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Case Report Open Access

Cardiotoxicity in Asymptomatic Patients Receiving Adjuvant 5-fluorouracil

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Abstract

Evolving evidence of cardiotoxicity in cancer patients treated with 5-fluorouracil (5-FU) has been reported.

We report two different clinical manifestations of asymptomatic 5-FU-associated cardiotoxicity in patients operated for colorectal cancer and treated with adjuvant chemotherapy of 5-FU (bolus-injection and continuous infusion for 46 hours), folinic acid and oxaliplatin (FOLFOX). For a research study evaluating cardiac events during 5-FU treatment, Holter monitoring, electrocardiogram (ECG) and echocardiography were done and cardiac markers monitored before and during the first treatment course.

Case report 1 presents a 75-year old woman with a medical history of paroxysmal atrial fibrillation, hypertension and hyperlipidemia. Holter monitoring revealed increasing paroxysms of atrial fibrillation, increased ventricular ectopic activity and episodes of sinoatrial arrest during infusion. Furthermore a 13-fold increase in N-terminal Pro Brain Natriuretic Peptide (NT-pro-BNP) occurred during infusion. No subjective cardiac symptoms were described, but the findings were interpreted as cardiotoxicity.

Case report 2 presents a 64-year old woman with a medical history of hypertension and hyperlipidemia as well as an incidental finding of negative T-waves in electrocardiogram years before 5-FU treatment. No subjective cardiac symptoms were described during infusion, but approximately 12 hours after infusion she suffered from cardiac arrest but was revived. Subsequent analysis of the Holter monitoring showed increasing episodes of bradycardia with accelerated junctional and junctional rhythm during infusion, furthermore episodes of ST-elevations and depressions just after completed infusion. The cardiac arrest was interpreted as cardiotoxicity.

We discuss predisposing factors and biomarkes for 5-FU induced cardiotoxicity. We want to emphasize the importance of obtaining a thorough history, physical examination and ECG prior to 5-FU treatment in order to risk-stratify the patients. We also stress the need for close monitoring of patients with cardiac comorbidity. We suggest Holter monitoring, and in a subgroup of patients with atrial fibrillation, measuring of NT-pro-BNP levels during infusion.

Keywords: 5-fluorouracil; Cardiotoxicity; Holter monitoring; N-terminal pro brain natriutic; Peptide; Cancer; Atrial fibrillation

Introduction

5-fluorouracil (5-FU) is widely used in the treatment of gastrointestinal, head/neck and breast cancer. During the past decades evidence of cardiotoxicity in cancer patients treated with 5-FU has evolved. The incidence of symptomatic cardiotoxicity due to treatment with 5-FU remains unclear, but large studies have suggested incidences ranging from 1.2-4.3% [1]. The most common symptoms are chest-pain (0-18.6%), palpitations (0-23.1%), dyspnea (0-7.6%) and hypertension (0-6%) [1]. Severe cardiac events such as myocardial infarction, cardiogenic shock and cardiac arrest also occur (0-2%) [1].

We here report two different clinical manifestations of 5-FU-associated cardiotoxicity, demonstrating the need of tools for risk stratification of patients.

Case Report 1

A 75 year old woman diagnosed with colon cancer (T4bN0V0M0) was offered adjuvant chemotherapy with 5-FU (bolus-injection and continuous infusion for 46 hours), folinic acid and oxaliplatin (FOLFOX). She had a medical history of paroxysmal atrial fibrillation, hypertension and hyperlipidemia. The patient was included in a research study evaluating cardiac events during 5-FU treatment. Therefore, Holter monitoring, electrocardiogram (ECG) and echocardiography were done and cardiac markers were monitored before and during the first treatment course.

ECG at baseline was normal. After infusion of chemotherapy the ECG showed sinus arrhythmia and a ventricular ectopic beat. Echocardiography at baseline and after infusion demonstrated normal ejection fraction and no valvulopathy. N-terminal Pro Brain Natriuretic Peptide (NT-pro-BNP (Upper normal limit (UNL) < 125 ng/L)) was increased at baseline (324 ng/L) and further increased during infusion, reaching a maximum at 1630 ng/L and steadily

declining in the days after treatment. Troponin I (TnI) and creatine kinase-MB (CK-MB) were within normal ranges.

The patient experienced no subjective cardiac symptoms. However, subsequent analysis of the Holter recordings during infusion showed more frequent episodes of atrial fibrillation, increased ventricular ectopic activity and episodes of sinoatrial arrest compared to baseline recordings. Specifically, short episodes of ventricular tachycardia (3-4 beats) and pairs of ventricular ectopic beats were more prevalent during infusion. Furthermore, at the end of infusion the patient developed several episodes, lasting up to 10 seconds, of sinoatrial arrest with infra junctional rhythm of 40-50 beats per minute (bpm). The latter evidenced by rate reduction and development of a broad QRS complex preceded by a P-wave of a different configuration than the sinus P-wave.

Because of the above-described cardiac events the dose of 5-FU was reduced by 25% during the second treatment course, and the patient was admitted for telemetry monitoring. Regardless of initiation of beta-blocker treatment, the patient persistently experienced increasing paroxysms of atrial fibrillation and ventricular ectopic activity. An increase in NT-pro-BNP was observed once again during this treatment course.

