Title

Utilization of cardiac monitoring tests in women with nonmetastatic breast cancer treated with trastuzumab

Journal

Personalized Medicine, 10(7)

ISSN

1741-0541

Authors

Shin, Jaekyu
Liang, Su-Ying
Hassett, Michael J
et al.

Publication Date

2013-09-01

DOI

10.2217/pme.13.68

Peer reviewed

Utilization of cardiac monitoring tests in women with nonmetastatic breast cancer treated with trastuzumab

Aims: Trastuzumab, one of the best known examples of personalized medicine, requires regular cardiac monitoring because it can cause heart failure. We aimed to assess the utilization of cardiac monitoring in women with nonmetastatic breast cancer receiving trastuzumab-based chemotherapy in routine clinical practice. **Patients & methods:** The medical records of women continuously enrolled in a large national health insurance plan who were diagnosed with nonmetastatic breast cancer and treated with trastuzumab from 2006 to 2008 were reviewed (n = 109). The primary outcome variables were the use and type of cardiac monitoring testing before and during trastuzumab therapy. An exploratory multivariable logistic regression analysis was performed to identify predictors for receiving cardiac monitoring both at baseline and during trastuzumab treatment. **Results:** Monitoring both before and during therapy was less common (62%), although 74% had cardiac monitoring before therapy and 80% had at least one test during therapy. Radionuclide ventriculogram was utilized more often than echocardiography (48 vs 42%). Only the use of anthracycline (odds ratio: 2.39; 95% CI: 1.01–5.71) was significantly associated with use of a cardiac monitoring both at baseline and during trastuzumab treatment. **Conclusion:** The use of cardiac monitoring testing was variable and opportunities to improve quality and reduce cost are evident. These results have clinical implications for other personalized medicine interventions requiring regular laboratory monitoring.

KEYWORDS: breast cancer ■ cardiac monitoring ■ personalized medicine ■ quality-of-care ■ trastuzumab

Jaekyu Shin*[1], Su-Ying Liang[1], Michael J Hassett[2], Kathryn A Phillips[1] & Jennifer S Haas[3]

[1]Department of Clinical Pharmacy, School of Pharmacy, University of California San Francisco & UCSF Center for Translational & Policy Research on Personalized Medicine (TRANSPERS), 521 Parnassus Street, C-152, Box 0622, San Francisco, CA 94143-0622, USA
[2]Division of Population Sciences, Dana-Farber Cancer Institute, Boston, MA, USA
[3]Division of General Internal Medicine, Brigham & Women's Hospital, Boston, MA, USA
**Author for correspondence:*
Tel.: +1 415 514 2747
Fax: +1 415 476 6632
shinj@pharmacy.ucsf.edu

Trastuzumab is one of the best known examples of personalized medicine. It targets HER-2-positive breast cancer and significantly reduces breast-cancer mortality in women who are HER-2 positive [1–4]. However, this drug can cause left ventricular dysfunction, a potentially serious side effect, by interfering with EGF receptor-2-mediated cell signaling, an important pathway for growth and protection of cardiomyocytes [1–5]. About 10% of trastuzumab recipients show a decline in left ventricular ejection fraction (LVEF) and 1–4% develop symptoms of systolic heart failure [1–3]. While trastuzumab-related left ventricular dysfunction can be reversible or treatable, some patients experience long-term adverse effects from the drug [6].

Trastuzumab product labeling and professional guidelines recommend monitoring cardiac function before trastuzumab-based therapy in order to avoid use of the drug among patients at elevated cardiac risk, and regularly every 3–4 months during therapy to detect left ventricular dysfunction early with the hope of stopping therapy before it becomes symptomatic [7,8,101]. Both radionuclide ventriculography (RVG; also known as multigated acquisition scan or MUGA scan) and echocardiography are commonly used to monitor left ventricular function. RVG has a high reproducibility and low intra- and inter-observer variability, but it exposes the patient to radiation and is expensive [9,10]. Echocardiography is easy to perform and does not expose the patient to radiation, but often requires the involvement of a cardiologist [10]. Neither the product labeling nor professional guidelines recommend a specific cardiac monitoring test.

Little is known about the use of cardiac monitoring in routine clinical practice, and more specifically about whether patient, diagnosis or health system factors are associated with the frequency or type of testing. Our objective was to use linked administrative claims and chart review data from a large national health plan to assess the utilization and predictors of cardiac monitoring among women with nonmetastatic breast cancer receiving trastuzumab-based chemotherapy.

