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Breast Cancer

Long-Term Survival of De Novo Stage IV Human Epidermal Growth Receptor 2 (HER2) Positive Breast Cancers Treated with HER2-Targeted Therapy

Yao Wong,[a] Akshara Singareeka Raghavendra,[b] Christos Hatzis,[a] Javier Perez Irizarry,[a] Teresita Vega,[a] Nina Horowitz,[a] Carlos H. Barcenas,[b] Mariana Chavez-MacGregor,[b] Vicente Valero,[b] Debu Tripathy,[b] Lajos Pusztai,[a] Rashmi K. Murthy[b]

[a]Yale University School of Medicine, New Haven, Connecticut, USA; [b]The University of Texas MD Anderson Cancer Center, Houston, Texas, USA

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

Key Words. Human epidermal growth receptor 2 • Breast cancer • De novo • No evidence of disease • Stage IV

Abstract

Background. An increasing proportion of human epidermal growth receptor 2 (HER2) positive (HER2+) metastatic breast cancer (MBC) is diagnosed as de novo stage IV disease. We hypothesize that a subset of these patients who achieve no evidence of disease (NED) status after multimodality HER2-targeted treatments may have prolonged progression-free survival (PFS) and overall survival (OS).

Materials and Methods. Patients with de novo stage IV, HER2+ MBC (n = 483) diagnosed between 1998 and 2015 were identified at two institutions (Yale and MD Anderson Cancer Centers). Clinical variables, treatment details, and survival outcomes were compared between those who achieved NED and those who did not.

Results. All patients received trastuzumab, and 20% also received pertuzumab as first-line therapy. The median OS was 5.5 years (95% confidence interval [CI]: 4.8–6.2). Sixty-three patients (13.0%) achieved NED; their PFS and OS rates were 100% and 98% (95% CI: 94.6%–100%), respectively, at 5 years and remained the same at 10 years. For patients with no NED (n = 420), the PFS and OS rates were 12% (95% CI: 4.5%–30.4%) and 45% (95% CI: 38.4%–52.0%) at 5 years and 0% and 4% (95% CI, 1.3%–13.2%) at 10 years, respectively. NED patients more frequently had solitary metastasis (79% vs. 51%, p = .005) and surgery to resect cancer (59% vs. 22%, $p \leq .001$). In multivariate analysis, NED status (hazard ratio [HR]: 0.014, p = .0002) and estrogen receptor positive status (HR: 0.72; p = .04) were associated with prolonged OS.

Conclusion. Among patients with de novo stage IV, HER2+ MBC, those who achieve NED status have a very high PFS and OS. Further randomized studies are required to fully understand the impact of systemic or locoregional therapy on achieving these excellent long-term outcomes. ***The Oncologist*** 2019;24:313–318

Implications for Practice: In this retrospective review at two institutions, it was demonstrated that 13% of patients with de novo stage IV, human epidermal growth receptor 2 positive metastatic breast cancer achieved no evidence of disease (NED) status with trastuzumab-based therapy plus/minus local therapies, and these patients had a very high progression-free survival (100%) and overall survival (98%) at both the 5- and 10-year time points. Achieving NED status may be an important therapeutic goal. However, further randomized studies are required to fully understand the impact of systemic or locoregional therapy on achieving these excellent long-term outcomes.

Introduction

Metastatic breast cancers (MBC) can present as either de novo stage IV disease or asynchronous metastatic recurrence of prior stage I–III cancers. An important difference between these two presentations is exposure to prior therapies. De novo stage IV disease implies the presence of distant metastasis at or near the time of initial diagnosis and no prior therapy for the cancer. Metastatic recurrence of stage I–III breast cancer typically implies recurrence despite systemic adjuvant therapy. Both classes are considered incurable and are treated with palliative intent, usually with sequential single-agent or doublet therapies [1].

