Published in final edited form as:

Breast Cancer. 2014 November ; 21(6): 780–785. doi:10.1007/s12282-014-0543-1.

Non-initiation and early discontinuation of adjuvant trastuzumab in women with localized HER2-positive breast cancer

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Abstract

One year of trastuzumab therapy is recommended for women with HER2-positive breast cancer 1.0 cm in size to increase survival and is considered for women with tumors 0.5–0.9 cm in size. We analyzed compliance with trastuzumab among women with HER2-positive breast cancer in a prospective cohort study. Of 1145 recruited patients with breast cancer, 152 were HER2-positive (13.2 %), of whom 126 had tumors 1.0 cm; 110/126 (87.3 %) of these initiated trastuzumab. Non-receipt was associated with older age, better prognosis tumors, and with non-receipt of adjuvant chemotherapy. Of the 110 who initiated treatment, 18 (15 %) did not complete treatment, 15 (83 %) of them because of cardiotoxicity. Of 20 women with tumors 0.5–0.9 cm, 5 (25 %) initiated trastuzumab. Compliance with trastuzumab was very high among those with HER2-positive breast cancer, as was the completion of the recommended therapy.

Keywords

Trastuzumab; Breast cancer; Adjuvant therapy; Adherence; Early discontinuation; Non-initiation

Introduction

Human epidermal growth factor 2 (HER2) is involved in various cellular processes, including growth and differentiation. About 15–20 % of breast cancers overexpress HER2 [1]; those tumors are associated with worse clinical outcomes [2]. In 1996, a recombinant monoclonal antibody that specifically targets HER2, trastuzumab, was approved for advanced cancer patients whose tumors overexpress HER2. In 2005, the combined results of two adjuvant trials showed a 50 % reduction in recurrence with a year of trastuzumab in addition to chemotherapy for those with tumors 1.0 cm in size. Trastuzumab was approved for adjuvant use in 2006 [3–5]. Despite the inclusion of tumors 1 cm in the trials, the National Comprehensive Cancer Network recommends consideration of trastuzumab therapy for patients with tumors 0.5–0.9 cm in size as well.

With regard to duration, a meta-analysis reported worse survival for subjects who received <12 months of therapy. A trial comparing 6–12 months showed superiority for 12 months of therapy [6]. It remains controversial as to whether trastuzumab in conjunction with hormonal therapy alone confers a survival benefit in women with early-stage disease. Because trastuzumab can cause cardiac dysfunction, it is contraindicated in patients with impaired left ventricular function.

While adjuvant treatment for breast cancer has improved its survival [7, 8], not all patients receive appropriate treatment [9]; some do not receive recommended therapy at all [10], while others discontinue therapy early [9, 11]. These deviations can be associated with worse survival [9, 12, 13].

The breast cancer quality of care study (BQUAL) is a multi-site prospective cohort study to identify the rates and reasons for non-initiation and early discontinuation of adjuvant therapy among women with resected breast cancer [14]. In this study, we previously reported on noninitiation of adjuvant chemotherapy [15] and hormonal therapy [16]. In the current

study, we investigate the rate of non-initiation of trastuzumab among women whose tumors overexpress HER2 and, among those who initiated trastuzumab, we determined early discontinuation rates.

Patients and methods

The BQUAL study has been previously described [14]. From 2006 to 2010, we recruited women newly diagnosed with primary breast cancer, stages I–III, from New York City (Columbia University Medical Center, CUMC, and Mount Sinai School of Medicine, MSSM), Detroit (Henry Ford Health System, HFHS) and Northern California (Kaiser-Permanente of Northern California, KPNC). We excluded women with a history of cancer other than nonmelanoma skin cancer and non-English speakers. Subjects were required to have a telephone, to be able to provide informed consent and to be 20 years or older.

Trained research assistants interviewed each subject by telephone three times: within 3 months of diagnosis or prior to receipt of a third cycle of chemotherapy; 4–6 weeks later; and 12–24 weeks post-diagnosis. Each participant provided written informed consent and HIPAA authorization prior to study entry.

Overexpression of HER2, defined as immunohisto-chemistry (IHC) 3+ or positive fluorescence in situ hybridization (FISH), was determined by electronic (KPNC, HFHS) and manual abstraction (MSSM, CUMC) of pathology records. Trastuzumab use was gathered from electronic pharmacy records (KPNC, HFHS) and manual chart abstraction (MSSM, CUMC).

All study procedures were approved by the Institutional Review Board of each recruitment site, and by the U.S. Army Medical Research and Materiel Command Office of Research Protections and Human Research Protection Office.

Study variables

Demographic and tumor factors—Demographic characteristics, including age, race/ethnicity, education, annual household income, employment, marital status, and recruitment site, were collected at baseline. Tumor characteristics (AJCC stage, tumor grade and size, nodal status, ER/PR and HER2 status) and comorbidities reported from 12 months prior to 3 months after diagnosis were abstracted from the medical record or obtained from administrative databases; comorbidities were used to derive a Charlson comorbidity index score [17].

