Editorial

Detection of Subclinical Trastuzumab-Induced Cardiotoxicity in Patients with Breast Cancer

Marília Harumi Higuchi dos Santos

Instituto do Câncer do Estado de São Paulo (ICESP), São Paulo, SP - Brazil

In recent decades, the treatment of cancer has shown great development in the fields of surgery, radiation therapy and the emergence of cytotoxic chemotherapy and targeted cancer therapies (including monoclonal antibodies, tyrosine-kinase inhibitors and angiogenesis inhibitors). Consequently, there has been an increase in survival of patients with cancer, making cardiovascular complications related to chemotherapy be more carefully taken into consideration by cardiologists and oncologists.

The most frequent clinical manifestation of cardiotoxicity is symptomatic or asymptomatic ventricular dysfunction that can progress to heart failure[1]. Ventricular dysfunction can occur not only after conventional chemotherapy with anthracyclines, but with the new antitumor agents, such as trastuzumab.

Several studies have shown that screening for cardiotoxicity by assessing the ejection fraction may be inadequate to detect subclinical disease[2]. It is known that the time of implementation of cardiovascular therapy is an important prognostic factor in heart function recovery and to prevent heart failure development[3]. Thus, several biomarkers have been studied in an attempt at early detection of cardiotoxicity, particularly troponin, BNP and microRNAs[4,5]. However, the optimal time of collection, or an ideal population to be submitted to this screening is yet to be determined. In addition, more sensitive methods for the assessment of cardiac structure and function, such as magnetic resonance imaging and strain echocardiography seem to detect the subclinical forms of the disease[2].

Some medications commonly used in the management of heart failure have shown a beneficial effect on chemotherapy-related cardiotoxicity. The use of angiotensin-converting enzyme inhibitors in patients with troponin increase during chemotherapy can be an effective tool to prevent left ventricular dysfunction and late cardiovascular events[6].

However, there are no large studies that evaluated the effect of these medications on anticancer therapy efficacy. In the treatment of cardiotoxicity associated with the use of chemotherapeutic agents, beta-blockers, enzyme inhibitors and angiotensin-converting enzyme inhibitors seem to be effective. However, early treatment of ventricular dysfunction is important, considering the correlation between the time of start of ventricular dysfunction treatment and cardiac function recovery[1].

The HER2 gene amplification and/or overexpression of its protein occurs in approximately 20% of breast cancers and is associated with a worse prognosis[7]. New chemotherapeutic agents, targeted at the HER2 receptor and its action pathway, have revolutionized the treatment of this type of cancer[8]. Trastuzumab, a humanized monoclonal antibody, was the first targeted therapy against the HER2 pathway and its use has changed the natural history of HER2+ breast cancer, resulting in improved survival similar to HER2- breast cancers. Thus, trastuzumab has become the key point in the treatment of HER2 + breast cancer.

However, despite the outstanding benefits in survival related to anti-HER2 treatment, a significant increase in drug-related cardiac toxicity has been observed[9], with several cardiac dysfunction events reported in clinical studies with the use of trastuzumab. Although cardiac toxicity induced by anti-HER2 therapy is not completely understood, preclinical studies have demonstrated an important role of HER2 signaling pathway in cardiac physiology, since both HER2 receptors and its ligands are expressed in cardiomyocytes. Despite the benefits offered by anti-HER therapy, there is justified concern about the potential adverse cardiac events and studies are needed to assess ways of early detection of this toxicity, as well as the best way of handling it, as the pathways of toxicity and therapeutics[10] may be superimposed.

It is believed that diastolic dysfunction may precede the onset of left ventricular systolic dysfunction[11]. In this issue, Dores et al[12] studied 51 women with HER2 + breast cancer for five months to assess the occurrence of early cardiotoxicity. Although they found no symptomatic heart failure, the authors showed that as early as the third month of treatment, there were differences in diastolic parameters after the use of trastuzumab. The authors found a statistically significant difference in the E/e' ratio from the beginning to the third month of follow-up related to a reduction in myocardial velocity, as assessed by tissue Doppler. More than half of patients (57.9%) showed a decrease in ejection fraction, but only one had a decrease below 55%.