Correspondence: Rashmi K. Murthy, M.D., The University of Texas MD Anderson Cancer Center, 1155 Pressler St., CPB5 3450, Unit 1354, Houston, Texas 77030, USA. Telephone: 713-792-2817; e-mail: rmurthy1@mdanderson.org Received April 9, 2018; accepted for publication July 16, 2018; published Online First on August 23, 2018. http://dx.doi.org/10.1634/theoncologist.2018-0213

In the past 10 years, the inclusion of human epidermal growth receptor 2 (HER2)-targeted agents into the adjuvant therapy of stage I–III HER2 positive breast cancers has significantly reduced distant metastatic recurrences and improved survival [2–4]. This has resulted in overall fewer HER2 positive MBC and in a relative increase in the proportion of de novo stage IV disease among patients with HER2 positive metastatic disease. Historically, de novo stage IV breast cancer accounted for 6%–20% of metastatic breast cancers across subtypes, but recent studies reported that over 50% of metastatic HER2 breast cancers today represent de novo stage IV disease [5–9].

Several studies examined whether clinical outcomes differ between de novo and recurrent MBC. A study that examined the prognostic impact of metastasis-free interval (i.e., the time between initial diagnosis and distant recurrence) on survival included 154 patients with de novo MBC and showed that these patients had a prolonged survival compared with patients who had a recurrence within 24 months. However, there was no difference in survival compared with patients who recurred >24 months after diagnosis [10]. Results were not presented separately for HER2 positive patients. Another study focused on the outcome of HER2 positive MBC and showed that patients with de novo disease (n = 113) receive more aggressive first-line treatments and experienced better survival compared with those with recurrent disease (n = 303). In the de novo cohort, 54 patients who underwent primary cancer surgery had significantly better progression-free survival (PFS) and overall survival (OS; hazard ratio [HR] = 0.44; 95% confidence interval [CI]: 0.26–0.72 and HR = 0.49; 95% CI: 0.26–0.93, respectively) than those who did not have surgery [11]. Several other studies that examined clinical features that are associated with long-term survival of HER2 positive MBC treated with HER2-targeted therapies identified hormone receptor positivity, oligometastatic disease, surgical resection of metastases and/or primary tumor, and no prior exposure to HER2-targeted therapies (in the adjuvant setting) as predictors of long-term survival [7–9, 12–15].

The treatment of metastatic HER2 positive breast cancer has improved substantially over the past 20 years due to the introduction of five distinct HER2-targeted drugs (trastuzumab, lapatinib, pertuzumab, ado-trastuzumab emtansine, and, more recently, neratinib) [16–19]. Both randomized clinical trials and population-based registries demonstrated substantial improvement in median survival of HER2 positive MBC [8, 9, 12–14]. Infrequently, patients achieving complete clinical response remain with no evidence of disease (NED) for prolonged periods. These results raise an important clinical question: Should de novo stage IV, HER2 positive MBC be treated differently from recurrent HER2 positive MBC?

We hypothesize that some patients with newly diagnosed, oligo-metastatic, stage IV, HER2 positive cancer with no prior HER2-targeted therapy who receive combined modality HER2-targeted therapies and achieve NED status may experience long-term remission and perhaps even cure. The primary objective of this study was to assess how often patients with de novo stage IV, HER2 positive MBC achieve NED with modern anti-HER2-targeted therapy and to determine PFS and OS.

Materials and Methods

Patient Population

The medical records of all metastatic HER2 positive breast cancers diagnosed between September 30, 1998, and December 31, 2015, were reviewed at Yale Cancer Center to identify patients who presented with de novo stage IV metastatic disease and received trastuzumab-containing therapy. A prospectively maintained electronic database that captures all patients seen at the Breast Medical Oncology Department of The University of Texas MD Anderson Cancer Center was also searched to find patients with de novo stage IV, HER2 positive MBC diagnosed during the same period and treated with trastuzumab-containing therapy. The electronic and paper record of each patient was manually reviewed by local study investigators, and each site completed an identical data acquisition form including demographics (birth, ethnicity/race), date of diagnosis, tumor grade, estrogen receptor (ER) and progesterone receptor status, the number and type of metastatic sites, and each sequential line of therapy including cancer surgery and radiation therapy until death or last follow-up. We also extracted from the charts best response to therapy that was classified as either NED—if all imaging, laboratory, and clinical evidence of active cancer was resolved at any time point during the course of the disease—or no-NED. Residual sclerotic bone lesions on a computed tomography (CT) image that has turned metabolically inactive on a positron emission tomography-CT or resolved on bone scan were included in the NED category. Survival status was categorized as alive with disease, alive without evidence of disease (i.e., NED), or deceased. This study was approved by the institutional review boards of each participating institution, and waivers of obtaining informed consent were granted.