Chemotherapy-related factors—Factors related to chemotherapy included self-reported referral to a medical oncologist, whether the participant was under oncologist care, if chemotherapy was discussed, offered or recommended, and if so, by whom.

Outcome measure

The patient's initiation of trastuzumab was determined as described above, by review of pharmacy records or chart abstraction. Early discontinuation was defined as stopping

trastuzumab before 9 months of therapy was completed. For those who discontinued trastuzumab early, medical records were reviewed to determine the reason.

Data analysis

Trastuzumab initiators and non-initiators were compared using Fisher's or Chi square tests for categorical variables and Student's *t* tests for continuous variables. Cronbach's alpha was used to assess internal consistency and reliability of scale measures. The sample size was too small to undertake multivariate analysis. Similar analyses compared those who discontinued trastuzumab therapy early to those who did not. All analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC, USA).

Results

Between May 2006 and June 2010, 1479 women with newly diagnosed non-metastatic breast cancer were identified and contacted. Of these, 122 (8.2 %) refused to participate and 212 (14.3 %) were ineligible, leaving 1145 women eligible for the study. Of these, 152 were HER2-positive (13.3 %). Twenty had tumors 0.5–0.9 cm in size (13 %), while 126 had a tumor ≥ 1.0 cm (79 %); we used this group as our main analytic sample because the guidelines for trastuzumab use are definitive for this population (Fig. 1). Of this group, 110 (87.3 %) initiated trastuzumab as part of their adjuvant therapy. Of the 20 women with tumors 0.5–0.9 cm, 5 (25 %) initiated trastuzumab.

Table 1 contains selected characteristics of the 126 women with HER2-positive tumors ≥ 1 cm. Patients who did not initiate trastuzumab were older, had earlier stage tumors, better grade, and were less likely to have received adjuvant chemotherapy than those who initiated trastuzumab.

We used 9 months of therapy as a cutoff for early discontinuation of trastuzumab. We found that, of the 119 initiators, 18 (15 %) discontinued early. None of the early discontinuers recurred or died prior to the 9-month cutoff. Of these 18 early discontinuers, 15 (83 %) had an indication of cardiotoxicity in their medical record, most commonly a reduced left ventricular ejection fraction from baseline.

Table 2 compares characteristics of the 119 women with HER2-positive tumors who initiated adjuvant trastuzumab, separated into those who discontinued early versus those who completed therapy. None of the factors examined were statistically associated with early discontinuation.

Discussion

In this prospective cohort study evaluating trastuzumab use in women with non-metastatic HER2-positive breast cancer, we were reassured to find that 87 % of women for whom there was a definitive indication for trastuzumab received the drug. Furthermore, of those who began treatment with trastuzumab, 85 % completed the year of prescribed therapy. Of those who stopped early, the vast majority did so appropriately because of signs of cardiotoxicity.

There have been a few prior studies of compliance with adjuvant trastuzumab in the community. One study utilized data from the North Trent Cancer Network in the United Kingdom. The study looked at 1319 early-stage breast cancer patients and found that 185 (14 %) were HER2-positive. Of these, 56 (30 %) did not receive trastuzumab. The majority were not treated because of age >75 years, frailty, poor performance status, and/or comorbidities, while 10 (15 %) had a prior cardiac history and 13 (20 %) refused therapy [18]. Barron and colleagues [19] used data from 3 health plans in the U.S. Of 3521 women diagnosed with non-metastatic breast cancer, a subset was identified who underwent HER2 testing ($N=335$). Of these, 72 were HER2-positive (21.5 %), of whom 51 received adjuvant trastuzumab (71 %). A French study reviewed 96 patients with early-stage breast cancer who received adjuvant trastuzumab at a single hospital. Only 12 (12.5 %) discontinued the therapy prior to 52 weeks. Of these, two discontinued because of cardiotoxicity while an additional six discontinued because of other side effects [20]. A recent study using the SEER-Medicare database reported that among elderly women with breast cancer who initiated adjuvant trastuzumab that 81.7 % completed 9 months of therapy, similar to our findings; of those who discontinued early, 8.1 % were hospitalized for cardiac problems [21].

In general, it appears that compliance with adjuvant chemotherapy treatment is high when there are clearcut guidelines supported by good evidence. We previously found within the BQUAL Study that for breast cancer patients whose indications for adjuvant chemotherapy were definitive by NCCN guidelines, 90 % were compliant [15].

Older age has been a deterrent to breast cancer adjuvant therapy use. Indeed, for those >65 years, adjuvant chemotherapy use has been significantly lower in colon, rectal, and ovarian cancer as well. We found, for example, that only 22 % of patients over age 70 initiated adjuvant chemotherapy for breast cancer [15], consistent with prior studies [22–25]. Clinical trials have shown that the elderly benefit from chemotherapy, and age is not the best criterion for these decisions [26]. For adjuvant trastuzumab, in this study we found that 4/13 (31 %) women >70 did not initiate its use.

This study has several strengths and limitations. Our patient population includes women from community practices, academic medical centers, and health maintenance organizations, increasing generalizability. We also had excellent recruitment and retention. The patient population was mostly insured, so it was probably of higher socioeconomic status than the general population. We excluded subjects without a telephone and non-English speakers, decreasing generalizability.

