Predictors of long-term durable response in de novo HER2-positive metastatic breast cancer and the real-world treatment experience at two institutions

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Abstract

Purpose HER2-directed therapies enable some patients with de novo HER2+ metastatic breast cancer (MBC) to achieve long-term, durable responses (DR). Expert opinion dictates indefinite HER2-directed therapies for patients who achieve DRs, but real-world examples of this practice are lacking in the literature. Patient factors that predict DR continue to be elucidated.

Methods This is a retrospective study of patients with de novo HER2+ MBC. DR is defined as absence of progression/death at any point after diagnosis. Controls are patients with evidence of progression/death. Age, ER/PR status, sites of metastasis, surgical resection of primary tumor, and initial treatment were analyzed.

Results 96 patients with de novo HER2+ MBC, 28 with DR, and 68 with progression were identified. 75% of patients with DR had a single metastatic site, compared with 47% of patients with progression (OR 3.7, p = 0.01). 64% of patients with DR received a regimen containing trastuzumab, pertuzumab, and a taxane, while 28% of patients who progressed did (OR 4.5, p < 0.001). 57% of patients with DR underwent surgical removal of breast primary, compared with 24% of patients who progressed (OR 4.3, p = 0.002.) Among patients with DR, nine patients have been receiving trastuzumab for over ten years with no evidence of disease and one patient opted to discontinue trastuzumab.

Conclusion Nearly a third of patients with de novo HER2+ MBC achieved DR. Factors that correlate with DR include single metastatic site, initial trastuzumab, pertuzumab and taxane therapy, and surgical resection of primary tumor. Among patients with DR, indefinite trastuzumab administration is the norm.

Keywords Breast Cancer · HER2 · Trastuzumab · Neoplasm metastasis

Introduction

Approximately 15–20% of breast cancers express the human epidermal growth factor receptor 2 (HER2) [1]. HER2-positive breast cancers are considered a more aggressive subtype of breast cancer and more likely to be metastatic at diagnosis than HER2-negative breast cancers. Prior to targeted therapy, HER2 positive would portend a worse prognosis [2]. However, the development of trastuzumab and its FDA approval in 1998 paved the way for the development of HER2-directed therapies that have revolutionized the treatment of HER2-positive breast cancer [3]. As established in the CLEOPATRA trial, first-line treatment for HER2 positive, metastatic breast cancer (MBC) consists of taxane chemotherapy in combination with dual HER2-targeted therapy using trastuzumab and pertuzumab (THP) [4, 5]. Patients treated with this combination had a median overall survival of 57.1 months. In patients who respond, cytotoxic chemotherapy is generally administered for 4–6 months, and trastuzumab/pertuzumab dual therapy is continued until disease progression [6].

Despite not considered curable, some patients with HER2-positive MBC may experience a clinically durable response (DR), which can be defined as no progression of disease since initial diagnosis. Patients with DR generally receive ongoing trastuzumab ± pertuzumab every three...
weeks for years without detectable disease [7–9]. There is a lack of evidence to guide the indefinite administration of anti-HER2 antibodies, but it has offered impressive survival outcomes for patients. In the most recent analysis of CLEOPATRA with approximately 8 years of follow-up, 16% of patients were still free from disease progression [5]. A retrospective study of HER2-positive de novo MBC patients in Japan who achieved complete clinical response at two years from diagnosis found that 80% were alive ten years after metastatic diagnosis [10]. Patient and disease-specific factors that predict long-term DR in de novo HER2-positive MBC include oligometastatic disease and surgical resection of primary tumor or metastatic site [11].

Furthermore, there is little data on the risk of cardiotoxicity with long-term trastuzumab use. Initially, the risks of cardiotoxicity with trastuzumab when combined with concurrent doxorubicin were quoted as high as 27% [12]. Current estimates of severe symptomatic congestive heart failure from trastuzumab and/or pertuzumab in HER2-positive MBC are around 2% [5]. Interval echocardiography is required with long-term trastuzumab use, indicating further testing and perhaps unnecessary cost to the patient and health care system.

In this retrospective case control study, our primary goal is to determine what clinical features including age, estrogen receptor (ER) and/or progesterone receptor (PR) status, initial chemotherapy treatment, surgical resection of primary, and sites of metastatic disease correlate with DR. Our additional aim is to report on the real-world prevalence and management of DR in de novo HER2-positive MBC, as well as the incidence of cardiotoxicity in this population.

