Concomitant Treatment with Ibrutinib and Amiodarone Causing Reversible Heart Failure Syndrome

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The concomitant use of ibrutinib and amiodarone is generally not recommended, as the inhibitory effect of amiodarone on cytochrome P450 3A4 (CYP3A4), which plays a crucial role in the clearance of ibrutinib, may lead to a rise in serum levels of ibrutinib and induce toxicity [1]. This interaction seems to be of potential importance due to the high prevalence of atrial fibrillation (AF) and the role ibrutinib may have in inducing this arrhythmia. We present a patient who was treated with ibrutinib for chronic lymphocytic leukemia (CLL) and developed atrial fibrillation.

PATIENT DESCRIPTION

A 65 year old male suffering from CLL presented to the cardio-oncology clinic of Rabin Medical Center with dizziness, lightheadedness, shortness of breath and a dry cough. He denied any chest pain or palpitations. His medical history included CLL stage C according to the Binet classification, and previous treatment with six courses of fludarabine, cyclophosphamide, rituximab (FCR), two courses of bendamustine and rituximab (BR), two courses of rituximab, cyclophosphamide, adriamycin, vincristine and prednisone (R-CHOP), high dose methylprednisolone and ibrutinib 420 mg daily during the 6 weeks prior to current presentation. His past medical history was remarkable for ischemic heart disease since 2007 when he underwent coronary artery bypass graft surgery. Since then he was asymptomatic with stable echocardiographic findings of inferior wall hypokinesis and left ventricular ejection fraction of 50%.

In January 2014, the patient presented with the first documented episode of paroxysmal AF (PAF) and began oral treatment with propafenone and apixaban 5 mg twice daily. In August 2014, 3 weeks after discontinuation of propafenone due to clinical stability, he suffered another episode of PAF with rapid ventricular response. The patient converted to sinus rhythm in the emergency room with intravenous amiodarone 300 mg. A loading of amiodarone 1200 mg daily had been initiated and after one week of loading, maintenance therapy of 200 mg daily was recommended. However, on the sixth day of amiodarone loading treatment the patient was admitted with dyspnea and signs of heart failure. On clinical examination, he had orthopnea with signs of volume overload: jugular vein distension, bilateral basal pulmonary rales, and moderate edema of the lower extremities. There was no hepatosplenomegaly. Cardiac auscultation revealed regular heart sounds with an evident fourth heart sound and a 3/6 holosystolic murmur heard mainly over the apex with no axillar radiation. No neurologic signs were noted.

Vital signs were stable, with room air oxygen saturation of 92–95%, a regular heart rate of 80 beats/minute and blood pressure 126/78 mmHg. There was no fever and the chest X-ray was remarkable for new-onset lung congestion. Relevant laboratory findings included hemoglobin 10.0 g/dl (12.0–16.0 g/dl) and leukocyte count 3.97 k/µl (5–10.8 k/µl). Renal, hepatic and thyroid functions were in the normal range. The electrocardiogram (ECG) showed a normal sinus rhythm and was not indicative of acute myocardial ischemia. The corrected QT interval (QTc) duration was 446 msec, compared with 360 msec in an ECG recorded prior to initiation of ibrutinib therapy.

An echocardiographic study revealed a new-onset restrictive left ventricular (LV) filling pattern, and mild mitral regurgitation with a progression of a trivial tricuspid regurgitation into moderate tricuspid regurgitation. Pulmonary artery pressure rose from 21 mmHg to 50 mmHg. Estimated LV ejection fraction of 50–55% was without change from the previous examination. Point-of-care brain natriuretic peptide (BNP) level was 376 pg/ml (< 100 pg/ml excludes acute heart failure, and > 400 pg/ml supports acute heart failure diagnosis).

Until presentation, the patient had already received a total dose of amiodarone reaching 7200 mg. We halted treatment for 2 days and then continued with a maintenance dose of 200 mg daily. Oral furosemide 40 mg was also added to the regimen. No dosage adjustments were made to ibrutinib or other medications. The symptoms regressed rapidly, and upon reevaluation 9 days later all the symptoms had resolved. A month later, there was no relapse of symptoms, and echocardiogram showed complete resolution of diastolic dysfunction, pulmonary hypertension and regression of valve insufficiencies to trivial levels. At the 6 month follow-up echocardiogram all parameters remained stable. Combined treatment with

amiodarone and ibrutinib was continued without recurrence of AF and with good control of his CLL disease. Nonetheless, the patient died several months later due to progression of his hematological malignancy.

COMMENT

Ibrutinib is a tyrosine kinase inhibitor, targeting Bruton's tyrosine kinase and subsequently leading to apoptosis of cells in CLL and mantle cell lymphoma (MCL). It has been associated with several adverse effects, mainly hematological and gastrointestinal but also cardiovascular disorders such as AF and hypertension [2]. Concomitant treatment with amiodarone may increase ibrutinib serum levels due to competitive activity upon CYP3A4 [1].

In view of the patient's presentation and clinical course, we suggest that transient heart failure was caused by delayed clearance of an elevated serum level of ibrutinib amplified by the co-administration of amiodarone at a high loading dose. Unfortunately, we could not measure serum levels of either drug to further verify this hypothesis. The temporal relation between heart failure with preserved ejection fraction symptoms and co-administration of ibrutinib with amiodarone at a loading dose suggests a causality effect. The dramatic regression of symptoms with the reduction of amiodarone dose may further support our hypothesis.

From the pharmacological perspective, both the Naranjo algorithm [3] and the Horn/Hansen drug interaction probability scale (DIPS) [4] classify this event as a "probable adverse reaction" with scores of 7 and 6, respectively. It should be noted that these scores occurred despite the fact that ibrutinib serum level measurement kits were not at our disposal at the time this patient presented.

The well-known favorable profile of amiodarone as a non-cardiotoxic agent reduces the probability that amiodarone alone caused the heart failure symptoms in this patient. It should be noted that since we could not measure serum levels of either drug, we cannot refute an alternative hypothesis for the adverse cardiac effect. Ibrutinib also inhibits other kinases with homologous cysteine residues, including TEC, ITK, JAK3, EGFR, HER2, HER4, BLK, and BMX. HER2 inhibition is associated with a well-known side effect of left ventricular systolic dysfunction due to the widely used HER2 receptor blocker trastuzumab. Recently, HER2 inhibition was associated with early onset of diastolic dysfunction well before the systolic reduction occurs [5]. Since ibrutinib treatment is associated with increased frequency of AF, the ability to maintain pharmacological rhythm control with amiodarone despite the risk of ibrutinib toxicity has practical implications, and physicians caring for these patients should be aware of this potential interaction. Reduction of amiodarone dosage reverts the effect without adversely influencing the anti-arrhythmic effect. Thus, lower dose of amiodarone during the loading phase (e.g., 600–800 mg instead of 1200 mg) and/or using other anti-arrhythmic medications should be considered for these patients at combined risk.

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