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Breast Cancer

Effectiveness of Trastuzumab in First-Line HER2+ Metastatic Breast Cancer After Failure in Adjuvant Setting: A Controlled Cohort Study

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Metastatic breast cancer • Overall survival • Record linkage • Trastuzumab

Abstract

Background. The evidence supporting the use of trastuzumab (T) in a metastatic setting comes from studies that included (almost) only patients who never received prior T. We investigated the effectiveness of T as first-line therapy for metastatic breast cancer (mBC) in women previously treated with T in the adjuvant setting.

Materials and Methods. By using record linkage of five administrative health care databases of Lombardy, Italy, we identified 2,046 women treated with T for early breast cancer (eBC) in 2006–2009, 96 of whom developed a metastasis and were retreated with T in first-line treatment for mBC (treatment group). We compared the overall survival (OS) of these women with that of 197 women treated with T in first-line treatment for mBC, who were treated with therapies other than T for early disease (control group). We computed Kaplan-Meier 2-year OS and used a proportional hazard model to estimate the multivariate hazard ratio (HR) of death in the intervention group compared with the control group, adjusted by age, use of endocrine therapy, and site of metastasis.

Results. Two-year OS was 60.0% in the treatment group and 59.5% in the control group. The adjusted HR of death in the treatment group compared with the control group was 0.79 (95% confidence interval, 0.50–1.26).

Conclusion. Our data provide convincing evidence that the outcome of women receiving first-line T treatment for mBC after T failure in the adjuvant setting is comparable to that of women not receiving T for eBC. These data are of specific interest, given the unavailability of data from randomized clinical trials. ***The Oncologist*** 2014;19:1209–1215

Implications for Practice: Trastuzumab (T) is the standard of care for HER2+ breast cancer in metastatic and early stages, but scant evidence is available on its effectiveness as first-line metastatic treatment in women who failed adjuvant T. Our findings that 2-year overall survival of women treated with T for early breast cancer and subsequently for metastatic disease is comparable to that of women treated with T only for metastatic disease suggest that T remains effective even after failure in early disease.

Introduction

HER2 overexpression occurs in 15%–20% of patients with breast cancer and is associated with aggressive disease and decreased survival [1]. A number of therapeutic approaches have been developed against HER2, including monoclonal antibodies and small molecule tyrosine kinase inhibitors. Trastuzumab (T), the first anti-HER2 agent, is a humanized monoclonal antibody that binds to the extracellular, juxtamembrane portion of the HER2 receptor and suppresses HER2 signaling activity, resulting in inhibition of downstream signaling pathways, cell cycle arrest, and a reduction in angiogenesis [2]. In patients with HER2-amplified metastatic breast cancer (mBC), T has antitumor activity [3, 4], improving survival in the first-line setting when combined with chemotherapy [5, 6]. The administration of T in the initial postoperative (adjuvant) setting, in combination and/or sequentially after chemotherapy, results in an improvement in disease-free survival, with a 50% reduction in the risk of relapse, and in overall survival (OS) of patients with HER2-positive early breast cancer (eBC) [7, 8].

Despite the advances that have been brought by T, a not negligible group of patients with HER2-positive eBC who received adjuvant T therapy will eventually experience disease

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recurrence and will be proposed for treatment in the metastatic setting. The robust evidence supporting the use of T in adjuvant and metastatic settings comes from studies that primarily included only patients who never received prior T. Limited evidence supports the use of T beyond progression in metastatic disease [9–11], and no evidence supports its use in patients with a first relapse who failed adjuvant T. Although it is now possible to consider different options (lapatinib, pertuzumab, trastuzumab emtansine) in patients with mBC experiencing progression of disease while taking T, limited approaches have been tested for patients who relapse after adjuvant T [12], and the optimal strategy of therapy for this growing group of patients remains elusive. However, because T also has been licensed for eBC, even in the absence of definite evidence, the daily clinical practice has addressed the problem, and in many cases patients relapsing after adjuvant T obtained retreatment, mostly in combination with chemotherapy and endocrine therapy, with variable and unpredictable outcomes.