Materials and methods

Study design

This is a retrospective case control study of all patients with de novo HER2-positive MBC at two large National Cancer Institute designated academic cancer centers, Duke Cancer Institute and affiliated clinics, and Oregon Health and Sciences University Knight Cancer Institute and affiliated clinics. Patients were identified through the electronic health system EPIC if they had been ordered to receive at least one dose of trastuzumab anytime between 2012 and 2019. Chart reviews were performed under approval from the IRB at each institution.

Patients

Patients were included if they had HER2-positive de novo MBC. Metastatic disease was defined radiographically or through confirmatory metastatic biopsy. Patients with a prior history of localized breast cancer were excluded unless the prior diagnosis was HER2-negative disease and was more than 10 years prior to diagnosis of metastatic HER2-positive de novo MBC. Positive HER2 status was defined as immunohistochemistry staining of 3+ and/or positive fluorescence in situ hybridization defined as a HER2/CEP17 ratio ≥ 2.0 according to American Society Clinical Oncology/College of American Pathologist guidelines [13]. Patients were only included if at least two years of follow-up data were available for review or the patient was deceased. We defined DR as patients with de novo HER2-positive MBC with radiographic stable disease, complete response, or partial response according to RECIST 1.1 without progression or death at any point after diagnosis. Controls are patients with de novo HER2 positive MBC with evidence of radiographic progression or death any point after diagnosis.

Outcomes

We assessed five variables at diagnosis: age at diagnosis, ER/PR status, sites of metastatic disease, initial treatment, and surgical resection of primary. Initial treatment was categorized as THP containing (including THP plus carboplatin (TCHP) and THP plus endocrine therapy), or non-THP treatment (including trastuzumab plus taxane, trastuzumab plus endocrine therapy, trastuzumab, carboplatin, taxane (TCH)). Progression-free survival (PFS) was defined as time from diagnosis to progression, discontinuation of therapy, or death, which ever came first. Progression was defined radiographically according to RECIST 1.1 criteria for progressive disease. Overall survival (OS) was defined as time from diagnosis to death, or end of study follow-up, whichever came first. Time to partial response (PR) and complete response (CR) according to RECIST 1.1 were recorded for patients with DR. Patients who experienced a decline in cardiac ejection fraction at any point while on trastuzumab therapy leading to treatment delays or discontinuation were recorded.

Statistical methods

Differences in age at diagnosis between the two groups was analyzed using an unpaired T test. ER/PR status, sites of metastatic disease, initial treatment, and surgical resection of primary breast tumor were analyzed using a Fisher’s exact test. A p value of < 0.05 was chosen as the threshold of statistical significance.
Results

A total of 96 patients with de novo HER2+ MBC were identified, 28 (29%) with DR and 68 (71%) with progression or death any point after diagnosis. Patients were diagnosed between the years 2000 and 2017. The average follow-up of patients with DR was 90 months (range 27–224), compared to 58 months (range 1–208) in patients with progression or death. The average year of diagnosis for patients with DR was 2011, while it was 2012 for patients without DR. Fifty nine patients (61%) had biopsy-proven metastatic disease whereas the rest were deemed to have metastatic disease based upon radiographic findings for reasons including negative biopsy attempt, biopsy not feasible, biopsy report missing from chart, but noted as positive in physician notes, patient preference, and/or treating physician preference. 79% (22/28) of patients with DR and 54% (37/68) of patients with progression or death had biopsy-proven metastatic disease.

The entire cohort of 96 patients had a median PFS of 23.5 months and a median OS of 88 months (Fig. 1). Seven patients declined any treatment or pursued naturopathic remedies, and all are deceased. Sites of progression were brain (34%), multiple areas (17%), bone, liver and breast/lymph nodes (14% each), lung (5%), and peritoneum (3%) (Fig. 2).

Among the 28 patients with DR, 2 achieved stable disease, 10 patients had documented PR at 4 months on average (range 2–6 months), and 26 patients had CR at 7.7 months on average (range 2–19 months). 16 (57%) of patients with DR received at least two years of pertuzumab with trastuzumab. Nine patients have been receiving trastuzumab for over ten years with no evidence of disease. Only one patient opted to discontinue this therapy a year after complete response and is disease-free five years from diagnosis (Fig. 3).

