



Original Report

Metastatic Hormone and Her-2 Positive Breast Cancer: A Community Approach

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Abstract: Metastatic hormone-receptor and HER-2 positive (triple-positive) breast cancer provides a treatment dilemma for oncologic clinicians. The current National Comprehensive Cancer Network (NCCN) Guidelines offer a variety of options in the first and second line for metastatic breast cancer. However, a more tailored treatment approach may be needed for the triple-positive metastatic breast cancer population. The aim of this study is to trend the therapeutic treatment selections for patients with metastatic, triple-positive breast cancer at a single, academic-affiliated community practice in the United States. The patient population included individuals with triple-positive, metastatic breast cancer who were treated over the span of six years at this institution. Ultimately, this patient population demonstrated variability across the various treating oncologists choice of therapy in the first, second and fourth line of treatment. The majority of patients (twelve out of fifteen) received combination therapy with trastuzumab in the first line of therapy. In the second line, seven out of eight patients received trastuzumab as part of their treatment regimen. In the third line, all three patients received trastuzumab emtansine as part of their therapy regimen. For patients who were able to survive until the fourth line and beyond, several other treatment options were utilized. Therefore, although metastatic, triple-positive breast cancer represents a subset of patients with vast treatment variability throughout the various lines of therapy, and there is a general lack of consensus on how to best treat this patient population. This study provides an opportunity for more expansive research in the field in order to help elucidate a treatment algorithm for all oncologic practitioners for patients with triple positive, metastatic breast cancer.

Keywords: Breast, Metastatic, Triple-Positive

1. Introduction

Breast cancer is the most common cancer diagnosed globally as well as the most common cancer amongst women [1]. In the United States, breast cancer remains one of the leading causes of cancer related deaths in women [2]. The American Cancer Society estimated that 40,610 women will die of breast cancer in 2017 with the majority breast cancer related deaths being due complications from distant organ metastasis, particularly the lung, brain, and liver [1]. The specific etiology of breast cancer is unknown, however many risk factors have been identified and include; female gender, increasing patient age, family history of breast cancer at a

young age, early menarche, late menopause, nulliparity, prolonged hormone replacement therapy, previous exposure to chest wall radiation (typically seen ages 10-30 for treatment of Non-hodgkins lymphoma), benign proliferative breast disease, and genetic mutations. Upon tissue diagnosis of breast cancer, all patients are assigned a clinical stage of disease that allows for identification of treatment options and for risk stratification to determine the patient's disease prognosis. In non-metastatic breast cancer, surgery can often be curative for localized tumors while systemic chemotherapy with or without radiation can help shrink and

eradicate disease [3].

Approximately 6-10% of new breast cancer cases each year are initially, clinically staged as de-novo metastatic (stage IV) cancer [1, 2]. Metastatic disease occurs by cancer cells detaching from the primary tumor, entering the circulation and seeding in other organs. Metastatic breast cancer is generally considered incurable and consequently all therapy is palliative in nature. 5-9% of women present with metastatic disease at the time of diagnosis and the five-year survival rate in women diagnosed with this stage are 22%, as reported by the American Cancer Society [1]. Metastatic breast cancer often remains an incurable malignancy that poses unique challenges in treatment options due to heterogeneity in the cancer cell population within the tumor [4].

Overall, breast cancer is a heterogeneous disease with much diversity throughout tumor cells. In addition to clinical staging, the American Joint Committee on Cancer (AJCC) recommends the collection of biomarkers from tumor tissue. These markers are estrogen receptor status (ER), progesterone receptor status (PR) and human epidermal growth factor status (HER2) [5]. 15-20% of breast tumors overexpress HER2 protein and are actually associated with decreased disease free survival and carry an overall worse prognosis [6, 7]. HER2 is a trans-membrane glycoprotein epidermal growth factor receptor (EGFR) with tyrosine kinase activity that is overexpressed on the surface of certain breast tumors and plays a key role in intracellular pathways of tumor cells. ER and PR are also known collectively as hormonal receptors (HR). These three biomarkers aid in tailoring the patient's treatment and overall care plan. When ER, PR and HER2 are positive, these tumors are classified as "triple-positive". Triple positive breast cancers represent roughly ten percent of breast cancers [6, 8]. While there has been impressive progress in treating triple positive breast cancer, metastatic disease continues to be a difficult task for oncologists and patients, as it is incurable. Initially, there was an inverse association described between HER2 receptor positivity and HR positivity. Recently, however, it has been reported that about 50% of HER2 positive tumors are also HR positive [4, 6]. The benefit of having a tumor that is HER2 positive lies in the option of HER2 targeted therapies. It is commonly believed that patients that are HER2 positive benefit from HER2 directed therapy, irrespective of HR status of the malignancy [7]. It has also recently been suggested that combination of dual HER2 blockade directed therapy plus endocrine therapy improves progression free survival [8, 10, 11]. Therefore, patients that are triple positive should have HER2 directed therapy included as part of the first line therapy regimen. The four HER2 directed agents that are used for the treatment of HER2 positive breast cancer include: trastuzumab, pertuzumab, ado-trastuzumab emtansine, and lapatinib. Trastuzumab, the most commonly known monoclonal antibody for HER2 positive cancers, binds the extracellular domain of HER2. Pertuzumab is a monoclonal antibody that binds the extracellular domain of HER2 and prevents it from binding to itself or other members