Statistical Analysis

OS was measured from the date of diagnosis of stage IV de novo MBC until the date of death or last follow-up. The PFS was calculated from the start of first-line therapy to the discontinuation of such therapy. Survival curves were plotted using the Kaplan-Meier method, and factors associated with overall survival and NED status were assessed using multivariate Cox and logistic regression analyses. Results are expressed in hazard ratios and 95% confidence intervals. All p values of <.05 were considered statistically significant, and all tests were two-sided.

Results

We identified 483 de novo stage IV, HER2 positive MBC patients who received first-line treatment with trastuzumab-based therapy. All patients received trastuzumab, and 94 patients (20%) also received pertuzumab as first-line therapy. The median follow-up for the entire

Table 1. Patient characteristics in the two response categories

Characteristics	NED (*n* = 63), %	No NED (*n* = 420), %
Median follow-up, years (range)	5.5 (1.5–11.3)	2.5 (0.1–10.6)
Median age, years (range)	49 (29–70)	50 (25–88)
Race		
White	73	71
Black	7	13
Hispanic	14	10
Other	6	6
Tumor grade		
Grade 1	1	0
Grade 2	26	25
Grade 3	73	75
Estrogen receptor status		
ER+	70	68
ER−	30	32
Metastatic site		
Visceral	46	59
Bone	48	53
Soft tissue or nodes	32	32
CNS	0	7
Number of metastatic sites		
1	79	51
2	21	37
≥3	0	12
First-line therapy		
T	73	82
T + P	27	18
Surgery	59	22
Palliative radiation	57	61

Abbreviations: CNS, central nervous system; ER, estrogen receptor; NED, no evidence of disease after therapy; P, pertuzumab; T, trastuzumab.

cohort was 2.8 years, and OS rates were 54% (*n* = 483; 95% CI: 48%–60.4%) and 18% (95% CI: 11.4%–28.3%) at 5 and 10 years, respectively. Sixty-three patients (13%) achieved NED status.

Those who achieved NED had a median age of 49 years, the majority were white (73%), with grade 3 (73%), ER positive (70%) cancers, and 79% had single-site metastasis. Of note, there was a higher proportion of black patients in the no-NED group (13%) compared with the NED group (7%). Fifty-nine percent of patients with NED underwent surgery of the primary lesion, 57% had radiation therapy, and 27% received pertuzumab. There were no significant differences in age, grade, race, ER status, or radiation treatment use between the NED and no-NED cohorts. However, patients in the NED cohort more frequently had single-organ-site metastasis (79% vs. 51%, $p = .005$) and more often had surgery for the primary tumor or a metastatic lesion (59% vs. 22%, $p < .001$). Patient characteristics of the two cohorts are shown in Table 1. Supplemental online Table 1 includes tumor characteristics and systemic treatment for each of the patients who achieved NED. In multivariate analysis, having a single metastatic site, having surgery (for the primary tumor or to metastatic site), and oligometastatic bone and central nervous system (CNS) involvement were associated with NED status (Table 2).

Table 2. Factors associated with achieving NED status in logistic regression analysis

NED status	OR	95% CI	*p* value
Age, years (>50 vs. ≤50)	0.953	0.529–1.711	.871
Grade (3 vs. 1 or 2)	0.989	0.535–1.881	.973
Hormone receptor status (ER+ vs. ER−)	0.854	0.471–1.556	.603
Number of metastatic sites (2 vs. 1)	0.207	0.075–0.520	.001
Number of metastatic sites (3+ vs. 1)	0.028	0.001–0.201	.002
Visceral involvement (yes or no)	1.809	0.873–3.854	.116
Bone involvement (yes or no)	2.376	1.129–5.169	.025
CNS involvement (yes or no)	4.586	1.111–16.41	.023
Trastuzumab only vs. trastuzumab + pertuzumab	1.655	0.841–3.160	.134
Surgery (yes or no)	4.422	2.398–8.343	<.001
Radiation (yes or no)	0.892	0.481–1.556	.716

Abbreviations: CI, confidence interval; CNS, central nervous system; ER, estrogen receptor; NED, no evidence of disease after therapy; OR, odds ratio.