Therefore, it is important to ascertain the role of T after failure in an adjuvant setting. In a large cohort of patients who received T for first-line treatment of metastatic disease, we compare the OS of women who received or did not receive T in an adjuvant setting.

Materials and Methods

The Italian National Health Service (NHS) provides universal coverage with standard care to all Italian citizens. Reimbursement to hospitals and other health care providers is performed through administrative health care databases at the regional level. T was first approved in Italy for HER2+ mBC and in July 2006 for eBC [13]. T is dispensed by hospital pharmacies only, and since January 2006 in Lombardy, it is mandatory to register each dispensation in a special file (File F). In previous work, we built a cohort of more than 2,000 women who had used T for eBC by record linkage of several regional administrative health care databases, and we analyzed cardiotoxicity [14] and estimated OS and progression-free survival [15, 16] in clinical practice.

Data Sources

Five regional health administrative databases were used: (a) the File F registry 2006–2009, in which any administration of T reimbursed by the NHS has been mandatorily recorded since 2006; (b) the regional hospital discharge forms (Scheda di Dimissione Ospedaliera [SDO]) database (1997–2010); (c) the Outpatients' Services database (2002–2010); (d) the Registry Office database of Lombardy, updated to April 2011; and (e) the drug prescription database.

Patient Identification by the Same Unique Anonymous Code in All Databases

A more detailed description of the databases used for the record linkage and of the operative procedures used to identify the various groups of women are given in supplemental Appendix 1 and previous publications [14, 16].

Selection of Intervention and Control Groups

We carried out a computerized record linkage through the unique anonymous patient identification code. We selected all women who resided in Lombardy, who were first treated with T between August 2006 and December 2009, and who had a SDO reporting a breast cancer diagnosis before the first T administration. By comparing the dates of the first SDO reporting a breast cancer diagnosis, the first SDO reporting a metastasis, and the first T administration, we divided them into (a) women first treated with T for eBC and (b) women treated with T for mBC only. We excluded women for whom we could not determine whether the first T treatment was for eBC or mBC (supplemental Appendix 1 shows the operative definitions).

Among women treated with T for eBC, we identified those who developed a metastasis and restarted or continued T treatment after the metastasis. We further excluded women who did not receive T for mBC as first-line treatment. Therefore, the "treatment group" consisted of women who were treated with T for eBC and were treated again with T as first-line therapy (supplemental Appendix 1 shows the operative definitions) for mBC (mBC/adjT+).

For the control group, we selected patients treated with T for mBC only. We excluded patients with "up-front metastatic disease" from the control group, that is, women who were not previously treated for eBC with a therapy other than T. We also excluded women treated with T for mBC, but not as first-line therapy. Therefore, the "control group" consisted of women who were treated for eBC, but not with T, and were treated with T as first-line therapy for mBC (mBC/adjT−).

Statistical Analysis

The OS was estimated using the Kaplan-Meier method [17] and was defined as the time from the first trastuzumab prescription for mBC to death from any cause (from the SDO database and/or the Registry Office database). Patients were followed up until death or April 30, 2011, whichever came first. Differences in OS curves were tested by the log-rank test [17].

We also estimated the hazard ratio (HR) of death of women previously treated with T for eBC (mBC/adjT+) compared with women treated with T for mBC only (mBC/adjT−), adjusted by age (<50, 50–59, 60–69, 70+ years), use of endocrine therapy, and site of metastasis (brain, liver/lung, other), using Cox proportional hazards models [17]. The proportional hazard assumption was assessed by both plotting minus log(log (survival function)) versus log(time) and using the analytic method based on comparison between observed residuals and a randomly generated sample process (Kolmogorov-type supremum test) [17].

