Acute Transient Diastolic Dysfunction Induced by 5-Fluorouracil Treatment: A Case Report

Ceyhun CEYHAN, MD, Nezih MEYDAN, MD*, Tarkan TEKTEN, MD, Alper O. ONBAŞILI, MD, Sabri BARUTCA, MD*, Banu ÖZTÜRK, MD**

Adnan Menderes University, Medical School, Department of Cardiology, Medical Oncology and Internal Medicine** Aydın*

Summary

Cardiac toxicity of 5-fluorouracil has been described in several medical reports including arrhythmias, angina pectoris, and myocardial infarction. The monitorization of the cardiac changes only by means of clinical signs, ECG and blood pressure leads to underestimation of 5-fluorouracil related cardiotoxicity. We report a cancer patient receiving 5-fluorouracil treatment with echocardiographic findings of reversible diastolic dysfunction. Serial echocardiographic evaluation of mitral inflow velocity patterns demonstrated abnormal relaxation pattern at baseline changing to restrictive type diastolic dysfunction at 48 hours after treatment with no symptoms or ECG changes. On the 15th day, diastolic dysfunction parameters returned to pre-treatment values. ***(Türk Kardiyol Dern Arş 2004; 32: 262-265)***

Key words: *Diastolic dysfunction, echocardiography, 5-fluorouracil*

Özet

5-Florourasil Tedavisine Bağlı Akut Geçici Diyastolik Disfonksiyonu: Olgu Bildirisi

5-Florourasilin kardiyak toksisitesine bağlı olarak gelişen aritmi, angina pektoris ve miyokard infarktüsü gibi birçok tıbbi sunum bildirilmiştir. 5-Florourasil'e bağlı kardiyak toksisitenin takibinin, sadece klinik bulgular, kan basıncı ve EKG ile yapılması bu durumun olduğundan daha az saptanmasına neden olabilmektedir. Biz 5-Florourasil tedavisi alan bir kanser hastasında, ekokardiyografik geçici diyastolik disfonksiyonun bulgularını bildirmekteyiz. Mitral akım hızı örneklerinin seri ekokardiyografik değerlendirilmesinde, başlangıçtaki anormal relaksasyon örneğinin tedaviden 48 saat sonra, semptom ve EKG bulgusu olmaksızın, restiriktif tip diyastolik disfonksiyona değişmesi gösterilmiştir. Onbeşinci günde diyastolik disfonksiyon parametreleri, tedavi öncesi değerlere dönmüştür. ***(Türk Kardiyol Dern Arş 2004; 32: 262-265)***

Anahtar kelimeler: *Diyastolik disfonksiyon, ekokardiyografi, 5-florourasil*

Address for Correspondence: Ceyhun Ceyhan, MD, University Medical School, Department of Cardiology, 09100 Aydın, Türkiye
Tel: 90 (256) 212 00 20 - 129 Fax: 90 (256) 214 64 95 e-mail: ceyhunceyhan@yahoo.com
Received: 19 December 2003, accepted: 13 April 2004

Cardiac toxicity of 5-Fluorouracil (5-FU) has been described in several medical reports including arrhythmias, angina pectoris, and myocardial infarction [1,2,3]. Large prospective studies have demonstrated an incidence ranging from 1.2-18% [1,4]. The underlying mechanisms of cardiotoxicity are not yet fully understood, however vasospasm may be responsible [5]. The cardiac function during 5-FU treatment has been probed by means of echocardiography or myocardial scintigraphy only in patients who developed cardiac symptoms or ECG alterations, whereas the cardiac function irrespective of the development of symptoms was not monitored in any studies [6].

We present a female cancer patient receiving 5-FU treatment with signs of reversible diastolic dysfunction demonstrated by serial echocardiographic evaluation but with no symptoms or ECG changes of cardiotoxicity.