of the EGFR family. Ado-trastuzumab emtansine is an antibody drug conjugate composed of trastuzumab, a thioether linker, and antimicrotubule agent, DM 1. Lapatinib is a tyrosine kinase inhibitor against EGFR-1 and HER-2 that results in the inhibition of signaling pathways downstream of HER2.

Clinical benefit has not been elucidated in patients that are positive for both HER2 and HR from treatment with endocrine-directed therapy. Data from several clinical trials suggest that there is cross talk between the kinase-mediated growth factor pathway, and it is conjectured that the HER2 and EGFR pathway activates the ER receptor both directly and indirectly by enhancing co-factors and down-regulating repressors [12]. Consequently, this causes an up-regulation of ER receptor which eventually enhances cross-talk and results in the circumvention of hormone related therapy and contribution of endocrine resistance. Endocrine therapy is associated with low toxicity, and therefore recommended by many organizations as an initial line of treatment for patients with hormone receptor positive tumors with asymptomatic visceral disease [13-15]. Endocrine therapy is determined by whether the patient has been exposed to endocrine therapy in the past and whether they are pre or post menopausal. In both pre and post menopausal women who have not received anti estrogen therapy in the past, the initial treatment is a selective ER modulator alone or ovarian suppression in addition to endocrine therapy. The common endocrine therapies used for stage IV disease are; non-steroidal aromatase inhibitors, steroidal aromatase inhibitors, ER modulators (tamoxifen or toremifene), ER down regulators, progestin, androgens, or high dose estrogen. The mainstay of HER2 positive and HR positive cancers have been HER2 directed therapy with chemotherapy [16-18]. Recently, however, there has been a conflicting set of data to suggest that there is a subset of the triple-positive cancers act more like HER2 negative/ HR positive cancers [10, 11]. Elucidating our understanding of the current available data is essential to avoid overtreatment and prevent patients from having to undergo the side effects of chemotherapy. Ultimately, it is the combination of HER2 directed therapy with endocrine therapy and chemotherapy that constitutes the variety of treatment plans seen with triple positive breast cancer. In the current NCCN guidelines, acceptable treatment plans for triple positive, advanced stage breast cancer patients are HER-2 agents with endocrine therapy or HER2 agents with chemotherapy [9]. The choice as to whether to decide on endocrine therapy versus chemotherapy is dependent on a combination of the progression of the patient's disease as well as their symptoms. The chemotherapy that is typically chosen in combination with the HER2 agent is a taxane, either docetaxel or paclitaxel [12-16]. This is dependent on patient and provider preferences. Per the NCCN guidelines, the preferred method for HER2 positive cancers is trastuzumab, pertuzumab and a taxane. Several clinical trials have attempted to elucidate the optimal combination regimen, safety, duration and efficacy as measured by progression free survival [14, 16-25]. Factors to consider in these decisions include, noting the progression

of disease on initial therapy, extent of disease on presentation and ECOG performance status [26].

There have been an increasing number of studies and clinical trials to answer the question of how the cross talk between HER2 and HR positivity affects the choice of treatment in patients with triple positive metastatic disease. While there have been exciting developments in attempting to identify therapeutic options in this specific patient population, there remains a lack of consensus on how to optimally approach and treat triple positive, metastatic patients. This study aims to bring to light the current heterogeneity that occurs in a single, academic-affiliated community oncologic program. The ultimate aim is to stimulate the discourse in order to eventually create validity in a single approach that can be used by our network to provide the utmost benefit to triple positive metastatic breast cancer patients.