We also compared the survival of women treated with T for eBC who did and did not restart or continue the treatment for the metastatic disease. In this case, OS was defined as the time from the diagnosis of metastasis to death from any cause or end of follow-up.

Results

Figure 1 presents a flowchart of the selection of the treatment and control groups. Overall, 2,879 patients received the first T prescription between August 2006 and December 2009. We excluded 9 men and 143 women with inconsistent data, or for whom we could not define whether T was first used for eBC or mBC. Of the 2,046 women first treated with T for eBC, 240 developed distant recurrence after the beginning of treatment; 113 did not use T after the diagnosis of metastasis, whereas 127 continued or restarted the therapy, 96 of whom received T as first-line treatment for mBC ("treatment group,"

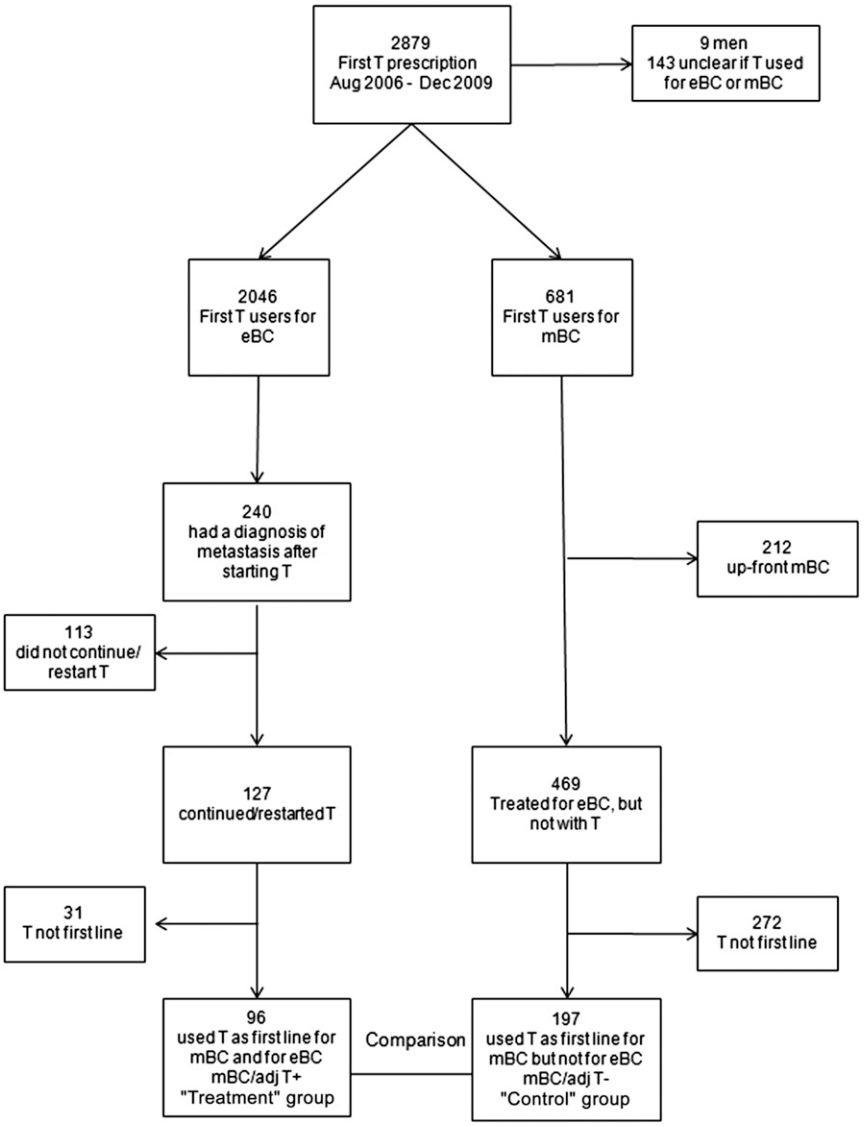


Figure 1. Flowchart describing the selection of the treatment and control groups from the cohort of women treated with T for breast cancer.