For the NED cohort, the median survival was not achieved at a median follow-up of 5.5 years. The OS rates were 98% (95% CI: 94.6%–100%) at both 5 and 10 years. The PFS was 100% at 5 and 10 years, indicating no progression events for any of the patients who achieved NED (Fig. 1A). Figure 2 shows the follow-up duration and disease status of each NED patient at last follow-up. For patients who did not achieve NED status, the median OS was 4.7 years (95% CI: 4.2–5.3) at median follow-up of 2.5 years. The OS rates were 45% (95% CI: 38.4%–52.0%) and 4% (95% CI: 1.3%–13.2%) at 5 and 10 years, respectively. The PFS rates were 12% (95% CI: 4.5%–30.4%) and 0% at 5 and 10 years, respectively (Fig. 1B). In Cox multivariate analysis, achieving NED status (HR 0.014, $p < .001$) and hormone receptor positive status (HR: 0.72; $p = .04$) were significantly associated with prolonged OS (Table 3). For PFS, the Cox model did not converge due to lack of events in the NED group.

Discussion

In this study, we examined long-term survival of patients with de novo stage IV, HER2 positive breast cancers who did, or did not, achieve NED status with therapy. We found that 13% of patients achieved NED with trastuzumab-based therapy. This is similar to findings by Bishop et al., who assessed 570 HER2 positive MBC patients and reported that 16% of them achieved NED with

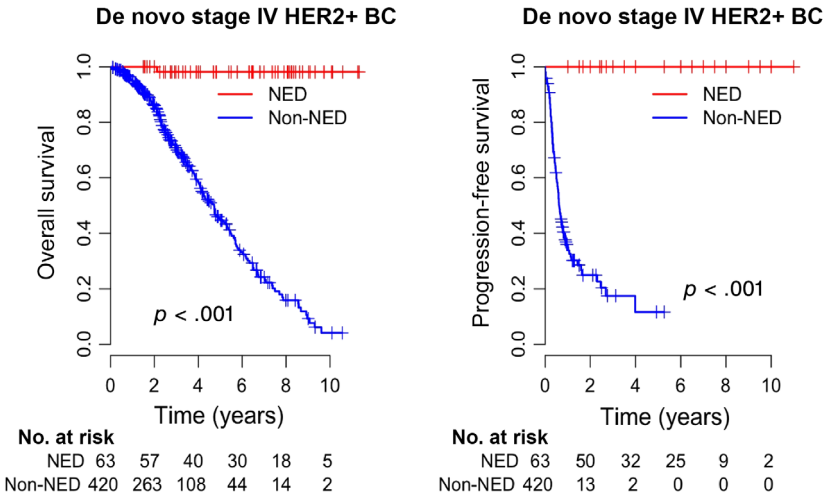

Figure 1. Kaplan-Meier survival curves of overall and progression-free survival by response status. One patient in the NED cohort has died without known recurrence. Log-rank test indicated statistically significant difference survival by response cohort ($p < .001$).
Abbreviations: BC, breast cancer; HER2+, human epidermal growth receptor 2 positive; NED, no evidence of disease after initial therapy.

initial therapy [20]. In our study, all NED patients were without disease progression at 5 years, and their OS was 98% at 10 years. In contrast, for patients who did not achieve NED, the 10-year OS was only 4%. Patients who achieved NED had unique disease characteristics. They typically had single metastasis, often in the bone or CNS, and more frequently underwent surgery to resect the primary tumor or solitary metastasis. These observations are also consistent with earlier reports that identified oligometastatic disease, HER2 positive status, and de novo stage IV presentation as predictors of long-term survival and clinical remission in MBC [9, 13, 21, 22]. We also observed that the no-NED group had a higher proportion of black women than the NED group, which suggests that these patients either receive less aggressive care for the same disease presentation possibly due to more comorbidities, personal choices, insurance restrictions, or physician bias, or they present with disease that is deemed too advanced for aggressive multimodality therapy. Because of the retrospective nature of the study, we cannot determine the contribution of these factors.