2. Methods

Investigators retrospectively reviewed the data and consultation notes for 206 patients who were treated at one academic-affiliated, community center between 2010-2016 via electronic medial records. Of 206, 15 eligible patients

with metastatic were identified. HER2-positive and receptor-positive breast cancer HER2-positive status was confirmed centrally, by means of immunohistochemistry (with 3+ indicating positive status) or fluorescence in situ hybridization (with an amplification ratio ≥ 2.0 indicating positive status). Tumor hormone-receptor status was determined locally. Results were tabulated to identify pertinent patient demographic information, therapy duration and course of action, and each line of therapy.

3. Results

A total of 206 patients who were treated between the years of 2010 to 2016 in one, academic-affiliated, community center with metastatic breast cancer were identified. A retrospective chart analysis demonstrated that 15 of these metastatic breast cancer patients were identified as HER2 and HR positive, or triple positive. Patient characteristics included women with ages ranging between 51-79. All patients were post-menopausal at the time of diagnosis. Of the 15 patients analyzed, 6 patients had metastatic disease to the bone, 7 patients had metastases to the lung, 2 to the brain or CSF, 1 to the liver, 1 to the adrenal gland, and 1 patient metastasized to the ovary (Table 1).

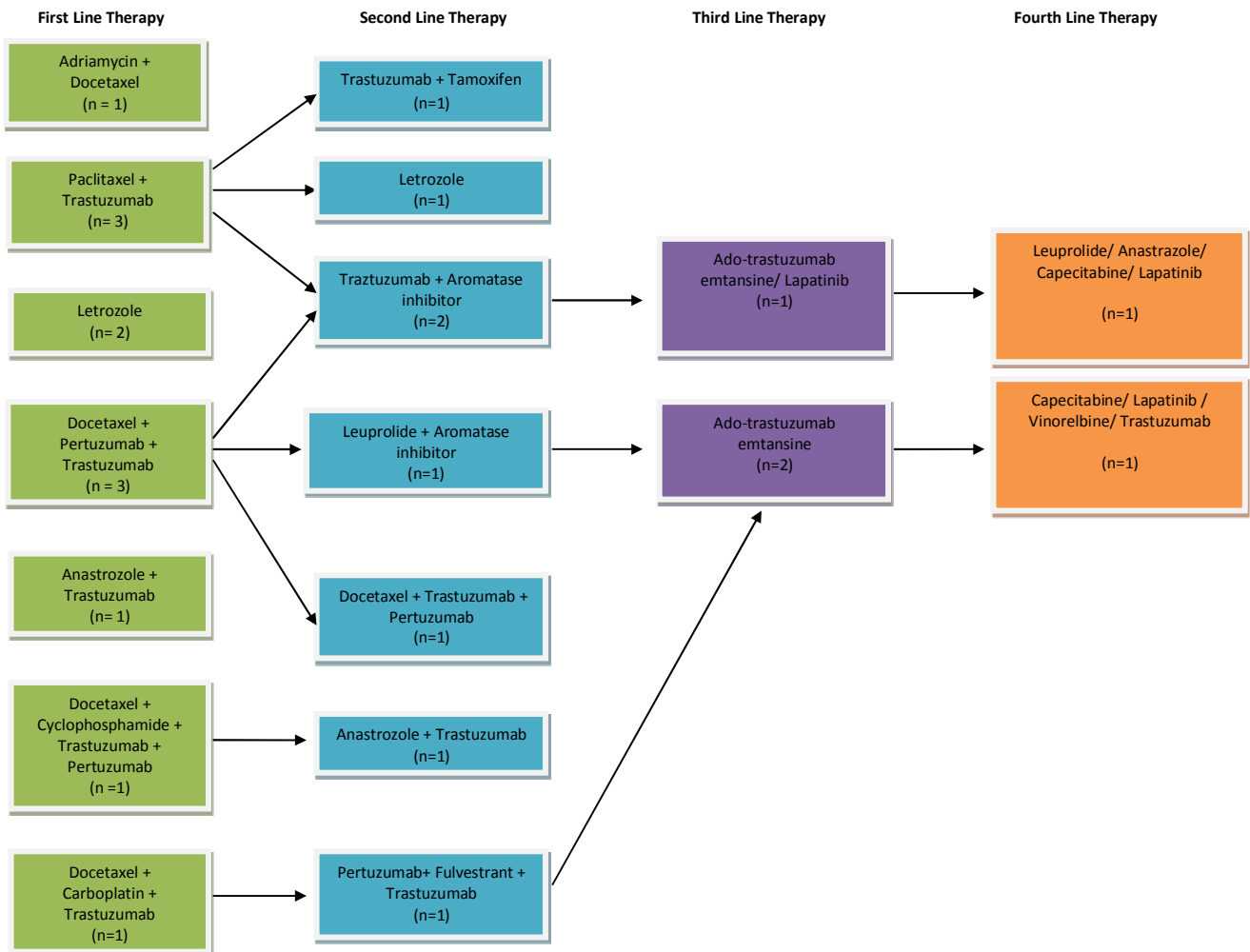


Figure 1. Therapeutic treatment regimens.

Table 1. Sites of metastases.

Site of Metastasis	Number of Patients (out of 15)
Bone	10/15
Lung	7/15
CSF	1/15
Adrenal	1/15
Ovary	1/15
Brain	1/15
Lymph Node	1/15
Liver	2/15

Out of the 15 total patients, 8 of the patients had received adjuvant chemotherapy; 7 received neo-adjuvant chemotherapy. 13 received combination first-line therapy, while 2 patients received single-agent therapy. The clinical rationale for both patients who received single-agent chemotherapy was for better tolerability and worse initial ECOG status, however both patients had progressive disease with an outcome of hospice after the first line of therapy.

A total of 12 out of 15 patients received HER2 directed therapy, trastuzumab, as a part of their first line of chemotherapy. Of the 13 patients who received combination first line therapy, 9 patients proceeded onto second line therapy, and one patient achieved remission. 7 out of 8 patients received HER2 directed therapy in the second line of therapy, and 1 out of 8 patients received single line hormone-based therapy. 5 out of 8 patients in the second line group received an aromatase inhibitor in addition to HER2 directed therapy. 3 patients out of the original 15 patients went onto third line therapy; two patients receiving ado-trastuzumab emtansine, and one patient received ado-trastuzumab emtansine and lapatinib combination therapy. 2 of the 15 patients received fourth line of agents, and 1 patient was able to undergo 8 lines of therapy (Figure 1).

4. Discussion