Abbreviations: AdjT, adjuvant trastuzumab; eBC, early breast cancer; mBC, metastatic breast cancer; T, trastuzumab.

mBC/adjT+). Compared with women who continued or restarted T ($n = 127$), those who did not receive T after the diagnosis of the metastasis ($n = 113$) were older (26.6% vs. 10.2% aged ≥70 years) and more frequently had brain metastases (34.5% vs. 9.5%) (supplemental online Table 1). One year after metastasis, OS was 39.8% in women who did not restart T and 88.0% in women who did. In the 96 women included in the treatment group, 64 (67%) of the metastases occurred during or within 6 months since stopping T treatment.

A total of 681 women first received T for mBC only. After exclusion of 212 women who had "up-front metastatic disease" and a further 272 women who received T for mBC not as first-line therapy, the control group included 197 women who received T as first-line treatment for mBC and were treated with therapies other than T for eBC (mBC/adjT−).

Table 1 shows the age and the site of metastasis of 96 T users for eBC and subsequent first-line treatment for mBC (mBC/adjT+, treatment group) and of 197 T users for first-line treatment for mBC only (mBC/adjT−, control group), excluding women with "up-front metastatic disease." Women in the treatment group were younger (41.7% vs. 23.8% aged <50 years) and more frequently had brain metastases (9.4% vs. 4.1%) than women in the control group. The median follow-up was 2.5 years. Survival estimates for the treatment group were 87.5% after 1 year of follow-up and 60.0% after 2 years of follow-up; corresponding figures for the control group were 80.6% and 59.5%, respectively (Fig. 2).

Table 2 presents the results of the proportional hazard model, including terms for age, use of endocrine therapy, metastatic site, and treatment/control group. No significant difference emerged with age. Compared with women with brain metastases, those with liver and lung metastases had a lower hazard of dying (HR, 0.28; 95% confidence interval [CI], 0.14–0.54), and those with only metastases at sites other than the brain, liver, or lung had an even lower risk (HR, 0.13; 95% CI, 0.07–0.27). The HR of death in the treatment group (mBC/adjT+) compared with the control group (mBC/adjT−),

Table 1. Age, use of endocrine therapy, and site of metastasis among 96 women treated with T for both early breast cancer (eBC) and mBC as first line of therapy (mBC/adjT+), and 197 women treated with other therapies for eBC and first-line T therapy for mBC (mBC/adjT−)

	mBC/adjT+ 96		mBC/adjT− 197	
	n	%	*n*	%
Age[a] (yrs)				
<40	11	11.5	16	8.1
40–49	29	30.2	31	15.7
50–59	25	26.0	48	24.4
60–69	20	20.8	57	28.9
≥70	11	11.5	45	22.8
p for heterogeneity	.009			
Use of endocrine therapy				
No	54	56.3	88	44.7
Yes	42	43.7	109	55.3
p for heterogeneity	.063			
Metastatic site				
Brain	9	9.4	8	4.1
Liver/lung	42	43.7	107	54.3
Other	45	46.9	82	41.6
p for heterogeneity	.083			

[a]Age at first trastuzumab prescription for metastatic breast cancer.
Abbreviations: AdjT, adjuvant trastuzumab; mBC, metastatic breast cancer.

adjusted by age, history of endocrine therapy, and metastatic site, was 0.79 (95% CI, 0.50–1.26), similar to the unadjusted HR (0.86; 95% CI, 0.55–1.34).

Discussion

Our study reports the OS of a cohort of patients with mBC, treated with first-line T-based combination therapy, who received or did not receive T in an adjuvant setting. Of 293 patients with mBC who received T as first-line treatment, the 96 women treated with T for eBC and retreated for metastatic disease showed an OS that was similar to the 197 women who received T for mBC only, that is, not treated with T before the diagnosis of metastasis (60% in both groups after 2 years; HR of death, 0.79; 95% CI, 0.50–1.26).

