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Cost-Effectiveness of Routine Screening for Cardiac Toxicity in Patients Treated with Imatinib in Brazil

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A B S T R A C T

We performed a cost-effectiveness study of different strategies of screening for cardiotoxicity in patients receiving imatinib, the first strategy based on yearly echocardiograms in all patients and the second strategy based on yearly B-type natriuretic peptide level measurement, reserving echocardiograms for patients with an abnormal test result. Results are presented in terms of additional cost per diagnosis as compared with not performing any screening. From the Brazilian private sector's perspective, strategies 1 and 2 resulted in additional costs of US $30,951.53 and US $19,925.64 per diagnosis of cardiotoxicity, respectively. From the perspective of the Brazilian public health system, the same strategies generated additional costs of US $7,668.00 and US $20,232.87 per diagnosis, respectively. In our study, systematic screening for cardiotoxicity in patients using imatinib has a high cost per diagnosis. If screening is to be adopted, a strategy based on B-type natriuretic peptide level measurement, reserving echocardiography for patients with abnormal results, results in lower costs per diagnosis in the private sector. From the public health system's perspective, costs per diagnosis will greatly depend on the reimbursement values adopted for B-type natriuretic peptide level measurement.

Keywords: cardiac toxicity, cost-effectiveness, economic analysis, imatinib, side effects.

Introduction

Cardiotoxicity remains the limiting factor for many forms of chemotherapy, and it is a cause for concern among physicians and patients due to its potential impact on the overall prognosis and survival of cancer [1]. Pathological changes in the myocardium do not necessarily translate into clinically significant cardiac toxicity [2], and distinguishing between symptoms of heart failure (HF) and chemotherapy-related adverse effects can be challenging [3]. Consequently, accurate and specific tests, including cardiac biomarkers, echocardiography, and radionuclide ventriculography, are essential for improving early detection of cardiac injury and dysfunction [2,4].

Screening and prevention strategies have been a growing field for research. Screening for cardiac dysfunction by using periodic imaging with two-dimensional echocardiography is a standard part of the care of patients receiving potentially cardiotoxic chemotherapy agents, such as anthracyclines and trastuzumab [5]. This strategy, however, is not established for other potential cardiotoxic drugs, such as the tyrosine-kinase inhibitors imatinib, dasatinib, nilotinib, sorafenib, and lapatinib [6].

Imatinib is a relatively recent option for the treatment of chronic myeloid leukemia, and its demonstrated effectiveness has made it the standard first-line therapy for that condition. It is also effective in treating gastrointestinal stromal tumors, Philadelphia chromosome-positive acute lymphoblastic leukemia, myeloproliferative diseases associated with PDGFR gene arrangements, advanced systemic mastocytosis, hypereosinophilic syndrome, chronic eosinophilic leukemia, and advanced dermatofibrosarcoma protuberans [7–11]. Therefore, its chronic use has been growing in the past years.

Regarding imatinib's potential for cardiotoxicity, initial studies and animal models showed evidence of potential imatinib-induced HF [12], but recent studies with larger samples suggest that the incidence of HF after long-term use of imatinib is much lower than what is observed with anthracyclines [13–16]. Retrospective analysis of a phase III trial including 1276 patients has shown an incidence rate of imatinib-induced HF of 0.2% per year, which is similar to the rate expected in an age- and gender-matched population [15]. Another retrospective study including 285 patients with a median treatment time of 3.0 years has shown an incidence rate of 1.0% [16]. In a cross-sectional study

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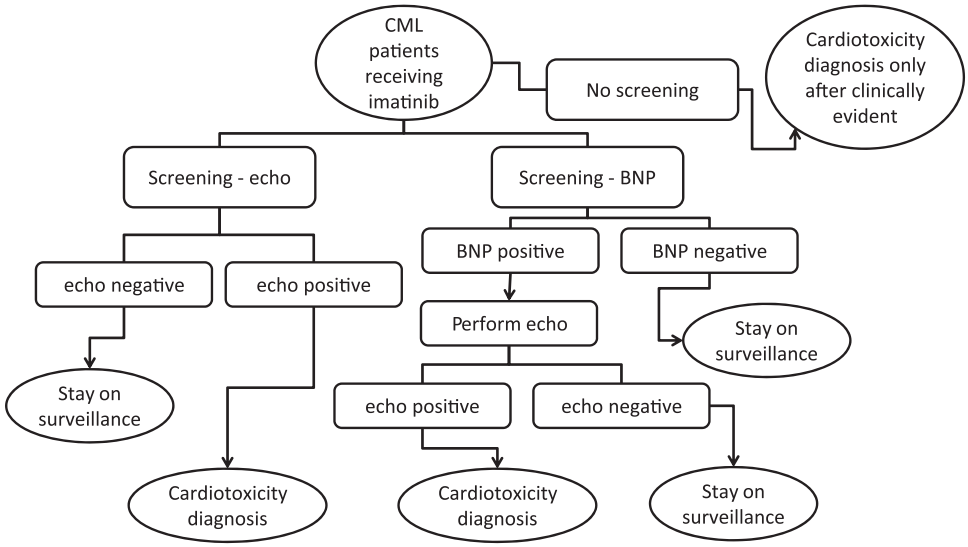