Patients & methods

■ Data sources & study sample

We utilized administrative claims data from a large national health plan, the name of which we cannot provide because of our data-use agreement. The data source and study sample, including identification of incident breast

Future Medicine part of fsg

cancer cases, have been previously described [11]. Briefly, the data set included 7575 women with incident breast cancer diagnosed between 2006 and 2008. The claim data set contained medical and pharmacy claims 6 months before, and up to 2 years after the date of cancer diagnosis. Of 7575 women, initially 2100 subjects were randomly selected. Of these 2100 subjects, 700 subjects whose primary oncologists or surgeons were willing to have their charts reviewed were selected for chart review to collect data such as demographic information, past medical history, pathology and laboratory test results, including dates, types and results of cardiac monitoring tests. A Charlson comorbidity index was constructed based on the patient's medical history [12]. For this analysis, we included women aged 30 to 64 years with nonmetastatic breast cancer who were treated with trastuzumab (n = 109). Women who had a disease requiring regular cardiac monitoring (i.e., cardiac valvular diseases, pulmonary arterial hypertension, congenital heart diseases, cardiomyopathy, endocarditis or heart failure) were excluded (n = 1).

Trastuzumab treatment, cardiac monitoring & primary outcomes

Duration of trastuzumab treatment was defined as the number of days between the starting and last dates of trastuzumab administration. Baseline (i.e., before trastuzumab) 'cardiac monitoring' was defined as any test within 180 days prior to the first trastuzumab administration date. During therapy, 'monitoring' was defined as any test from the first trastuzumab administration to the last available claim. We identified patients who had baseline and/or during-therapy monitoring, and patients who had monitoring during therapy at least every 90 days. We chose every 90 days as the study interval because it is recommended by many guidelines [7,101]. We described the type of cardiac monitoring test used: echocardiography, RVG, or both. We also described the rate of significant left ventricular dysfunction during trastuzumab treatment, defined as LVEF ≤40% or both LVEF <55% and an LVEF drop >10% from baseline.

Statistical analysis

We conducted bivariate analyses to examine the association between potentially important factors and cardiac monitoring. We hypothesized that the following patient and clinical characteristics might be associated with the use of cardiac monitoring: age, race, region, grade, Charlson index, use of an anthracycline chemotherapy agent, receipt of radiation therapy, type of breast surgery (mastectomy or lumpectomy) and cancer stage. Exploratory multivariate logistic regression analyses were performed to assess the relationship between these variables and the use of a cardiac monitoring both before and during treatment. Only variables with a p-value <0.2 on bivariate analysis were entered into multivariate analysis. p-values were two-tailed and considered statistically significant if they were <0.05. All analyses were performed using SAS 9.1 (Cary, NC, USA).

Results

The median age was 50 (range: 30–63; Table 1). More than half of the study population was white, resided in the southern part of the USA, and had stage II breast cancer at the time of diagnosis. Few women had a pre-existing cardiovascular comorbid condition (two women with cerebrovascular disease and six women with diabetes mellitus). Over 60% received radiation therapy and anthracycline-based chemotherapy before starting trastuzumab. The median duration of trastuzumab treatment was 358 days (range: 98–805 days).

The number of cardiac monitoring tests performed ranged from 0–10, with a median of 3. A total of 92% received a cardiac test either at baseline or during trastuzumab treatment. At baseline, 74% had cardiac monitoring and the median LVEF was 62% (range: 45–78). Trastuzumab treatment was started a median of 21 days (range: 0–153 days) after the baseline cardiac monitoring test. During trastuzumab treatment, 80% received a test at least once, but only 28% had testing once every 90 days. About 62% of the women received a cardiac monitoring test at baseline and at least once during trastuzumab treatment; only 21% had testing at baseline and at least every 90 days during trastuzumab treatment.

Of the 100 women who had at least one cardiac monitoring test, 21% had only one test (Table 2). Type of testing was only echocardiography for 24% of the cohort, only RVG for 32% and both for 44%. Of 297 cardiac monitoring tests, RVG was utilized more often than echocardiography (48 vs 42%), especially at baseline (RVG, 62.5% vs echocardiography, 37.5%) (Table 3).

In the bivariate analysis, tumor stage and receipt of anthracycline were significantly associated with use of cardiac monitoring, both at baseline and during trastuzumab treatment: (69% in the subjects with stage II or III vs 49% in the subjects with stage I, p = 0.04; 70% in the subjects who used an anthracycline chemo-agent vs 46%

in the subjects who did not use an anthracycline chemoagent, p = 0.014). On multivariate logistic regression analysis, only use of anthracycline (odds ratio: 2.39; 95% CI: 1.01–5.71) was significantly associated with use of cardiac monitoring both at baseline and during trastuzumab treatment.