T is the well-established mainstay treatment of women affected by HER2+ breast cancer. The effectiveness of T has been widely demonstrated in both adjuvant and metastatic HER2+ breast cancer, and some observations suggested a potential role of T beyond disease progression [9–11, 18]. According to this evidence, T has been predicted to be effective in the first-line setting of mBC after T adjuvant failure. Although novel potential anti-HER2 options have been developed, at the present time, the retreatment of patients with metastatic cancer with T still represents a widely used option, notwithstanding that the clinical impact of such a strategy has never been formally ascertained in controlled randomized clinical trials (RCTs).

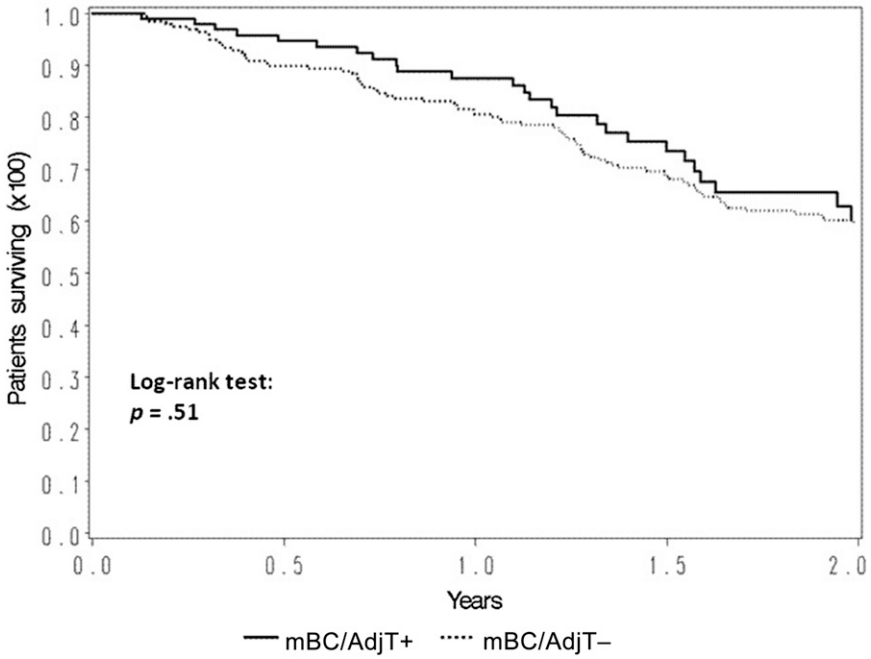
The Italian guidelines for breast cancer treatment (Associazione Italiana di Oncologia Medica [AIOM] 2012) [19] advise to restart T in association with chemotherapy (taxanes, vinorelbine, capecitabine) as first-line treatment of mBC in women treated with T in the adjuvant setting. The level of evidence of this recommendation is rated on the basis of expert opinion alone, that is, without any support from analytic studies, and the strength of this recommendation is rated as weak positive, adapted from the GRADE method [20]. The U.S. National Comprehensive Cancer Network (NCCN) guidelines accept taxotere, trastuzumab, and pertuzumab as the preferred first-line therapy for patients with metastatic HER2+, including patients who received prior trastuzumab in the adjuvant setting (NCCN 2014) [21]. The National Institute for Health and Clinical Excellence 2009 guidelines [22] do not specifically address the problem, but suggest discontinuation of T for mBC in case of disease progression outside the central nervous system. Thus, there are different attitudes, reflecting the lack of solid data on the matter, in the absence of information generated from dedicated clinical trials. At the same time, it is unlikely that such trials will be launched in the near future because of the evident ethical and clinical concerns these investigations would implicate. Consequently, information in this field is mostly confined to retrospective studies and post hoc subgroup analyses of existing datasets.