REPORT of CASE

A 67 year-old-female patient was admitted to our hospital due to sigmoid adenocarcinoma. Subsequently, sigmoid colon resection and end to end anastomosis were performed. The infusional 5-FU and leucovorine combination, which was composed of leucovorin 200 mg/m^2/day intra-venous (IV) infusion in two hours and 5FU 400 mg/m^2/day IV bolus infusion followed by 600 mg/m^2/day IV infusion in 22 hours, was started three weeks after the operation. There were no history of heart disease and risk factors. The physical examination, vital signs, laboratory findings and chest x-ray of the patients were all normal in the pre-treatment evaluations. Baseline echocardiographic evaluation revealed left ventricular (LV) end-diastolic: 42 mm, LV end-systolic diameter: 29 mm, diastolic interventricular septum: 10 mm and diastolic posterior wall 10 mm. LV ejection fraction (EF) and fractional shortening (FS) were 75% and %42, respectively. The mitral inflow velocity pattern was recorded with the pulsed-wave Doppler sample volume positioned between the tips of the mitral leaflets. The LV outflow pattern was recorded from the apical 5-chamber view with the pulsed wave Doppler sample volume positioned just below the aortic valve. Two-dimensional and Doppler tracings were recorded over five cardiac cycles at a sweep speed of 50 mm/s. Mitral inflow and LV outflow pulse wave Doppler velocity patterns were measured: Early diastolic peak velocity (E): 0.52 m/sec, late diastolic peak velocity (A): 0.76 m/sec, ratio of the early to late flow velocity peaks (E/A): 0.68, deceleration time of early diastolic peak velocity (EDT): 180 msec and isovolumetric relaxation time (IVRT): 70 msec (Figure 1). These results were concomitant with abnormal relaxation pattern of diastolic dysfunction. The treatment of the first course was well tolerated and there were no symptoms of cardiotoxicity. Also, there were no changes on ECG and blood pressure measurements during infusion. Echocardiographic examination was repeated after 48 hours of 5-FU treatment to evaluate the effect of infusional 5-FU on myocardial functions. In the second measurements LV dimensions, EF and FS were not changed. However, E velocity (0.90 m/sec), E/A ratio [3] were increased and A velocity (0.30 m/sec), EDT (70 msec), IVRT (55 msec) were all dramatically decreased (Figure 2). These alterations were suggested diastolic dysfunction of restrictive type. The patient's monitorization for any clinical and laboratory signs of cardiotoxicity was normal in following 48 hours. The patient was discharged and the control echocardiography after 15 days from the treatment was the same as baseline measurements (Figure 3).

DISCUSSION

Fluorouracil-related cardiotoxicity is usually acute and appears during the first course of the

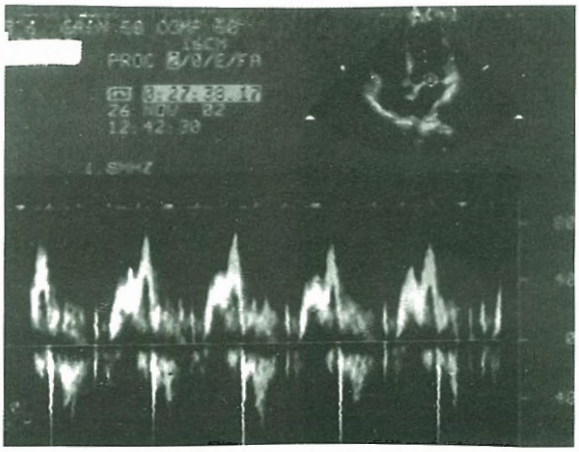

Figure 1. The patient's baseline mitral inflow pulse-wave Doppler examination showing abnormal relaxation pattern of diastolic dysfunction

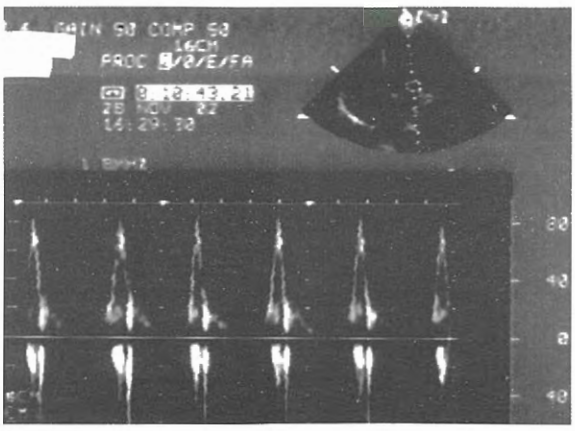

Figure 2. The mitral inflow pulse-wave Doppler examination after 5-FU treatment showing restrictive pattern of diastolic dysfunction

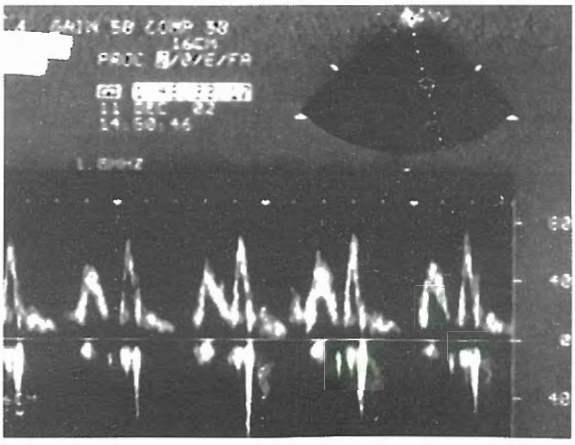

Figure 3. The patient's control pulse wave Doppler examination after 15 days of therapy that is not different from baseline measurements

treatment in most of the patients. Clinical symptoms are usually similar to acute coronary syndromes and differ from the other well-known cardiotoxic antineoplastics such as anthracyclines [7]. The drug is not familiar to many cardiologists. Therefore, awareness of its existence is the most important factor for determining the recognition of cardiotoxicity.