Five women developed an LVEF ≤40%, or an LVEF <55% and a LVEF drop >10% from baseline, during trastuzumab treatment. Of these, four (80%) had trastuzumab treatment interrupted as a result of the identified left ventricular dysfunction, but subsequently resumed treatment. All four had cardiac monitoring before resuming trastuzumab therapy.

Discussion

Using chart review and national claims data for patients with nonmetastatic breast cancer treated with trastuzumab-based chemotherapy, we found variable use of cardiac monitoring. While most patients had some form of cardiac testing, a substantial minority had no baseline testing (14%) or no testing during therapy (13%). While 92% had testing before or during trastuzumab-based therapy, only 62% had testing both at baseline and during trastuzumab therapy, and only 21% had testing before and at least once every 90 days during therapy.

Few other studies have evaluated the use of cardiac monitoring in routine clinical practice. Subar *et al.* identified a 67% rate of baseline cardiac monitoring, an 88% rate of testing before or during therapy and a 16% rate of testing according to the standard monitoring schedule by using administrative data from 664 patients with nonmetastatic breast cancer treated with trastuzumab in 2007 [13]. While it is reassuring that our findings are similar, it is disappointing that both studies identify a subset of patients who do not have testing. Our findings have clinical implications for other personalized medicine interventions, such as ivacaftor and crizotinib, because their successful use in clinical practice may depend on regular laboratory monitoring.

Using exploratory multivariable analysis, we found a positive relationship between cardiac monitoring and receipt of anthracycline-based chemotherapy. The anthracycline-related finding is not surprising, considering that anthracycline chemotherapy agents cause cardiac toxicity, and is consistent with the result of the study by Subar *et al.* [13]. To our surprise, age, region and race were not associated with cardiac monitoring, possibly due to the small sample size. The study by Subar *et al.* was not able to evaluate the relationship between detailed patient, diagnosis and

Table 1. Baseline characteristics of the study population (n = 109).

Characteristics	n (%)
Age at diagnosis	
30–49 years (%)	54 (49.5)
Race	
African–Americans (%)	5 (4.6)
Asian (%)	5 (4.6)
White (%)	56 (51.4)
Hispanic (%)	2 (1.8)
Unknown (%)	41 (37.6)
Geographical region	
North east	8 (7.3)
Midwest	22 (20.2)
South	67 (61.5)
West	12 (11.1)
Stage	
I	35 (32.1)
II	57 (52.3)
III	17 (15.6)
Tumor size	
<1.0 cm	11 (10.1)
1.0–3.0 cm	77 (65.7)
≥3.1 cm	13 (11.9)
Unknown	8 (7.3)
Lymph node involvement	
Yes	52 (47.7)
Unknown	2 (1.8)
Grade	
Good	1 (1.0)
Moderate	28 (25.7)
Poor	76 (69.7)
Unknown	4 (3.7)
Previous medical history	
Heart failure	0 (0)
Diabetes mellitus	6 (5.5)
Charlson comorbidity index	
0	94 (86.2)
1+	15 (13.8)
Surgery	
Lumpectomy	50 (45.9)
Mastectomy	59 (54.1)
Radiation	68 (62.4)
Anthracycline-containing regimen	74 (67.9)
Hormonal therapy	66 (60.5)

Table 2. Utilization of echocardiography and radionuclide ventriculography at individual level (n = 100).

Number of cardiac monitoring tests	Type of cardiac monitoring test	n (%)
One	Total number of subjects	21
	Echo	4 (19.0)
	RVG	9 (42.9)
	Unknown	8 (38.1)
Multiple times	Total	79
	Echo only	20 (25.3)
	RVG only	23 (29.1)
	Both Echo and RVG	16 (20.3)
	Unknown	20 (25.3)
Combined	Number of subjects	100
	Echo only	24 (24)
	RVG only	32 (32)

Echo: Echocardiography; RVG: Radionuclide ventriculography.

treatment characteristics and the use of cardiac monitoring because it was based only on claim data [13].

There may be several reasons for the variable utilization of cardiac monitoring. First, the clinical trials that established trastuzumab as an effective component in the treatment of nonmetastatic breast cancer used different cardiac monitoring schedules [1,13,14]. Second, while the trastuzumab product labeling and several guidelines describe who, how and when to test, they provide inconsistent advice regarding the frequency of testing and the specific LVEF value or change from baseline that should prompt an alteration in therapy [7,8,101]. For example, the product labeling recommends monitoring cardiac function every 3 months while on therapy, and discontinuing trastuzumab if the LVEF drops ≥16% from the baseline or the LVEF becomes below institutional limits of normal values and drops ≥10% from the baseline [101]. On the other hand, the UK National Cancer Research Institute recommends monitoring cardiac function at 4 and 8 months while on therapy and interrupting trastuzumab treatment if the LVEF is ≤40% [8]. Finally, the lack of data on clinical utility of cardiac monitoring in this population contributes to the inconsistent guideline recommendations and variable utilization of cardiac monitoring in our study. Thus, a study rigorously evaluating the need for and frequency of cardiac monitoring in this population is needed.