This uncertainty also is reflected by the fact that of the 240 women who developed a metastasis while treated with T for eBC, 127 (53%) were retreated with T and 113 (47%) were not. This is not surprising given the lack of solid evidence about T use in this context, particularly at the time of the study. Older age, comorbidities, and the presence of a brain metastasis were strong predictors for not receiving T for mBC after failure in the adjuvant setting in our data. There is strong evidence that older patients are undertreated [23]. Moreover, the cardiotoxicity of T [14] has likely discouraged its use in women at high risk of cardiac disease, as did the presence of a brain metastasis, for which the use of T has been debated [24, 25].

An issue to bear in mind is that because of the short timeframe of this study and the introduction of adjuvant T only in mid-2006 in Italy, two thirds of the women who received T for both eBC and mBC were refractory to T, that is, developed a metastasis during T treatment or within 6 months from stopping T treatment. Thus, our cohort is mostly composed of women for whom the response to T in the adjuvant setting has been worse, at least in terms of efficacy. Thus, strictly speaking, our results do not apply to women who develop a metastasis long after stopping T for eBC, although these women should, if anything, have a better prognosis than the women in our treatment group.

The control group was not treated with the most effective therapy in the beginning. However, the use of T in the adjuvant setting was authorized in Italy in mid-2006; thus, women with a HER2+ early breast cancer in the few years before that date were not treated with T. Moreover, T-naïve women are exactly those for whom the efficacy of T for mBC has been demonstrated.

Our data are consistent with those recently reported in two RCTs, partially focusing on the same theme as our study. First, the CLEOPATRA RCT, while comparing first-line pertuzumab, trastuzumab, and docetaxel with placebo, trastuzumab, and docetaxel for HER2+ mBC, included 80 patients with mBC (10% of the entire study population) in the analysis who were treated with T in the neoadjuvant/adjuvant setting [26]. In



mBC/Adj T+		
No. at risk	68	21
Survival (%)	87.5	60.0
mBC/Adj T-		
No. at risk	156	95
Survival (%)	80.6	59.5

Figure 2. Kaplan-Meier estimates of overall survival among 96 women treated with T for both eBC and mBC as first line of therapy (mBC/adjT+) and 197 women treated with other therapies for eBC and first-line T therapy for mBC (mBC/adjT−).
Abbreviations: AdjT, adjuvant trastuzumab; eBC, early breast cancer; mBc, metastatic breast cancer.

Table 2. Estimated HR and corresponding 95% CIs from multivariate Cox model among 197 women treated with other therapies for early breast cancer (eBC) and first-line T therapy for mBC (mBC/adjT−), and 96 women treated with T for both eBC and mBC as first line of therapy (mBC/adjT+)

	No.	No. (%) of events	HR[a] (95% CI)
Group			
mBC/adjT−	197	77 (39.1)	1[b]
mBC/adjT+	96	26 (27.1)	0.79 (0.50–1.26)
Age, yrs			
<70	237	82 (34.6)	1[b]
≥70	56	21 (37.5)	1.16 (0.98–1.37)
Use of endocrine therapy			
No	142	63 (44.4)	1[b]
Yes	151	70 (46.4)	0.87 (0.59–1.29)
Metastatic site			
Brain	17	12 (70.6)	1[b]
Liver/lung	149	63 (42.3)	0.28 (0.14–0.54)
Other	127	28 (22.1)	0.13 (0.07–0.27)

[a]Estimated by multivariate Cox model adjusted by intervention group, age, use of endocrine therapy, and metastatic site.
[b]Reference category.
Abbreviations: AdjT, adjuvant trastuzumab; CI, confidence interval; HR, hazard ratio; mBC, metastatic breast cancer.

a post hoc subgroup analysis, the favorable effect on OS of adding pertuzumab to T and docetaxel in women previously treated with T (HR, 0.68; 95% CI, 0.30–1.55) was similar to that for the whole intention-to-treat population (HR, 0.69; 95% CI, 0.58–0.81). However, the authors did not compare the OS of women previously treated with T with those who were not.

