-like chest pain. While underlying mechanisms of cardiac ischemia are still unknown, most likely mechanism is coronary vasospasm.[8] Transient coronary vasospasm may cause angina pectoris (either stable or unstable), while persistent vasospasm may result in acute myocardial infarction (AMI). Canale et al.[9] reported that a patient developed AMI during 5-FU infusion; this patient did not have classic risk factors for coronary heart disease and had no evidence of coronary stenosis on coronary angiography.

Gemcitabine-induced acute coronary syndromes have rarely been described in the literature. Bdair et al.[10] reported case of a patient with history of previous myocardial infarction who developed AMI 3 days after gemcitabine therapy. Present patient, who had no history of CAD, developed chest pain accompanied by newly developed ST segment elevation in D2, D3, as well as aVF derivation on ECG shortly after drug infusion. She also had mild biomarker increases; however, both her symptoms and ST elevation were resolved with antianginal treatment. We speculate that our patient's gemcitabine-induced coronary vasospasm was successfully treated with antianginal therapy, and that it would not have resolved on its own. Dumontet et al.[11] reported case of AMI 4 days after infusion of gemcitabine in patient with history of cardiac disease. In a case reported by Oztürk et al.,[12] patient with metastatic leiomyosarcoma presented with typical angina pectoris and left bundle branch block identified via ECG 30 minutes after gemcitabine+docetaxel infusion. The patient was treated with antianginal therapy in coronary intensive care, after which the patient's ECG returned to normal and angina ceased. That case was somewhat different from ours, in that in case of Oztürk et al., the patient had previously been diagnosed with CAD, and coronary angiography results recorded during angina were similar to those of the patient's previous angiography. In a case report presented by Kalapura et al.,[13] coronary event was documented 6 hours after fifth cycle of gemcitabine in patient with no previous cardiac history.

The mechanism of gemcitabine-induced coronary ischemia is still unclear. Similar to 5-FU, coronary spasm is possible with gemcitabine. Other potential explanations include endothelial dysfunction and coronary thrombosis. Physicians should take rare but severe complication of gemcitabine treatment into consideration, as intensive cardiac monitoring is essential to preventing development of fatal cardiac complications, including AMI and severe arrhythmias, particularly in patients with previous cardiac disease and well-known risk factors. Patients undergoing gemcitabine treatment, even those who have never been diagnosed with CAD, should undergo detailed cardiac examination and antithrombotic and nitrate prophylaxis should be initiated before chemotherapy, regardless of whether the cytotoxic agent is known to be cardiotoxic This observation[9,10] supports vasospastic hypothesis for gemcitabine-induced angina. Although rare, the type of cardiotoxicity caused by gemcitabine is a potentially lethal side effect. Patients should be treated promptly if they experience this side effect and therapy with gemcitabine should be discontinued.

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Anahtar sözcükler: Akut koroner sendrom; koroner spazm; gemsitabin.