The fifteen patients analyzed at our single, academic-affiliated community center with metastatic triple positive breast cancer in this case series were treated heterogeneously. It can be stated that the two patients who received single agent therapy performed poorly in comparison to the patients who received combination regimens with the final outcome of hospice. However, it should also be stated that these patients had an ECOG performance status greater than 1 at the time of the initiation of therapy. The two other patients who did not progress past initial first line of therapy included a patient who was treated without HER2 directed therapy, with only two chemotherapeutic agents. The last patient who did receive HER2 and HR directed therapy in the first line also was moved to hospice and was unable to complete the first line of therapy.

Interestingly, the second line of therapy was varied across the seven remaining patients. Six of the seven patients received trastuzumab in the second line of chemotherapy,

and arguably HER2 in addition to HR directed therapy appears to have been a preferred option in the second line of therapy. Four of the seven remaining patients who were able to move onto third line of therapy had received HER2 guided therapy in the initial line of therapy. Of the three patients who moved to hospice after the second line of therapy, two patients received HR and HER2 guided therapy, while one patient received single agent HR guided therapy. The patient who received HR guided single agent therapy in the second line again had a poor ECOG status at the time of therapy initiation.

In the third line of therapy, ado-trastuzumab emtansine was used at the HER2 guided therapy of choice, and both patients were able to participate in fourth line of therapy after disease progression. All three patients who were able to progress onto third line of therapy received both HR and HER2 directed therapy in the second line. Interestingly, both of the patients who survived onto third and fourth line of therapy had received HER2 directed therapy with chemotherapy in the first line of therapy.

5. Conclusion

Although the primary limitation of this study is the number of subjects, the population reflects the true occurrence of triple positive metastatic breast cancer in the community setting. In the metastatic breast cancer population, triple-positive patients represent a small subset of patients. As is seen in smaller, community-affiliated practices, variability of therapy options also coincided with an array of oncologists who do not specialize only in breast cancer. The complexity of this patient subset is the variety of possible therapeutic options without clear clinical treatment guidelines or algorithms that may help elucidate treatment plans for providers. Further directions of research should include possible elucidations on choices and duration of therapy in the various lines of treatment. Ultimately, a treatment algorithm could potentially be beneficial in this population in regards to less toxicity, better quality of life, and longer progression-free survival.

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