Second, a nonrandomized, multicenter, open-label phase II study in mBC (Retreatment after HErceptin Adjuvant [RHEA] trial) reported an encouraging activity of T in previously treated eBC [27]. Indeed, the RHEA study investigated the efficacy and safety of T plus a taxane in patients who experienced a relapse after adjuvant T. For the 41 included patients, partial response was observed in 25 (61%), and median progression-free survival was 8.0 months [27]. To the best of our knowledge, this retrospective analysis represents the most extensive study exploring the effectiveness of T after adjuvant failure.

Given the lack of data from RCTs on this issue, our study offers a valuable contribution, despite its limitations. Our study is based on record linkage of administrative databases, and therefore it is conceivable that some misclassification in defining the various groups has occurred. The fact that our cohort of women treated with T for eBC had an OS comparable to that of the HERceptin Adjuvant trial [16, 28] is reassuring against substantial misclassification of T treatment for mBC as eBC. Another limitation is the lack of detailed clinical information, which also prevented the evaluation of progression-free survival in our cohort of patients.

Moreover, given the "real-world" nature of our data [15, 29], the modes of patients' metastatic workup at diagnosis and follow-up were heterogeneous. The Italian guidelines, from the National Society of Medical Oncology (AIOM), provide regular recommendations for tumor assessment at the time of the first breast cancer diagnosis. Because the population is derived exclusively from the Lombardy region, we do have reasons to expect a consistent approach in this population regarding the diagnostic metastatic workup. The retrospective nature of this observation and the sources of our database prevented us from obtaining a centralized assessment of HER2 status. However, our analysis moved from drug (T) rather than cancer subtype (HER2), and the criteria for patients' enrollment were based on T administration. We have discussed the problem of the quality of HER2 status ascertainment in a previous article [14]. However, there is no reason why the quality of ascertainment of HER2 status should differ between our two groups. Thus, these potential limitations do not attenuate the message of T effectiveness emerging from the OS analysis. If, as the evidence from RCTs shows, T is effective in T-naïve women treated for mBC, then our results indicate that it is also effective after T failure in the adjuvant setting, and to approximately the same extent.

Conclusion

Given the lack of data from RCTs, our study provides the strongest evidence that the outcome of women receiving first-line T treatment for mBC after T failure in an adjuvant setting is comparable to that of women not exposed to T during eBC therapy.

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Disclosures

The authors indicated no financial relationships.

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See http://www.TheOncologist.com for supplemental material available online.

For Further Reading:

Francisco J. Esteva, Sandra X. Franco, Maura K. Hagan et al. An Open-Label Safety Study of Lapatinib Plus Trastuzumab Plus Paclitaxel in First-Line HER2-Positive Metastatic Breast Cancer. ***The Oncologist*** 2013;18:661–666.

Implications for Practice:

Dual targeting of the HER2 receptor using trastuzumab and lapatinib has been shown to be effective in HER2-positive metastatic breast cancer. In this study, we evaluated the safety of paclitaxel in combination with trastuzumab and lapatinib. The main side effect was diarrhea, which occurred in the majority of patients at the standard dosing of all three drugs. A pharmacokinetic interaction was found between paclitaxel and lapatinib, resulting in increased exposure of both drugs. We evaluated three dose levels of lapatinib and paclitaxel (all patients received standard trastuzumab dosing). A dose of lapatinib 750 mg/day had the lowest incidence of diarrhea in combination with paclitaxel 80 mg/m^2 per week and trastuzumab 2 mg/kg per week. These doses should be used if the triplet is considered for further development in patients with HER2-positive metastatic breast cancer.