In conclusion, we found that the majority of women with HER2-positive breast cancer initiated trastuzumab adjuvant therapy. Once initiated, the majority completed the recommended one year of treatment. Most who discontinued early did so because of the drug's known cardiotoxic effects. As in other settings, adjuvant chemotherapy utilization is high among those for whom it is most likely to be beneficial, and oncologists appear to adhere to the guidelines best under those circumstances.

Acknowledgments

Supported by a Department of Defense Breast Cancer Center of Excellence Award (BC043120) to Dr. Neugut, NCI R01 (CA105274), NCI R25 fellowship (CA094601) to N. Leoce, Department of Defense (DAMD-17-01-1-0334) to Dr. Bovbjerg, NCI R01 (CA100598) to Dr. Ambrosone, and NCI R01 (CA124924 and 127617), and K05 (CA96940) to Dr. Mandelblatt. Drs. Hershman and Ambrosone are recipients of funding from the Breast Cancer Research Foundation.

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Fig. 1. Initiation of adjuvant trastuzumab therapy among breast cancer patients interviewed within the BQUAL study, 2006–2010, whose tumors were ≥ 0.5 cm and overexpressed HER2

Patient and tumor characteristics (univariate) of breast cancer patients interviewed within the BQUAL study, 2006–2010, whose tumors were 1.0 cm and overexpressed HER2 divided by adjuvant trastuzumab initiation

Table 1

Patient characteristics	Initiated (N = 110)		Did not initiate (N = 16)		P value
	N	%	N	%	
Age					
<40–49	37	34	3	19	0.03
50–59	38	35	2	13	
60–69	26	24	7	44	
70–79	9	8	4	25	
Race					
Asian	15	14	1	6	0.79
African American	22	20	3	19	
Hispanic	4	4	0	0	
White	68	62	12	75	
Other	1	1	0	0	
Tumor characteristics					
AJCC Stage					
I	23	21	9	56	0.01
II	62	56	7	44	
III	22	20	0	0	
Unknown	3	3	0	0	
Grade					
Well differentiated	1	1	2	13	0.03
Moderately differentiated	40	36	7	44	
Poorly differentiated	40	36	4	25	
Unknown	29	26	3	19	
Node status					
Positive	55	50	12	75	0.11
Negative	55	50	4	25	
ER/PR status					

Patient characteristics	Initiated (N = 110)		Did not initiate (N = 16)		P value
	N	%	N	%	
Positive	75	68	13	81	0.55
Negative	34	31	3	19	
Unknown	1	1	0	0	
Charlson comorbidity score					
0	94	85	11	69	0.14
1	14	13	5	31	
Unknown	2	2	0	0	
Congestive heart failure					
Present	2	2	0	0	0.41
Absent	77	70	9	56	
Unknown	31	28	7	44	
Chemotherapy recommendation (as per NCCN guidelines)					
Recommended	68	62	4	25	0.007
Discretionary	42	38	12	75	
Use of adjuvant chemotherapy	110	100	4	25	<0.0001

Patient and tumor characteristics (univariate) of breast cancer patients interviewed within the BQUAL study, 2006–2010, whose tumors were 0.5 cm and initiated adjuvant trastuzumab therapy, divided by early discontinuation

Table 2

Patient characteristics	Discontinued early (N = 18)		Received full course (N = 101)		P value
	N	%	N	%	
Age					
<40–49	4	22	36	36	0.72
50–59	7	39	35	35	
60–69	5	28	22	22	
70–79	2	11	8	8	
Race					
Asian	3	17	12	12	0.54
African American	3	17	19	19	
Hispanic	2	11	3	3	
White	10	56	66	66	
Other	0	0	1	1	
Tumor characteristics					
AJCC Stage					
I	5	28	22	22	0.83
II	10	56	53	53	
III	2	11	20	20	
Unknown	1	6	6	6	
Grade					
Well differentiated	0	0	2	2	0.91
Moderately differentiated	7	39	36	36	
Poorly differentiated	6	33	38	38	
Unknown	5	28	25	35	
Nodal status					
Positive	6	33	51	51	0.21
Negative	12	67	50	50	
Tumor size					

Patient characteristics	Discontinued early (N = 18)		Received full course (N = 101)		P value
	N	%	N	%	
1.0 cm	0	0	8	8	0.30
>1.0 cm	18	100	89	89	
Unknown	0	0	4	4	
ER/PR status					
Positive	11	61	71	71	0.64
Negative	7	39	29	29	
Unknown	0	0	1	1	
Charlson comorbidity score					
0	16	89	85	85	0.79
1	2	11	14	14	
Unknown	0	0	2	2	
Congestive heart failure					
Present	1	6	1	1	0.38
Absent	12	67	71	71	
Unknown	5	28	29	29	
Chemotherapy recommendation (as per NCCN guidelines)					
Recommended	11	61	59	58	0.76
Discretionary	7	39	39	39	
Could not be determined (missing data)	0	0	3	3	
Use of adjuvant chemotherapy	18	100	100	99	1.0