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

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ABSTRACT

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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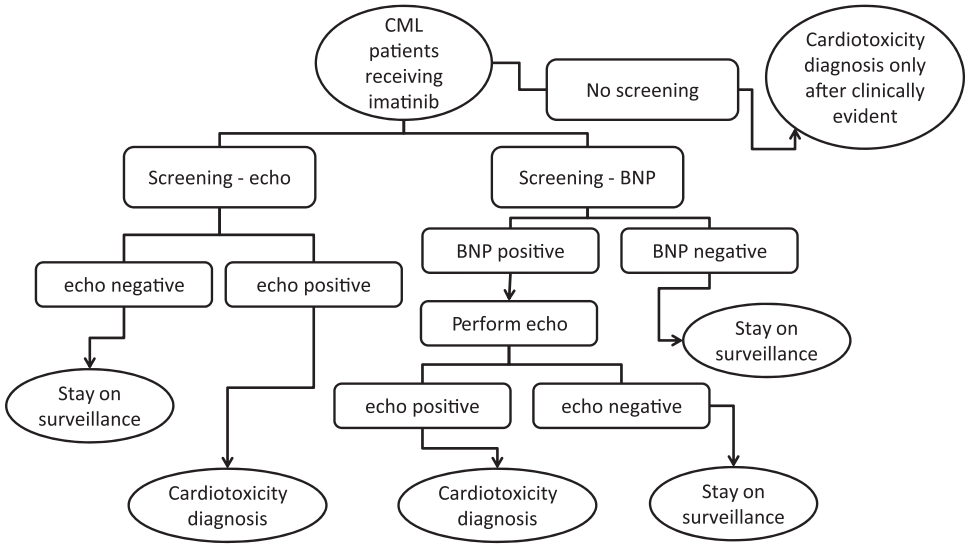

Fig. 1 – Decision tree representing the evaluated screening strategies. BNP, B-type natriuretic peptide; CML, chronic myeloid leukemia; echo, echocardiogram.

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%

Table 1 – Input data and limits for sensitivity analysis.

	Baseline	Lower limit	Upper limit	Reference
Probabilities (%)				
Abnormal echocardiogram (per year)	0.33	0.17	0.66	[14]
Abnormal BNP level (per year)	1.33	0.66	2.66	[14]
Abnormal echocardiogram (after abnormal BNP level)	25.00	12.50	50.00	[14]
Costs (US $)				
Echocardiogram (private sector)	103.04	51.52	154.56	[18]
Echocardiogram (public health system)	25.56	12.78	38.34	[19]
BNP level measurement	66.31	33.16	99.47	[18]

BNP, B-type natriuretic peptide.

and 1.7% [13–16]. We considered, however, that the small number of events in these studies warrants larger margins for sensitivity analyses. Therefore, we performed one-way sensitivity analysis for all the model's parameters, using half the original value for the lower limit and double the original value for the upper limit.

Results

Base Case

In the analysis from the private sector's perspective, the first strategy, based on annual echocardiography, generated mean costs per patient of US $103.20 per year, resulting in a final cost of US $30,951.53 per diagnosis of cardiotoxicity, as compared with not performing any screening. The second strategy, based on annual BNP level measurement, followed by echocardiography only in patients with an abnormal result, generated mean costs per patient of US $66.42 per year, resulting in a final cost of US $19,925.64 per diagnosis of cardiotoxicity versus no screening, and making it the dominant strategy.

In the analysis from PHS's perspective, the strategy based on annual BNP level measurement (assuming costs of BNP level measurement in the PHS to be equal to those in the private sector) resulted in mean costs per patient of US $67.44 per year and a final cost of US $20,232.87 per diagnosis of cardiotoxicity. In this perspective, the strategy based on annual echocardiography was dominant, with mean costs per patient of US $25.56 and final costs of US $7,668.00 per diagnosis of cardiotoxicity.

The main results are summarized in Table 2.

Sensitivity Analysis

When a higher frequency of cardiotoxicity was assumed (0.66% per year), costs per diagnosis of cardiotoxicity in the private sector's perspective fell to US $15,475.76 for the echocardiogram-based strategy and US $9,962.82 for the BNP-based strategy. A lower frequency (0.17%) raised the costs per diagnosis to US $61,903.06 for the echocardiogram-based strategy and US $29,851.28 for the BNP-based strategy.

As expected, costs of BNP level measurement and echocardiogram had a large influence on the results, keeping the dominance with the strategy that uses the least costly screening test. In the analysis from the PHS perspective, the BNP-based strategy becomes dominant if the cost of BNP level measurement falls below US$25.56.