Table 3. Utilization of echocardiography and radionuclide ventriculography at test level (n = 297).

Timing of cardiac monitoring test	Type of cardiac monitoring test	n (%)
At baseline	Total	81
	Echo	30 (37.5)
	RVG	50 (62.5)
	Unknown	1 (1.2)
During trastuzumab treatment	Total	216
	Echo	95 (44.0)
	RVG	92 (42.6)
	Unknown	29 (13.4)
Combined	Number of tests	297
	Echo	125 (42.1)
	RVG	142 (47.8)

Echo: Echocardiography; RVG: Radionuclide ventriculography.

Analysis of the types of tests ordered as part of cardiac monitoring before and during trastuzumab-based therapy found that RVG was used more often than echocardiography. This difference was more prominent at baseline than during treatment, though this could reflect sampling bias for the subset of patients who continued on trastuzumab for a longer period of time. We are unaware of another study describing utilization patterns of echocardiography and RVG among women with nonmetastatic breast cancer receiving trastuzumab. The two testing modalities offer similar results and guidelines tend to avoid recommending one over the other. Choice of test could be influenced by cost, ease of scheduling, and/or the availability of the specialist who conducts and interprets the test (radiologist vs cardiologist). Given the substantial cost difference (US$248.13 per RVG vs US$148.40 per echocardiogram in 2012), the choice of testing modality could have significant policy implications [102].

Five patients (4.5% of our study sample) developed a LVEF ≤40% or both LVEF <55% and a LVEF drop >10% from baseline during trastuzumab therapy, and only one did not recover her LVEF. These rates of asymptomatic decline in ejection fraction and persistent abnormal cardiac function are consistent with previous estimates of the risks associated with trastuzumab-based therapy and of the chances that the cardiac-related adverse effects of trastuzumab can be reversed [1]. It is reassuring to confirm these findings in a routine care cohort, although, given the small sample size and relatively short duration of follow-up in this study, caution should be taken when interpreting these results.

Given the lack of research on this topic, our study provides useful findings despite several limitations. First, the small sample size limits our ability to model factors associated with the use of cardiac monitoring tests or to fully explore how trastuzumab and cardiac monitoring tests were utilized in patients with trastuzumab-induced left ventricular dysfunction. Second, our results may not be applicable to patients >65 years old. Third, our data were collected between 2006 and 2008, and may not be representative of utilization patterns at present. Finally, although the combined chart review and claims methodology helped identify cardiac monitoring tests, patients still could have had undocumented tests.

Conclusion

The utilization of cardiac monitoring among patients with nonmetastatic breast cancer receiving trastuzumab found many patients received testing as recommended, but identified potential opportunities for improvement. Some patients have no baseline monitoring and some have no or infrequent monitoring during therapy. In addition, given similar efficacy and variable use of RVG and echocardiography, opportunities to improve the efficiency of care may also exist.

Future perspective

In the near future, several strategies may be employed to improve quality-of-care for patients with nonmetastatic breast cancer who receive trastuzumab. For example, payers may send alerts to any provider who administers trastuzumab in a patient with no claim for cardiac monitoring or may require report of ejection fraction as part of preauthorization of trastuzumab. In addition, ordering cardiac monitoring may be included in the assessment of performance of providers who prescribe trastuzumab. Because it is currently unclear whether regular cardiac monitoring reduces the risk of developing heart failure and how often cardiac monitoring should be performed, studies addressing these questions should be conducted. Since trastuzumab is one of the best known examples of personalized medicine, these may help implement other personalized medicine interventions in clinical practice in the future.

Financial & competing interests disclosure

This project was supported by the National Cancer Institute through P01 CA130818 and, in part, by NIH/NCRR UCSF-CTSI Grant Number UL1 RR024131. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

Executive summary

Background

- Trastuzumab, one of the best known examples of personalized medicine, requires regular cardiac monitoring because it can cause heart failure.
- Trastuzumab product labeling and professional guidelines recommend monitoring cardiac function before trastuzumab-based therapy, and every 3–4 months during therapy to detect left ventricular dysfunction early.