Due to increasing efficacy of therapies, median survival of patients with MBC has increased in the past decades and a growing minority of patients experience complete clinical response with systemic therapies or achieve an NED status with multimodality therapy, particularly among HER2 positive patients [5, 6, 23]. However, the primary goal of treatment in the metastatic setting remains palliative [1]. Several editorials in the past few years hypothesized that cure may be accomplished in MBC [24–26]. Our findings suggest that aiming to achieve NED status among patients with stage IV de novo, oligometastatic, HER2 positive breast cancer may be an important therapeutic goal. Dual HER2-targeted therapies combined with chemotherapy result in high rates (60%–80%) of pathologic complete response in early-stage disease [27, 28], and aggressive multimodality therapy has reduced distant metastatic recurrence rates and improved survival in locally advanced HER2 positive breast cancers. Similar to early-stage disease, further investigation is needed to explore the merits of applying a multidisciplinary treatment strategy to patients with oligometastatic disease. Such a strategy would involve upfront aggressive systemic HER2-targeted therapy in combination with chemotherapy to induce a complete response or best response, resecting or radiating residual disease, if any, and continuing maintenance therapy with an HER2-targeted agent and endocrine therapy if appropriate. Currently, one randomized trial (NRG BR002, NCT02364557) examines the value of adding stereotactic radiosurgery and/or surgery to standard-of-care systemic therapy in treating patients with limited metastatic breast cancer. Because most patients with metastatic disease eventually receive many, if not all, available therapies, including palliative radiation, intensifying treatment early in the course of the disease in the hope of cure may be reasonable for a select group of patients and should be further explored.

Our study has important limitations. Although our findings are intriguing, we cannot firmly conclude that it was the aggressive treatment that led to the excellent survival of these patients, because selection bias may have led to more aggressive treatment of patients whom physicians perceived to have better prognosis. Treatment decisions for individual patients represented in our database were made in the context of routine care and were influenced by patient preference, performance status, comorbid conditions, physician judgement, and evolving practice standards over time. This leads to highly variable therapies for individual patients. We could not adjust for performance status and comorbidities because these were not consistently captured in a standardized manner in the medical records that span many years across multiple providers in two different institutions. We also acknowledge that our median follow-up is short and that with additional follow-up time, late recurrences may occur in our cohort.