Fig. 1 – Decision tree representing the evaluated screening strategies. BNP, B-type natriuretic peptide; CML, chronic myeloid leukemia; echo, echocardiogram.

specially designed to investigate the cardiac effects that included 90 patients with chronic myeloid leukemia under imatinib therapy for a median treatment time of 3.3 years, a comprehensive cardiac evaluation has shown that 2.2% of the patients had signs of cardiotoxicity [13].

This raises an important question: If HF induced by imatinib is a rare event, should routine screening be advised? Measurement of plasma B-type natriuretic peptide (BNP) level has been suggested as a useful marker for the detection of imatinib-related cardiotoxicity. Considering the importance of the adverse effect, some authors recommended a strategy of monitoring all patients by serial BNP plasma level measurement [17], but the current utility and cost-effectiveness of this approach are not known. Screening would allow early detection of myocardial injury, but it could increase costs significantly, and still result in a great majority of negative test results.

On the basis of findings of recent studies on the risk of imatinib-induced cardiotoxicity [13,14], we performed a cost-effectiveness study of different screening strategies, based on two-dimensional echocardiography and BNP levels.

Methods

Model Structure

We built a decision tree comparing two different strategies for cardiotoxicity screening in patients taking imatinib (Fig. 1). The first strategy was based on performing an echocardiogram once a year in all patients, while the second strategy used yearly BNP level measurement as the initial screening test, and only patients with an abnormal test result had echocardiography.

Input Parameters

To obtain the frequency of abnormal examination results and of cardiotoxicity, we used data from a cross-sectional study in which consecutive patients with chronic myeloid leukemia using imatinib were included, from the outpatient clinic of the Hematology Service of the Federal University of Minas Gerais, Brazil, an academic tertiary referral center. Exclusion criteria were any kind of established heart disease (valvular or congenital heart disease, HF, pacemaker usage, and history suggestive of coronary heart disease), history of atrial or ventricular arrhythmias, resistant arterial hypertension (blood pressure above goal in spite of the concurrent use of three antihypertensive agents of different classes at optimal dose amounts), significant anemia (hemoglobin level lower than 9 g/dl), chronic obstructive pulmonary disease (suggested by clinical signs, symptoms, risk factors, and radiologic alterations or confirmed by spirometry), and history of alcohol or substance abuse or dependence. Included patients (mean age 48 ± 15 years) were in treatment with imatinib for a median of 3.3 years. Patients were submitted to extensive cardiac screening, which consisted of an evaluation of the medical history, a physical examination with special attention to signs and symptoms related to HF, electrocardiography, echocardiography, and BNP plasma level measurement. Detailed results have been published previously [14], and the observed frequency of cardiotoxicity was 1% per year.

We defined cardiotoxicity as a significant decline in left ventricular systolic function, as measured by echocardiography. All relevant parameters used in the model are described in Table 1.

Costs

In our first analysis, costs for echocardiograms and BNP level measurements are based on reimbursement values paid by private health insurance companies in Brazil. In a second analysis, we used reimbursement values from the public health system (PHS) for the cost of echocardiography. The Brazilian PHS does not, at this moment, however, reimburse BNP level measurement; therefore, in the analysis, we assumed the cost of BNP level measurement in the PHS to be the same as in the private sector and explored the possibility of a significantly lower value in the sensitivity analysis. Costs can be found in Table 1.

Because the World Bank's purchasing power parity conversion rates for the Brazilian currency (R $) have not been updated in the last year [20], and significant changes in the Brazilian real and United States dollar (US $) exchange rate have occurred in that period, we chose to report all costs in US $, using current official exchange rates [21], in which R $1.56 = US $ 1.00.

Sensitivity Analyses

The largest available studies evaluating the issue have reported a similar incidence rate of imatinib cardiotoxicity, between 0.97%