Results

- Despite these recommendations, only 62% of patients had testing both at baseline and during trastuzumab therapy, and only 21% had testing before and at least once every 90 days during therapy.
- In addition, a substantial minority had no baseline testing (14%) or no testing during therapy (13%).
- Radionuclide ventriculography was used more often than echocardiography. Given the substantial cost difference (US$248.13 per radionuclide ventriculography vs US$148.40 per echocardiogram in 2012), the choice of testing modality could have significant policy implications.

Conclusion

- Our data suggest potential opportunities to improve quality and efficiency of care in women with nonmetastatic breast cancer receiving trastuzumab.
- Our findings have clinical implications for other personalized medicine interventions, such as ivacaftor and crizotinib because their successful use in clinical practice may depend on regular laboratory monitoring.

References

Papers of special note have been highlighted as:
▪▪ of considerable interest

1 Piccart-Gebhart MJ, Procter M, Leyland-Jones B *et al.* Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N. Engl. J. Med.* 353(16), 1659–1672 (2005).

2 Slamon D, Eiermann W, Robert N *et al.* Adjuvant trastuzumab in HER2-positive breast cancer. *N. Engl. J. Med.* 365(14), 1273–1283 (2011).

3 Romond EH, Perez EA, Bryant J *et al.* Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *N. Engl. J. Med*. 353(16), 1673–1684 (2005).

4 Slamon DJ, Leyland-Jones B, Shak S *et al.* Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N. Engl. J. Med.* 344(11), 783–792 (2001).

5 Tocchetti CG, Ragone G, Coppola C *et al.* Detection, monitoring, and management of trastuzumab-induced left ventricular dysfunction: an actual challenge. *Eur. J. Heart Fail.* 14(2), 130–137 (2012).

6 Ewer MS, O'Shaughnessy JA. Cardiac toxicity of trastuzumab-related regimens in HER2-overexpressing breast cancer. *Clin. Breast Cancer.* 7(8), 600–607 (2007).

7 Mackey JR, Clemons M, Cote MA *et al.* Cardiac management during adjuvant trastuzumab therapy: recommendations of the Canadian Trastuzumab Working Group. *Curr. Oncol.* 15(1), 24–35 (2008).

▪▪ **Recommendation on cardiac monitoring for patients receiving trastuzumab by the Canadian Trastuzumab Working Group.**

8 Jones AL, Barlow M, Barrett-Lee PJ *et al.* Management of cardiac health in trastuzumab-treated patients with breast cancer: updated United Kingdom National Cancer Research Institute recommendations for monitoring. *Br. J. Cancer.* 100(5), 684–692 (2009).

▪▪ **Recommendation on cardiac monitoring for patients receiving trastuzumab by the UK National Cancer Research Institute.**

9 Ganz WI, Sridhar KS, Ganz SS, Gonzalez R, Chakko S, Serafini A. Review of tests for monitoring doxorubicin-induced cardiomyopathy. *Oncology* 53(6), 461–470 (1996).

10 Walker J, Bhullar N, Fallah-Rad N *et al.* Role of three-dimensional echocardiography in breast cancer: comparison with two-dimensional echocardiography, multiple-gated acquisition scans, and cardiac magnetic resonance imaging. *J. Clin Oncol.* 28(21), 3429–3436 (2010).

11 Haas JS, Liang SY, Hassett MJ, Shiboski S, Elkin EB, Phillips KA. Gene expression profile testing for breast cancer and the use of chemotherapy, serious adverse effects, and costs of care. *Breast Cancer Res. Treat.* 130(2), 619–626 (2011).

12 Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J. Chronic Dis.* 40(5), 373–383 (1987).

13 Subar M, Lin W, Chen W, Pittman DG. Lack of uniformity in cardiac assessment during trastuzumab therapy. *Breast J.* 17(4), 383–390 (2011).

▪▪ **The first study evaluating the use of cardiac monitoring tests in patients receiving trastuzumab. The study is limited because it used only claims data.**

14 Joensuu H, Kellokumpu-Lehtinen PL, Bono P *et al.* Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer. *N. Engl. J. Med.* 354(8), 809–820 (2006).

▪▪ **Contains recommendations on cardiac monitoring in patients receiving trastuzumab.**

Websites

101 Genentech, Inc. Herceptin prescribing information, 2012. www.gene.com/gene/products/information/pdf/herceptin-prescribing.pdf (Accessed 1 March 2013)

102 Centers for Medicare & Medicaid Services. Physician Fee Schedule, 2012. www.cms.gov/apps/physician-fee-schedule (Accessed 1 March 2013)