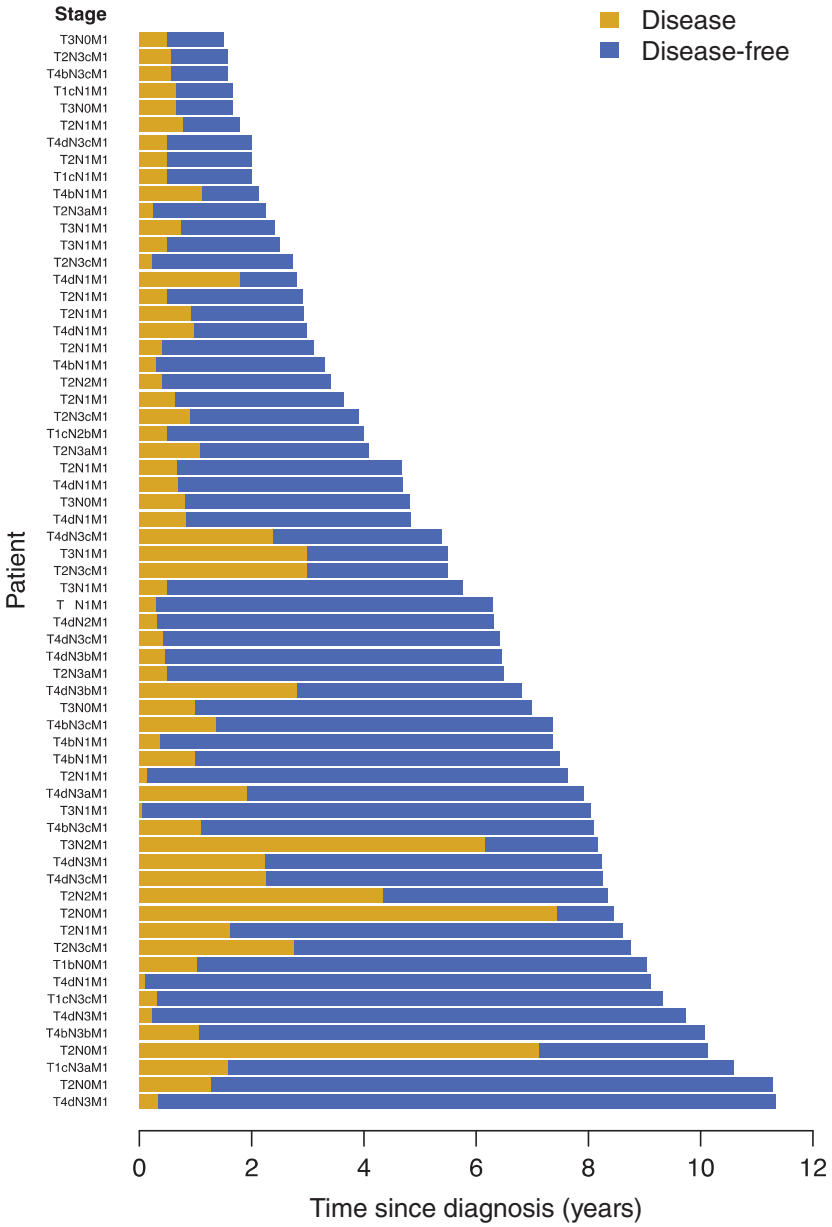

Figure 2. Disease course of patients who achieved no evidence of disease after initial therapy status. The time axis corresponds to time from date of diagnosis to last follow-up.

Table 3. Factors associated with overall survival in Cox multivariate analysis

Overall survival	Hazard ratio	95% CI	*p* value
NED vs. non-NED status	0.014	0.002–0.01	<.001
Age, years (>50 vs. ≤50)	1.006	0.746–1.357	.968
Grade (3 vs. 1 or 2)	1.129	0.806–1.583	.480
Hormone receptor status (ER+ vs. ER−)	0.722	0.528–0.987	.041
Trastuzumab vs. trastuzumab + pertuzumab	0.962	0.537–1.722	.895
Surgery (yes vs. no)	0.716	0.505–1.013	.059
Radiation (yes vs. no)	1.174	0.856–1.611	.319
Number of metastatic sites (1 vs. ≥3)	0.702	0.359–1.373	.301
Visceral involvement (yes vs. no)	1.336	0.901–1.981	.150
Bone involvement (yes vs. no)	1.429	0.941–2.171	.094
CNS involvement (yes vs. no)	1.431	0.795–2.577	.232

Abbreviations: CI, confidence interval; CNS, central nervous system; NED, no evidence of disease after therapy.

Conclusion

In this study, we highlight the excellent outcome for a select group of patients who presented with previously untreated HER2 positive metastatic breast cancer and achieved NED status with systemic therapy alone plus/minus combined modality treatment. Our findings warrant a randomized trial to confirm that aggressive treatment of de novo stage IV HER2 positive cancers improve survival compared with treatment with palliative intent as recommended by current guidelines.

Author Contributions

Conception/design: Yao Wong, Lajos Pusztai, Rashmi K. Murthy
Provision of study material or patients: Javier Perez Irizarry, Teresita Vega, Lajos Pusztai, Rashmi K. Murthy
Collection and/or assembly of data: Yao Wong, Akshara Singareeka Raghavendra, Christos Hatzis, Javier Perez Irizarry, Teresita Vega
Data analysis and interpretation: Yao Wong, Akshara Singareeka Raghavendra, Christos Hatzis, Lajos Pusztai, Rashmi K. Murthy
Manuscript writing: Yao Wong, Nina Horowitz, Carlos H. Barcenas, Mariana Chavez-MacGregor, Vicente Valero, Debu Tripathy, Lajos Pusztai, Rashmi K. Murthy
Final approval of manuscript: Lajos Pusztai, Rashmi K. Murthy

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Mariana Chavez-MacGregor: Pfizer, Roche (C/A). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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