With the development of cardio-oncology and the constant advent of new chemotherapeutic agents, surveillance studies and the search for early markers of cardiac abnormalities in cancer patients is of great importance for the adequate management of these patients.

"Editorial under the responsibility of Cardiosource in Portuguese. http://cientifico.cardiol.br/cardiosource2/default.asp"

Keywords

Antineoplastic, Agents; Cardiotoxins; Breast Neoplasms; Ventricular Dysfunction; Heart Failure.

Mailing Address: Marília Harumi Higuchi dos Santos •
Rua Capote Valente 361 ap. 142. Jd America, São Paulo - SP - Brazil - CEP 05409-001
E-mail: mhhsantos@yahoo.com
Manuscript received June 11, 2013; revised manuscript June 11, 2013; accepted June 11, 2013.

DOI: 10.5935/abc.20130143

References

1. Colombo A, Meroni CA, Cipolla CM, Cardinale D. Managing cardiotoxicity of chemotherapy. Curr Treat Options Cardiovasc Med. 2013. May 16 [Epub ahead of print].
2. Fallah-Rad N, Walker JR, Wassef A, Lytwyn M, Bohonis S, Fang T, et al. The utility of cardiac biomarkers, tissue velocity and strain imaging, and cardiac magnetic resonance imaging in predicting early left ventricular dysfunction in patients with human epidermal growth factor receptor II–positive breast cancer treated with adjuvant trastuzumab therapy. J Am Coll Cardiol. 2011;57(22):2263-70.
3. Seicean S, Seicean A, Alan N, Plana JC, Budd GT, Marwick TH. Cardioprotective effect of Beta-Adrenoceptor blockade in breast cancer patients undergoing chemotherapy: a follow-up study of heart failure. Circ Heart Fail. 2013;6(3):420-6.
4. Lipshultz SE, Miller TL, Scully RE, Lipsitz SR, Rifai N, Silverman LB, et al. Changes in cardiac biomarkers during doxorubicin treatment of pediatric patients with high-risk acute lymphoblastic leukemia: associations with long-term echocardiographic outcomes. J Clin Oncol. 2012;30(10):1042-9.
5. Pellegrino L, Stebbing J, Braga VM, Frampton AE, Jacob J, Buluwela L, et al. miR-23b regulates cytoskeletal remodeling, motility and metastasis by directly targeting multiple transcripts. Nucleic Acids Res. 2013;41(10)5400-12.
6. Cardinale D, Colombo A, Sandri MT, Lamantia G, Colombo N, Civelli M, et al. Prevention of high-dose chemotherapy-induced cardiotoxicity in high-risk patients by angiotensinconverting enzyme inhibition. Circulation. 2006;114(23):2474-81.
7. Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med. 2001;344(11):783-92.
8. Dawood S, Broglio K, Buzdar AU, Hortobagyi GN, Giordano SH. Prognosis of women with metastatic breast cancer by HER2 status and trastuzumab treatment: an institutional-based review. J Clin Oncol. 2010;28(1):92-8.
9. Seidman A, Hudis C, Pierri MK, Shak S, Paton V, Ashby M, et al. Cardiac dysfunction in the trastuzumab clinical trials experience. J Clin Oncol. 2002;20(5):1215-21.
10. Martín M, Esteva FJ, Alba E, Khandheria B, Pérez-Isla L, García-Sáenz JA, et al. Minimizing cardiotoxicity while optimizing treatment efficacy with trastuzumab: review and expert recommendations. Oncologist. 2009;14(1):1-11.
11. Edvardsen T. Can modern echocardiographic techniques predict drug-induced cardiotoxicity? J Am Coll Cardiol. 2011;57(22):2271-2.
12. Dores H, Abecasis J, Correia MJ, Gândara F, Fonseca C, Azevedo J, et al. Detecção de Cardiotoxicidade Subclínica Induzida por Trastuzumabe em Portadoras de Câncer de Mama. Arq Bras Cardiol. 2013;100(4):328-32.