The most common initial chemotherapy regimens given to patients with DR were TCHP (11/28, 39%), THP (7/28, 25%), and trastuzumab plus taxol (5/28, 18%). The most common initial treatments for patients who experienced progression were trastuzumab plus endocrine therapy (15/68, 22%), THP (14/68, 21%), and TCH (10/68, 15%). All 15 of the patients with progression treated with frontline trastuzumab plus endocrine therapy were treated prior to the 2012 FDA approval of pertuzumab for metastatic disease. When compared, 64% (18/28) of patients with DR received a THP-containing frontline treatment, compared to 28% (19/68) of patients who progressed, (OR 4.5, p < 0.001). For the entire patient cohort, patients with ER/PR-negative disease received more intravenous cytotoxic chemotherapy than ER/PR-positive disease 83% and 57%, respectively. Cytotoxic chemotherapy regimens included a taxane, platinum, and/or vinorelbine.

Patients with DR were more likely than patients who progressed to undergo surgical resection of a breast primary tumor, 57% vs. 24%, (OR 4.3, p = 0.002). Of the patients with durable response who did receive locoregional therapy, this was lumpectomy with radiation or mastectomy and in the majority of cases done after clinical complete response. A few patients without durable response underwent breast surgery for palliation of symptoms. It was rare that a patient underwent targeted radiation to a metastatic site. 75% of patients with DR had a single organ involved by metastatic disease at diagnosis compared with 47% of patients with progression (OR 3.7, p = 0.01). The most common sites of metastasis in the patients with DR were bone only (9/28, 32%), and liver only (9/28, 32%). 6/28 patients (21%) with DR had ≥ 2 organs involved compared with 50% (34/68) of patients who progressed. Of the patients who progressed, 29% (20/68) had bone only disease. No patients with DR had brain metastasis, compared with 5 patients (5/68, 7%) who progressed. Average age at diagnosis was not different between those who achieved DR and those who progressed, 54 and 52 years, respectively (p = 0.61). There was
no difference in ER/PR-positive status between patients with DR and patients who progressed, 54% and 68% positive, respectively ($p = 0.24$). (Table 1).

Six patients (6.3%) developed reduced ejection fraction requiring treatment interruption or cessation, five in the group who progressed, one in the DR group. Of the five who progressed, two patients experienced progression while holding trastuzumab, the rest were able to resume. The patient with DR who experienced reduced ejection fraction was able to resume trastuzumab without further cardiomyopathy and had been receiving trastuzumab for 10.8 years at the time of final analysis.

### Table 1 Clinical characteristics of de novo HER2-positive metastatic breast cancer that predict durable response

|                        | Durable Response No. (%) | Progression No. (%) |
|------------------------|--------------------------|---------------------|
| No. Patients           | 28                       | 68                  |
| Age (years)            | 54 (range 33–77)         | 52 (range 28–80)    |
| ER/PR status           |                          | $p = 0.6$           |
| ER and/or PR positive  | 15 (54%)                 | 46 (68%)            |
| ER and PR negative     | 13 (46%)                 | 22 (32%)            |
| 1 organ involved       |                          |                     |
| Bone only              | 9 (32%)                  | 20 (29%)            |
| Liver only             | 9 (32%)                  | 8 (12%)             |
| Lung only              | 3 (11%)                  | 4 (6%)              |
| $\geq 2$ organs involved | 6 (21%)                | 34 (50%)            |
| Any brain              | 0                        | 5 (7%)              |
| Initial Chemotherapy   |                          |                     |
| TCHP or THP            | 18 (64%)                 | 19 (28%)            |
| Other$^a$              | 10 (36%)                 | 43 (63%)            |
| Surgery                |                          |                     |
| Surgical resection of primary | 16 (57%)         | 16 (24%)            |
| Surgical resection of metastasis | 1 (4%)          | 4 (6%) all brain    |

$^a$Other therapies included trastuzumab + taxol, trastuzumab + endocrine therapy, trastuzumab + carboplatin + taxol, trastuzumab + other cytotoxic chemotherapy, lapatinib + taxol. 6 patients in this group did not receive any initial therapy as they opted for hospice or were deceased prior to therapy initiation.

**Fig. 3** Clinical trajectory of patients with de novo HER2-positive metastatic breast cancer with durable response. Each patient with DR is plotted along the Y-axis with time on the X-axis. Patients with a gray bar are those who received trastuzumab (H) with pertuzumab (P) for more than two years. Blue bars are those patients who received less than two years of pertuzumab and only continued trastuzumab therapy. Purple triangles denote partial response and red triangles denote complete response. There are two patients who only ever met RECIST criteria for stable disease. Only one patient opted to discontinue H and this is denoted with X. All patients except for this one patient are ongoing H treatment at the time of data cutoff.
Discussion

