Case Report

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Plasma N-Terminal Pro-Brain Natriuretic Peptide as Prognostic Marker in Fatal Cardial Decompensation with Sunitinib Malate Therapy

Michael Staehler Nicolas Haseke Katja Zilinberg Thomas Stadler
Christian G. Stief

Department of Urology, University of Munich, Klinikum Grosshadern, Munich, Germany

Key Words
Renal cell cancer · Sunitinib · Cardiac failure · Side effects

Abstract
A 74-year-old man with metastatic renal cell carcinoma and a history of cardiac failure was treated with sunitinib malate. MUGA echocardiography could not detect a relevant change in the ejection fraction although the clinical situation of the patient worsened dramatically. The only parameter to hint at the deteriorated cardiac function was plasma N-terminal pro-brain natriuretic peptide (BNP). Finally, the patient died after only one cycle of sunitinib treatment. We propose to prospectively include BNP for the early detection of cardiovascular decompensation in high-risk patients. Future studies concerning the relevance of BNP in drug-related cardiotoxicity are urgently needed.

Introduction

Sunitinib malate has demonstrated high efficacy in metastatic renal cell carcinoma (mRCC). Compared to interferon therapy, progression-free survival was doubled with a trend towards improved overall survival [1]. This high efficacy is accompanied by a new set of side effects. In the pivotal phase III mRCC trial, updated data indicates that 21% of sunitinib-treated patients experienced a reversible decline in left ventricular ejection fraction to below normal [2]. Although we were aware of cardiac toxicity, we had to experience a surprising course of a patient which we report here.

Case Report

A 74-year-old male patient was admitted with bilateral disseminated lung metastases and mediastinal and hilar lymph node metastases from clear cell RCC. Recurrent RCC was also suspected in the left kidney. The initial diagnosis of RCC was made 5 years prior to detection of metastases when right-sided radical nephrectomy including lymphadenectomy and adrenalectomy was performed and revealed pT3a (7 cm) pN0 cM0 G2 R0 clear cell RCC. Surgery was complicated by perioperative resuscitation due to ventricular tachyarrhythmia. Three years after nephrectomy the patient suffered from myocardial infarction and consecutively developed dilatative cardiomyopathy. He was given a pacer (AICD). Further anamnesis included chronic pulmonary obstructive disease and insulin-independent diabetes mellitus. The patient was in a good clinical condition with a Karnofsky index of 80% and occasionally worked as a gardener.

Prior to systemic therapy, MUGA echocardiography was performed which revealed a dilated left ventricle with a reduction of the ejection fraction to 42%. The dorsal wall was hypokinetic with

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Michael Staehler, MD
Department of Urology, University of Munich, Klinikum Grosshadern
Marchioninistrasse 15, DE–81377 München (Germany)
Tel. +49 89 7095 3722, Fax +49 89 7095 6722
E-Mail michael.staehler@med.uni-muenchen.de

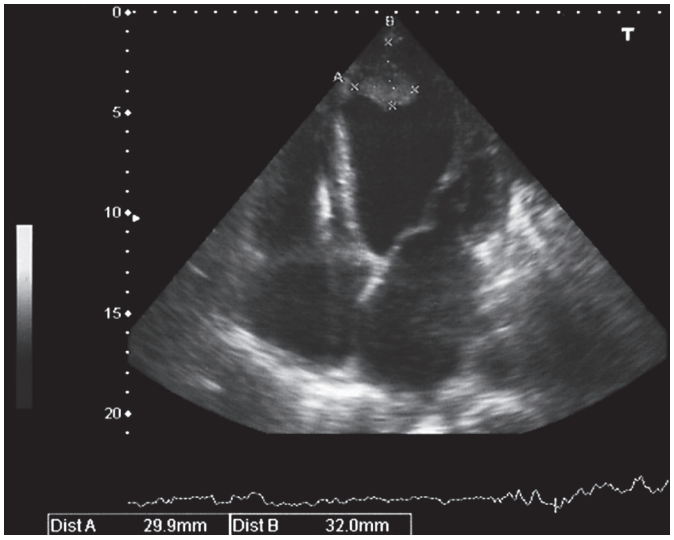

Fig. 1. Left ventricular thrombus with a size of 29.9 × 32.0 mm in subsequent cardial echography (first control after one cycle of sunitinib therapy).

a small thrombus of 2.6 × 0.6 cm, primarily overlooked in the initial computed tomography. Further grade I insufficiency of the mitral and tricuspid valves was seen.

