Myocardial Ischemia during Combined Chemotherapy with Etoposide and Cisplatin for Non-Small Cell Lung Cancer

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Abstract
Cardiovascular ischemia has been recognized as a serious but uncommon complication of chemotherapy. We report a case of myocardial ischemia during combined chemotherapy with cisplatin and etoposide for non-small cell lung cancer. A 58-year-old man with non-small cell lung cancer and previous history of coronary artery disease suffered chest pain with ECG changes during the third course of chemotherapy with cisplatin and etoposide. Chemotherapy should be used cautiously in patients with coronary risk factors.

Keywords: Myocardial ischemia; Cisplatin; Etoposide; Non-small-cell lung cancer

Introduction
Cisplatin, a platinum-based chemotherapy drug, is the cornerstone agent in the treatment of a variety of malignancies, such as carcinomas of the ovary, lung, lymphomas, sarcomas, and germ cell tumors [1]. One of the most important complications of cisplatin-based chemotherapy is the high risk of thromboembolic events, namely cardiovascular complications. In most of the cases, heart (myocardial infarction), brain (ischemic stroke), and lower limb arteries are involved [1].

Case Report
A 58-year-old man was diagnosed with right lung squamous cell carcinoma, stage IIIb (T2aN3M0), in October 2011. He had smoked 20 cigarettes a day for 20 years and had been an ex-smoker for seven years. Past medical history included hypertension and myocardial infarction 7 years ago, for which he had undergone a triple vessel coronary artery bypass surgery. Since then the patient had remained well with no cardiac symptoms. A pre-chemotherapy ECG showed only minor non-specific ST-T wave changes (Figure 1).

The patient was treated with endoluminal brachytherapy and chemotherapy which consisted of cisplatin and etoposide. The endoluminal brachytherapy was performed in November 2011 with a total dose of 14 Gy in 2 fractions. The chemotherapy was started on 22nd February 2012., with cisplatin (60 mg/m², day 1) and etoposide (100 mg/m², day 1-3), in a four-week schedule. The first two cycles were administered without complications.

On day 2 of the third cycle of chemotherapy, the patient presented with precordial burning pain. Physical examination on admission was normal, blood pressure was 120/70 mmHg and his heart rate was 86 beats per minute.

Initial electrocardiogram (ECG), obtained during chest pain, showed ST elevation in lead aVR, diffuse significant ST depression in precordial leads (Figure 2). Echocardiography showed inferolateral wall hypokinesia with mild impairment systolic function and ejection fraction of 50 per cent.

Serial troponin and pro-BNP (B-type natriuretic peptide) levels were within normal limits. The patient was treated with nitroglycerin sublingually, beta blockers, ACE inhibitors and aspirin, with resolutions of symptoms. ECG taken several hours later showed a reduction of ischemic changes (Figure 3). Coronary angiography revealed multiple stenoses of anterior interventricular branch of the left coronary artery. Considering his cardiac status, further chemotherapy was discontinued.

Discussion
Cardiotoxicity occurs during therapy with several cytotoxic drugs and may be the dose limiting factor in cancer treatment and hence tumor response. Furthermore, cardiotoxicity can also be responsible for long term side effects and may cause severe morbidity in surviving cancer patients [2]. Cardiotoxicity includes a wide range of cardiac effects from small changes in blood pressure and arrhythmias to cardiomyopathy [2].

The underlying mechanisms of coronary artery diseases in cancer patients who are treated with anticancer agents may include:
1. Coexistent coronary atherosclerosis
2. Coronary compression or embolization by the tumor
3. Tumor-associated hypercoagulopathy
4. Vasculitis
5. Non-bacterial thrombotic endocarditis
6. Complications directly related to antineoplastic therapy [3-5]

Cisplatin is a known chemotherapy agent related to thrombosis. The proposed mechanisms are direct endovascular damage; decreased activity of anticoagulant protein C; elevated plasma vWF level, activation of an arachidonic pathway in platelets and hypomagnesemia [5,6]. In retrospective study 87 long term survivors of metastatic testicular cancer treated with cisplatin major cardiac events were found in five (6%) of the 87 patients [7]. In a study of 21 patients with testicular cancer treated with cisplatin, vinblastine and bleomycin, Stefenni et al. found that 38% developed angina pectoris during chemotherapy [8]. In another study of, 78 patients with lung cancer treated with cisplatin and etoposide, 3 patients developed myocardial infarction during chemotherapy [9]. Sawant et al. presented cases of 2 young
patients with acute myocardial infarction during chemotherapy with bleomycin, etoposide and cisplatin [10].

There is limited evidence to indicate that etoposide may be cardiovascular toxic. Sharwzer et al. suggested that etoposide had no such effect. The patient in their report continued treatment with etoposide for 14 months following a myocardial infarction which occurred during the treatment protocol containing bleomycin and etoposide. They proposed that the cardiovascular effects were caused by the combinations of the two agents rather than any individual effect [11]. However, Schecter et al. [10] reported a case of myocardial infarction in a 27-year-old female receiving etoposide treatment as a single agent for persistent Hodgkin’s disease [12].

In our patient endoluminal radiotherapy may have contributed to the myocardial ischemia, as it is known to cause endothelial injury and an increase in the inflammatory markers [13]. The exact mechanism for radiation-induced CAD is not understood. One possible mechanism is that radiation induces endothelial injury. Ionizing energy accelerates the deposition of cholesterol in the arterial wall and produces intimal and adventitial proliferation [13].

Our patient had important known risk factors for the occurrence of myocardial ischemia. He was ex-smoker, with known history of hypertension and Coronary artery disease. The use of cardiotoxic chemotherapy agents in patients with established cardiovascular risk factors is challenging. Cardiotoxic chemotherapy can be used in special situations after considering the risk and benefit. Patients treated with chemotherapeutic agents, which are associated with vascular toxicity, should be monitored for cardiac ischemia, and these agents should be at least temporarily discontinued if a patient presents with acute coronary events [13,14].

**Conclusion**

Patients with cancer in particular those with known cardiac risk factors are at risk for development of cardiotoxicity and need careful assessment of risk and benefit before initiation of chemotherapy agents which are known to have cardiac side effects.

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