The pathogenesis of 5-FU cardiotoxicity is still unknown: one of the most frequently proposed theories refer to impairment of coronary circulation, possibly vasospastic, as shown in animal studies [8]. Recently, a novel mechanism was proposed as responsible from the cardiotoxicity, that some active metabolites of 5-FU might cause diffuse cellular hypoxia, imitating ischemic heart disease due to adverse effects on myocardial energy metabolism [6,9]. These may cause alterations in the myocyte structure (mitochondrial, nucleic acid metabolism, structural proteins, ionic channels) that causes myocardial dysfunction without evidence of necrosis and similar to a post-ischemic myocardial daze [10]. This may possibly explain the reversible diastolic dysfunction parameter changes without clinical and electrocardiographic ST, T wave abnormalities. As a potential mediator of vasospasm, in vivo, high plasma levels of endothelin have been found in patients treated with 5-FU and particularly in those developing cardiotoxicity [2].

The patients treated with 5-FU are now regularly monitored by ECG. Other examinations, such as echocardiography or myocardial scintigraphy, have been used only in patients who developed cardiac symptoms or ECG alterations. In our clinical practice as in this case, we serially monitored, the cardiac function before and after treatment with 5-FU, irrespective of symptoms or ECG changes. The cardiac function has been evaluated using two-dimensional echocardiography to assess segmental LV wall motion, and M-mode echocardiography in order to evaluate the rates of change of cavity dimension in systole and diastole. These indexes of LV function have proven effective in defining systolic and diastolic dysfunction, even in the preclinical phase [11]. It might be proposed that the treatment with 5-FU induces a reversible impairment of LV diastolic function detected by mitral inflow pulse Doppler velocity patterns. This diastolic impairment might develop without clinical and ECG signs of 5FU cardiotoxicity. There is only one study evaluating the influence of 5-FU treatment on diastolic indexes that showed a progressive reversible decrease in all patients [6]. This is our first experience that we detected reversible diastolic dysfunction in our

clinical practice. It is reported that sub-clinical cardiac dysfunction may develop in the subjects with the absence of cardiac risk factors and pre-existing cardiac disease [6].

In conclusion, 5-FU treatment might possibly cause transient, reversible diastolic dysfunction that develops with no symptoms even in patients without pre-existing heart diseases. Monitoring the cardiac alterations only by means of clinical signs, ECG and blood pressure may lead to underestimation of 5-FU related cardiotoxicity.

REFERENCES

1. Robben NC, Pippas AW, Moore JO: The syndrome of 5-fluorouracil cardiotoxicity: An elusive cardiopathy. Cancer 1993; 71: 493-509

2. Porta C, Moroni M, Ferrari S, Nastasi G: Endothelin-1 and 5-fluorouracil-induced cardiotoxicity. Neoplasma 1998; 45: 81-2

3. Görgulu S, Oguz E, Zor A, Zor U, Gurdogan M, Tezel T: A Case of Myocardial Ischaemia Induced by 5-fluorouracil. Anadolu Kardiyoloji Derg 2002; 3: 259-61

4. Shober C, Papageorgiou E, Harstrick A et al: Cardiotoxicity of 5-Fluorouracil in combination with folinic acid in patients with gastrointestinal cancer. Cancer 1993; 72: 2242-7

5. Luwaert RJ, Descamps O, Majois F, Chaudron JM, Beauduin M: Coronary artery spasm induced by 5-fluorouracil. Eur Heart J 1991; 12: 468-70

6. Grandi AM, Pinotti G, Morandi E, et al: Noninvasive evaluation of cardiotoxicity of 5-fluorouracil and low doses of folinic acid: A one-year follow-up study. Annals of Oncology 1997; 8: 705-8

7. de Forni M, Malet-Martino MC, Jaillais P, et al: Cardiotoxicity of high-dose continuous infusion fluorouracil: a prospective clinical study. J Clin Oncol 1992; 10: 1795-1801

8. Mosseri M, Fingert HJ, Varticouski L, Chokshi S, Isner JM: In vitro evidence that myocardial ischemia resulting from 5-Fluorouracil chemotherapy is due to protein kinase-C mediated vasoconstriction of vascular smooth muscle. Cancer Res 1993; 53: 3028-33

9. Arellano M, Malet-Martino M, Martino R, Gires P: The anti-cancer drug 5-fluorouracil is metabolized by the isolated perfused rat liver and in rats into highly toxic fluoroacetate. Br J Cancer 1998; 1: 79-86

10. Lujan J, Garcia De Burgos F, Jordan A, Garcia M, Reyes F, Espinosa MD. Angina related to 5-Fluorouracil. Rev Esp Cardiol 2002; 55: 764-7

11. Lee CH, Hogan JC, Gibson DG: Diastolic disease in left ventricular hypertrophy: Comparison of M-mode and Doppler echocardiography for assessment of rapid ventricular filling. Br Heart J 1991; 65: 194-200