The patient was 170 cm tall and weighed 69 kg. Initial blood pressure was 105/70 mm Hg. Medication consisted of ramipril 2.5 mg b.i.d., bisoprolol 2.5 mg b.i.d., furosemide 20 mg o.d., aspirin 100 mg o.d., and pravastatin 20 mg o.d. Initial serum chemistry showed normal values for sodium, potassium, calcium, BNP (6,700 pg/ml), CRP, creatinine, AST, ALT, AP, LDH, albumin, serum protein and TSH. Blood chemistry showed a lowered hemoglobin level of 13.6 g/dl with normal values for thrombocytes and leukocytes.

The situation was intensively discussed with the patient and he was started on sunitinib with the knowledge of an increased risk for a cardiac event. Therapy was initially well-tolerated without development of hypertension. The only adverse event seen was discrete peripheral edema that was treated with a slight increase of the diuretic therapy. In week 4 of the first treatment course, the patient's general condition worsened with complete recovery in the planned 2-week therapeutic break of sunitinib therapy.

After one cycle, MUGA echocardiography was controlled and revealed an ejection fraction of 36%. The preexisting thrombus had grown to 3.0 × 3.2 cm (fig. 1). In serum chemistry, plasma N-terminal pro-brain natriuretic peptide (BNP) had increased to 27,000 pg/ml with all other parameters unchanged. To prevent further thrombosis the patient was started on coumarin with an INR of 2.0.

Three days after restarting sunitinib therapy the patient's general condition deteriorated and he had to be admitted to the ward. Progressive cardiac failure with central venous congestion developed. Consecutively, liver-compensated failure developed and renal function deteriorated without the need for dialysis. BNP increased to 45,000 pg/ml. Sunitinib was immediately withdrawn. No deep vein thrombosis was seen but the left ventricular thrombus had grown to 3.5 × 4.0 cm without a change in ejection fraction. After a further radiological diagnostic evaluation, no progression of the disease was seen. The patient died 8 weeks after initiation of sunitinib therapy with only one cycle and 3 days of systemic treatment due to progressive heart failure.

Discussion

Cardiac side effects are commonly described with tyrosine-kinase inhibition therapy for mRCC, some of which may be fatal. In the first publication on sunitinib efficacy as a second-line indication [3], 1 of 106 patients was suspected to have died from a cardial event, but no further information on this incident was obtainable. Thus, study protocols performed with tyrosine-kinase inhibitor drugs thoroughly control electrocardiograms and echocardiography to detect changes in the ejection fraction.

In a retrospective analysis at Stanford, 7 of 48 patients (15%) developed grade 3/4 heart failure. Of these patients, 3 had persistent cardiac dysfunction after discontinuation of sunitinib and initiation of heart failure therapy. A history of congestive heart failure, coronary artery disease and lower body mass index were factors associated with increased risk [2].

Although most of the cardiac events are controllable, some patients do not recover from the cardiac changes induced by the therapy and thus can no longer be treated with the selected drug [4]. There is evidence that the switch to another multi-kinase inhibitor will not overcome this situation [5]. BNP has been shown to be consistently associated with an increased risk of all-cause mortality in patients with congestive heart failure, even in those cases where no change in the ejection fraction can be seen [6, 7].

The only parameter in our patient to reveal the cardiac function and the dramatic course was BNP in serum chemistry. Therapy was restarted after clinical recovery of the patient without this parameter being considered. We propose to prospectively include BNP as a diagnostic tool for early detection of cardiovascular decompensation in high-risk patients. Future studies concerning the relevance of BNP in drug-related cardiotoxicity are urgently needed.

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