Discussion

Concerns have been raised regarding imatinib's potential to induce cardiotoxicity [12]. Although recent data suggest that this is a rare complication [13–15], HF may seriously affect prognosis in these patients [1]. In addition to increased long-lasting morbidity and mortality, dose limitation and suboptimal usage are important adverse effects.

Cardiac screening is usually recommended in patients taking chemotherapy drugs more prone to induce cardiotoxicity, such as anthracyclines. In the case of imatinib, however, the low frequency of this adverse effect may not justify systematic screening, because it can generate significant additional costs with little potential benefit in the great majority of patients. The clinical relevance of imatinib-induced HF and the real necessity of monitoring all patients are questionable; consequently, an economic analysis is extremely important to develop a recommendation regarding cardiac screening.

This study has the merit of being the first economic analysis to determine the cost-effectiveness of two different screening strategies for patients receiving imatinib. In addition, it used data

Table 2 – Results of cost-effectiveness analysis (vs. no screening).

	Mean annual cost per patient	Effectiveness*	Cost per diagnosis of cardiotoxicity
Private sector's perspective			
Strategy 1—annual echocardiogram	103.20	0.01	30,951.53
Strategy 2—annual BNP level measurement, echocardiogram if test result abnormal	74.04	0.01	22,213.33
Public health system's perspective			
Strategy 1—annual echocardiogram	25.56	0.01	7,668.00
Strategy 2—annual BNP level measurement, echocardiogram if test result abnormal	67.44	0.01	20,232.87

BNP, B-type natriuretic peptide.
* Annual rate of detected cardiotoxicity.

from a large recent study on the frequency of cardiotoxicity in patients receiving imatinib. Its reliance on a relatively simple model intends to keep most of the input parameters as reliable as possible, minimizing assumptions.

Results of our cost-effectiveness analysis reflect the low frequency of cardiotoxicity observed in the observational studies, with both screening strategies obtaining similar effectiveness, and dominance determined essentially by the costs of screening.

In the Brazilian private sector's perspective, there is evidence of superior cost-effectiveness of a screening strategy based on BNP level measurements, reserving echocardiography for patients with an abnormal test result. Even the BNP-based strategy, however, would generate costs that approach US $20,000 per diagnosis of cardiotoxicity. Currently, there is no broadly accepted willingness-to-pay threshold for additional costs per correct diagnosis. The World Health Organization–recommended willingness-to-pay threshold of one to three times the nation's gross domestic product per capita is based on results per quality-adjusted life-year; the logical conclusion would be that cost-per-diagnosis results should be acceptable only at lower thresholds than these. Currently, the Brazilian gross domestic product per capita is US $10,800 [20]; the results for the BNP-based strategy in the private sector are about two times higher than that, and may be considered excessively high for systematic adoption.

For the Brazilian PHS's perspective, an assumption had to be made regarding costs of BNP measurement, as it is not currently reimbursed. Assuming the same costs found in the private sector, the BNP-based strategy was dominated. It should be noted, however, that in the Brazilian PHS, reimbursement values are centrally defined by the government's Ministry of Health. These values are most often lower than values found in the private sector, many times to the point of not covering actual health spendings [22,23]. It is reasonable to assume that if BNP level measurements become available for the PHS, the value of reimbursement will likely be lower than the one encountered in the private sector.

Therefore, the results of our analysis for the PHS should probably not be used for final decisions regarding the relative cost-effectiveness of screening strategies in the public sector, but rather as an additional tool to be considered during the process of defining a reimbursement value for BNP. This study has some limitations. The study that supplies the input data had a low frequency of the primary outcome, which may compromise its power to predict the incidence of the outcome in other populations. Other studies, however, have confirmed that imatinib-induced HF is an uncommon event [15,24–26].

Our model does not incorporate the potential benefit derived from early diagnosis of cardiotoxicity, which may underestimate the benefits of screening. It should be noted, however, that objective data on the actual benefits of this early diagnosis are scarce, and their addition would significantly increase the uncertainty of the model.

Conclusions

In the Brazilian private sector, systematic screening for cardiotoxicity in patients using imatinib has a high cost per diagnosis. If screening is to be adopted, a strategy based on BNP level measurement, reserving echocardiography for patients with abnormal test results, is preferred.

For the Brazilian PHS, the cost per diagnosis of cardiotoxicity would be lower, due to the lower reimbursement values for echocardiograms in this context. Selection of the best strategy would depend on the reimbursement values adopted for BNP level measurement, which is currently unavailable in the PHS.

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