In our multi-center, retrospective cohort study of de novo HER2 + MBC, 29% of patients achieved a DR during an average 7.5 years of follow-up. Except for one patient, all patients identified as having a DR opted to continue long term, every three week trastuzumab plus/minus pertuzumab, some for over 10 years. Therefore, this practice appears to be common place in the real world. Long-term trastuzumab therapy does not appear to have significant cardiac toxicity, only 1 of 28 patients developed asymptomatic ejection fraction reduction and was ultimately able to resume without issues. The effects of indefinite trastuzumab plus/minus pertuzumab on other symptoms, quality of life, and financial toxicity deserve further study. The addition of pertuzumab to trastuzumab may not be cost effective in the up-front treatment of MBC, begging the question of whether indefinite pertuzumab would also not be cost effective. [14] Prospective clinical trials or registry studies identifying which subsets of HER2 + MBC patients with DR can de-escalate such maintenance therapy are needed. Options could include switching to subcutaneous forms of trastuzumab or pertuzumab, increasing the dosing interval, or treatment holidays. Patient opinions on de-escalation of maintenance therapy are critical to assess.

In our study, predictors of DR were initial THP-containing chemotherapy, surgical removal of the primary breast tumor, and a single organ involved by metastasis. It is well established that up-front THP-containing chemotherapy improves survival in HER2 + MBC; thus, this finding is not novel [4, 15]. However, our approach of comparing characteristics of DR and non-DR patients does provide a different viewpoint on this special patient population. Most of the patients in our study who did not receive up-front THP were diagnosed and treated prior to the 2012 FDA approval of THP as standard of care, frontline therapy. The most common regimen given to patients who achieved DR was actually TCHP. This begs the question of whether patients with de novo HER2 + MBC with oligometastatic disease should receive even more intensive up-front therapy than THP, including the addition of carboplatin, or additional treatment modalities such as surgery and radiation.

We found that surgical removal of the breast primary tumor and oligometastatic disease were associated with DR. This is in line with another retrospective study of de novo HER2 + MBC [11]. In all-comers with MBC, there appears to be no benefit in OS, PFS, or quality of life to early locoregional therapy to the primary breast tumor as demonstrated in the ECOG-ACRIN (EA2018) trial [16]. This trial included patients with HER2 + disease but was not designed to study individual biologic subtypes. While a phase II trial suggested a benefit to radiation to sites of oligometastatic disease [17], the prospective, randomized trial did not show a benefit for PFS. (NRG BR002) [18]. However, this trial was also not designed to address this question in biologic subtypes. Accumulating data from our research and others suggests that a sizeable proportion of patients with de novo HER2 + MBC can achieve functional “cure,” and that locoregional therapy to the breast primary tumor, intensive chemo- and dual antibody therapy should be studied in a randomized fashion among de novo, HER2 + patients with oligometastatic disease.

Our study has several important limitations. Our patients had a lower rate of biopsy-proven metastatic disease than expected. While we believe this reflects real-world challenges pertaining to the technicality of biopsy, it is possible some patients in this cohort did not truly have metastatic disease and lesions seen on imaging were due to another pathology. We did not collect data on radiation to sites of metastatic disease, which would have been an interesting variable, although this practice was uncommon in our patients and unlikely to have been different between the two groups. We also did not collect data on the timing or locoregional therapy to the breast primary tumor. As this study is retrospective, we cannot conclude that more aggressive up-front therapy is what lead to DR given the possibility of selection bias influencing the patients selected in this study. We have attempted to limit selection bias by including all patients diagnosed with de novo HER2 + MBC at our institutions.

Conclusion

In conclusion, our study found that almost one third of patients diagnosed with de novo HER2 + MBC achieved long-term durable responses in our institutions. Ongoing dual-antibody treatment for many years is a common place practice and appears to be well tolerated. Predictors of DR include initial THP-containing chemotherapy, surgical removal of breast primary tumor, and a single organ involved by metastatic disease. Given the success of HER2-targeting therapies for early-stage HER2 + breast cancer, a greater proportion of HER2 + MBC is presenting as de novo disease, highlighting the need to refine treatment paradigms specifically for this clinical scenario [15]. While more intensive up-front multi-modality therapy, including HER2-targeting tyrosine kinase inhibitors and antibody drug conjugates should be studied in a randomized fashion in de novo HER2 + MBC with the goal of long-term, functional “cures”, our data suggest that some de novo patients may achieve this with current standard treatment approaches.
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Data availability The datasets generated during and/or analyzed during the current study are not publicly available due to patient privacy concerns but are available from the corresponding author on reasonable request.

Declarations

Conflict of interest We have no disclaimers. PKM is a full-time employee at Veracyte, Inc, but otherwise declares no conflicts of interests. The other authors declare no conflicts of interest.

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