The symptoms were interpreted as cardiotoxicity, and the adjuvant regimen was discontinued.

Case Report 2

A 64 year old woman diagnosed with rectal cancer (T3N2V1M0) was offered adjuvant chemotherapy with FOLFOX. She had a medical history of hypertension and hyperlipidemia. Four years prior to treatment, ischemic heart disease had been suspected, because of an incidental finding of negative T-waves in the inferolateral leads in ECG. She experienced no subjective cardiac symptoms and exercise ECG and echocardiography at that time were normal. For research purposes this patient too was Holter monitored and ECG and cardiac markers were monitored.

ECG at baseline and after infusion showed sinus bradycardia with a significant reduction of heart rate from 49 to 38 bpm after infusion. ECGs were otherwise normal. NT-pro-BNP increased from 45 ng/L at baseline to 152 ng/L during infusion. TnI and CK-MB were within normal ranges. The patient described no cardiac symptoms during infusion.

Approximately 12 hours after completion of the first treatment course, the patient felt unwell and suffered a cardiac arrest. ECG showed ventricular fibrillation. Two electric shocks were delivered and return of spontaneous circulation occurred after 10 minutes. On arrival at hospital the ECG showed significant inferolateral ST-elevations and Troponin T (243 ng/L (UNL<15 ng/L) and CK-MB (4.1 µg/l (UNL<4 µg/L)) were elevated. Coronary arteriography revealed no significant stenosis.

Subsequent analysis of the Holter monitoring revealed episodes of ST-elevations starting immediately after completed infusion. Eight episodes lasting more than 60 seconds and one episode lasting 40 seconds were recorded the following three hours until the monitor was removed. Maximum elevation was four millimeters. One episode with significant ST-depression for approximately three minutes was also recorded. Consistent with the ECG findings, increasing episodes of bradycardia with accelerated junctional and junctional rhythm of 60-70 bpm and 35-55 bpm respectively, were observed during infusion.

The patient recovered slowly with mild cerebral affection. The cardiac arrest was interpreted as cardiotoxicity, and the adjuvant regimen was discontinued.

Discussion

As shown in the two case reports above, the manifestations of 5-FU-induced cardiotoxicity are diverse but may represent severe adverse cardiac events. Both women were asymptomatic regarding cardiac symptoms during 5-FU infusion. However, both had a history of cardiac disease, risk factors for ischemic heart disease (IHD) and increased NT-pro-BNP after 5-FU infusion.

Predisposing factors implying a risk of 5-FU induced cardiotoxicity are not fully understood. A previous study demonstrated that preexisting cardiac disease of any type was a significant risk factor for 5-FU related cardiotoxicity [2]. In other studies, IHD was also found to be a risk factor [3,4], even though known risk factors for IHD were not associated with development of 5-FU associated cardiotoxicity [2,5].

Reviewing the two case reports, we found Holter monitoring useful in discovering asymptomatic arrhythmias and significant ST-segment deviations, the latter possibly due to spasm in coronary arteries. Similarly, previous studies with Holter monitoring before and during 5-FU infusion have revealed a decrease in mean heart rate and a significant increase in atrial and ventricular premature complexes secondary to 5-FU infusion [6]. Furthermore, asymptomatic ST-segment deviations occurred in 68 % of the patients during 5-FU infusion, the ECG changes being more common among patients with cardiac comorbidity [7].

However, Holter monitoring of every patient treated with 5-FU would be very expensive and pose extra challenges in the setup and daily work routines. We suggest that Holter monitoring might be beneficial in patients with cardiac comorbidity. The case reports emphasize the importance of obtaining a thorough history, physical examination and ECG prior to 5-FU treatment in order to risk-stratify the patients. It also stresses the need for close monitoring of patients with cardiac comorbidity.

Regarding biomarkers, in one study an increase from baseline NT-pro-BNP was observed in patients receiving 5-FU regimens [8]. In patients with cardiotoxicity the increase was significant, suggesting that NT-pro-BNP may be a predictive marker of 5-FU-induced cardiotoxicity [8]. However, elevated serum brain natriuretic peptide (BNP) in cancer patients is a poorly understood phenomenon and is not always related to cardiac events [9]. Hence, the general utility of NT-pro-BNP as a marker of cardiotoxicity remains unresolved [8,10]. It is known that the level of NT-pro-BNP is increased in patients with atrial fibrillation (AF) [11]. Evidence exists that a significant elevation of NT-pro-BNP in patients with AF is predictive of all-cause mortality and cardiovascular mortality [12,13]. Thus keeping case report 1 in mind, we cautiously suggest that patients with AF and a substantial increase in NT-pro-BNP during 5-FU infusion might be in increased risk of developing cardiotoxicity. Therefore, patients with AF might benefit from NT-pro-BNP measurement in addition to Holter monitoring.

In conclusion, we observed severe cardiotoxicity in two asymptomatic patients with a history of cardiac disease, treated with

adjuvant 5-FU. We recommend obtaining a detailed anamnesis, examination and close monitoring with Holter monitoring and cardiac biomarkers in this subgroup.

Further research is needed to clarify the role of cardiac comorbidity and cardiac natriuretic peptides in predicting 5-FU-induced cardiotoxicity. In this work, a close collaboration between oncologists and cardiologists is essential.

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